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Innovation and Marketing in the Pharmaceutical Industry

Emerging Practices, Research, and Policies

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Innovation and Marketing in the Pharmaceutical Industry

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Chapter 1
The Pharmaceutical Industry: Specificity, Challenges, and What You Can Learn from this Book

Min Ding, Jehoshua Eliashberg, and Stefan Stremersch

The pharmaceutical industry is an industry that is in a class of its own (Stremersch and Van Dyck 2009). It is significantly more linked to science and more regulated than any other industry. Because pharmaceutical drugs substantially impact people's quality-of-life, both regulation and the unique channel of healthcare provider (e.g., doctor or pharmacist) and payer (i.e., government or insurer) are designed to protect the patient's wellbeing at reasonable cost.

The industry consistently grows 4–7 % per year and is fast approaching the magic US$1 trillion market size. At the same time, it faces tremendous innovation and marketing challenges. These two factors drive the success of a branded drug company. A firm with subpar innovation for an extended period will see its

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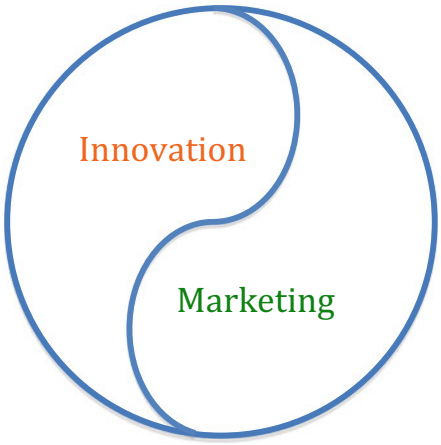

Fig. 1.1 Innovation and marketing in pharmaceutical industry

differentiation potential decrease, with deteriorating margins as a consequence. It will succumb under price competition with generic drug firms and may, ultimately, be forced to merge with or be acquired by another company. A firm without strong marketing capabilities will not fully unlock the value of innovation and thus it stands to miss out on billions of dollars for its stakeholders and on the resources needed to sustain continued innovation. The graveyard of former pharmaceutical firms is littered with once-mighty corporate brands, such as American Home Products, Pharmacia, and Wyeth, that mismanaged either their innovation or marketing, or both. Firms that are strong in both innovation and marketing have successfully navigated the challenges and will continue to create value for their stakeholders (Fig. 1.1).

1.1 The Specificity of Innovation and Marketing in the Pharmaceutical Industry

Innovation and marketing in the pharmaceutical industry are not run-of-the-mill processes and challenges that an outsider to the industry can immediately grasp. To explain these complex processes, we discuss below the very specific nature and characteristics of innovation and marketing in the pharmaceutical industry.

1.1.1 Innovation

Innovation in the pharmaceutical industry has three characteristics: *live or die*, *large in size*, and *finite lifespan*. A considerably large percentage of the profit of a typical branded pharmaceutical firm comes from drugs under patent protection.

The characteristic "live or die" refers to the fact that a firm cannot possibly survive if its innovation level decreases substantially and it can no longer generate new drugs with sufficiently profitable patent protection.

"Large in size" means each innovation (new drug) tends to generate a large amount of revenue for a firm. Since the late 1990s, firms have adopted the strategy of developing the so-called blockbuster drugs, which are drugs that will generate at least US$1B per year in revenue. In their search for blockbusters products, some pharmaceutical firms such as GlaxoSmithKline have already started to design medicines based on bioelectronics, which entails treating the disease through electrical signals in the brain and elsewhere rather than targeting biochemical structures (*Financial Times* 8/1/2012). While this may sound like good news, it means that a firm's loss of income from an innovation is usually accompanied by a sharp drop in its overall performance in terms of profit, which makes the challenge of delivering consistent results at the firm level every year nontrivial.

Finally, "finite lifespan," means innovations in the pharmaceutical industry, with the exception of a few biological drugs, have a finite time to create value for its shareholder. The standard lifespan is in general defined by the patent validity. Chemical drugs, which are the overwhelming majority of drugs, have no other tools (e.g., trade secret, manufacturing know-how) for extending their standard lifespan. The manufacture of chemical drugs is standardized and, in general, once the patent expires, they can be easily reproduced as generics by many competitors. The situation of biological drugs is much more complex in most cases because they are often harder to manufacture and have higher manufacturing variable costs as well, as compared to chemical drugs.

These three characteristics (i.e., live or die, large in size, and finite lifespan) set the context of pharmaceutical innovation. Within this context, a pharmaceutical firm must consider and balance four key dimensions: *cost*, *uncertainty*, *return*, and *time*. Figure 1.2 graphically illustrates the relationship and potential tradeoff in supporting various projects along these dimensions. Project 1, in this case, has large return, medium uncertainty, and will take medium time to reach the end of its development. Project 2, on the other hand, has small return, small uncertainty, and can be completed in short time. Comparing Project 1 and Project 2, we also can see the cost of supporting Project 1 is larger than that for Project 2 (represented by the size of the oval).

The *cost* of pharmaceutical innovation is gigantic. According to the most recent estimates, the average cost of developing a successful new drug has surpassed US$1B, increasing from an estimate of US$360M in the mid-1990s. While this sounds like an astronomical number, the actual cash needed to develop *one* drug is substantially smaller. The US$1B+ price tag includes two large components that people are not aware of sometimes. First, the price tag includes the cost of dry holes. If on average, 1 in 10 new drug projects succeed and 9 fail, the cost of developing one successful drug includes as well the cost of the 9 failed projects (dry holes). The second component is the opportunity cost (interest) due to the long time horizon of development. $1M in year 1 is worth much more 12 years later, which is the average time for developing a drug.

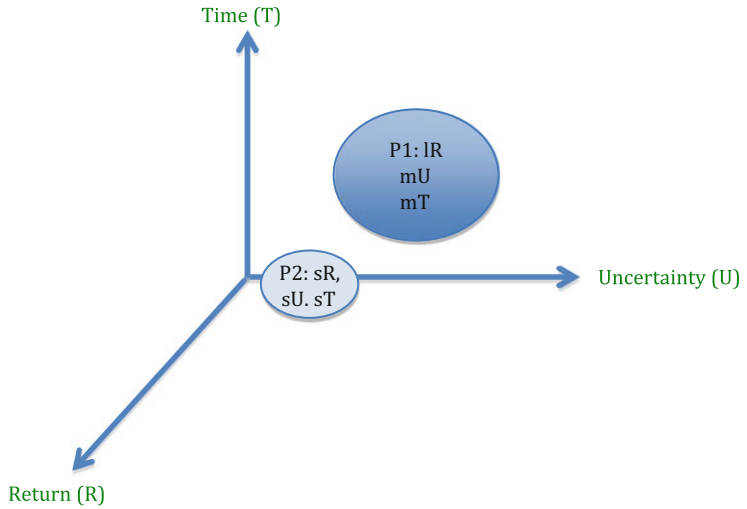

Fig. 1.2 Four key dimensions of innovation strategy. *s* small or short, *m* medium, *l* large or long. The size of the *oval* denotes the magnitude of the cost. P1 and P2 refer to Project 1 and Project 2

Even when one leaves out these two big chunks of the cost, the money needed to develop a drug is still substantial. It can easily cost $20–$50 million to conduct 1 year of clinical phase-III testing for one drug candidate. Although drug candidates target very different diseases, in general, there is actually relatively little variation in the costs of developing these drugs. This is because most costs are associated with steps that vary little across projects. According to PhRMA (Pharmaceutical Research and Manufacturers of America 2010), on average, 53.6 % of the innovation cost is spent on clinical trials that are dependent on the number of patients needed, another 4.7 % is spent on the approval process, and 14.4 % on phase IV (postlaunch market surveillance). The general process of discovery is also similar across a variety of therapeutic categories. As a result, the cost of developing a drug plays a constraining role in the innovation decision, thus limiting the number of new drug projects that a firm can support at a given time. However the cost of developing a drug plays less of a strategic role in innovation decisions compared to the other three factors: uncertainty, time, and return.

Uncertainty plays a critical role in a firm's innovation strategy. The probability of success is low across therapeutic categories, and there is a need for a firm to actively manage the success rate. The challenge is that the uncertainties associated with passing each stage of the innovation process (i.e., preclinical trial, clinical phase I, clinical phase II, clinical phase III, …) are different for different drug candidates. For example, central nervous system (CNS) drug candidates have a higher probability of failure in later stage clinical trials than other drug candidates. Furthermore, managers need to actively manage the probability of eventual success in two ways: by supporting correlated drug candidates (e.g., molecules with similar

structure or ones that target a similar signal pathway) and/or redundancy strategy where a firm funds two or more molecules treating the same disease (Ding and Jehoshua 2002); and/or by developing expertise in the same therapeutic category so learning can be more fruitful and uncertainty is reduced.

Uncertainty is closely associated with *return*: a firm needs to balance uncertainty with potential return. As mentioned above, each innovation (new drug) tends to create substantial value for the firm. A firm must select innovation projects that can potentially provide large-scale return (to at least make up for future lost income due to patent expiration of existing blockbuster drugs). Conditional upon this, the firm must also assess how much uncertainty it is willing to bear to target an even larger return. For example, many firms now settle for developing me-too drugs instead of aiming for first-in-class molecules. This is not necessarily a viable long-term strategy, and it creates a public opinion backlash. The flipside of this strategy is that the time between the launch of the first and the second drugs in a therapeutic class has shrunk from an average of 10.2 years in the 1970s to 1.2 years for drugs launched between 1990 and 2003 (Tufts CSDD). This creates additional pressure on the first-in-class innovator.

Finally, firms need to consider another moving part in their innovation strategy: *time*. The majority of the income of a pharmaceutical firm comes from drugs with patent protection, and this income will evaporate as soon as the protection ends. As a result, the revenue of a pharmaceutical firm undergoes large-scale discrete changes instead of even increase/decrease as in most other industries. To smooth out these kinks, it is critical for a firm to plan ahead so that new drugs can be launched at least in time to replace the expected loss in revenue due to patent expiration. Due to the long time horizon of development, which usually lasts 12 years, this balancing act is extremely challenging. In sum, a successful pharmaceutical firm must be able to balance return, uncertainty, and time, while constrained by a finite budget. This is not easy, especially given the constant pressure from financial analysts for firms to deliver results on a regular basis. This pressure has brought about more short-term rather than long-term optimization of innovation.

1.1.2 Marketing

Society sees pharmaceutical drugs as having "double personalities": as a conventional product that addresses certain consumer needs, and as something to which human beings have a fundamental right. As a conventional product, all rules of commerce should apply to it. However, as something human beings have a basic right to, many standard marketing practices must be modified. For example, nobody will complain if his or her neighbor owns a BMW sports car while he or she cannot afford one. However, if his or her neighbor is able to receive expensive but effective medicine for a disease, he or she will most likely demand that, if the need arises, he or she too should have access to the same medicine regardless of his or her financial status.

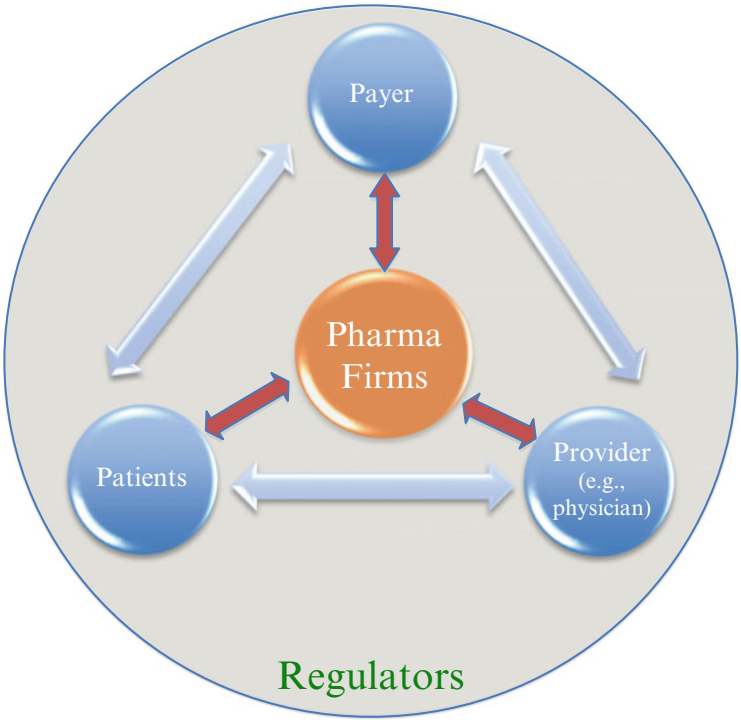

Fig. 1.3 Players and relationships in the pharmaceutical market

Pharmaceutical companies must take into account these two conflicting characteristics/attributes of pharmaceutical drugs as they extract maximum value from their innovation. This task requires careful management of the firm's relationship with three key players—patient, provider (e.g., physician), and payer—as well as the relationship among themselves, within an environment controlled by the regulators (Fig. 1.3).

Pharmaceutical drug purchase is a joint decision made by the user (patient) and gatekeeper (physician or other healthcare provider). In this relationship, the gatekeeper has the final decision-making power on what drug a patient should use. However, on the other hand, the patient is not completely powerless, although his or her power differs across therapeutic areas (Ding and Jehoshua 2008) and countries. In most countries, a patient can easily "fire" his or her gatekeeper by switching to another physician. A patient can also passively protest by either not getting the prescription filled or not using the drug according to the recommended schedule (noncompliance). This patient–gatekeeper relationship is evolving and has changed substantially over the last 10–20 years, largely due to the availability of information about the drug itself and about other patients' experience and knowledge. Such information is now available to any individual who is willing to spend half hour on the Internet

before seeing a physician. A firm must take into consideration the delicate relationship between the two parties (i.e., patient and gatekeeper) when formulating and executing its marketing strategies. Social networks have also enabled information exchange and learning among physicians (e.g., Sermo) and patients (e.g., PatientsLikeMe) in a way that was not possible in the past. Firms have to closely monitor and understand the impact of such physician and patient social networks in medical decision making.

To complicate matters further, the majority of the drugs are paid for by a third party, which exerts tremendous influence on firms, physicians, and patients. The payers demand health economic analysis of a new drug from pharmaceutical firms and determine, among other things, whether a drug will be included in a formulary and whether it should be used as first-line or as second-line therapy. The payers also put substantial pressure on physicians, and on pharmacists in some cases, regarding what kind of drugs they should prescribe, often steering them towards low cost and older drugs. Sometimes the physicians need to get prior authorization for using a particular drug, with appropriate justification. In some cases, physicians and pharmacies receive financial incentives from payers for prescribing more generics and preferred drugs. In addition, a third-party payer may induce patients to choose lower cost drugs by imposing different levels of copayments for drugs, with only a small fixed payment (deductible) if a patient uses generics. On top of all these, the payers also use their market power to demand drug discounts.

In the background of the dynamic relationship among the firms, patients, physicians, and payers, lie the vigilant regulators. Regulation takes many forms in this industry, including new drug approval, drug monitoring, manufacturing, promotion/advertising practices to physicians, and direct-to-consumer advertising (DTCA). In the more recent phenomenon of DTCA, firms can communicate their drugs to patients, but all advertisements are subject to the oversight of the FDA and must include a balanced presentation on both efficacy and side-effects as in the corresponding label approved by the US Food and Drug Administration (FDA). Outside of the USA, DTCA is only allowed in New Zealand, and to some extent, in Canada.

Therefore, firms strongly rely on promotion to physicians to market their drugs. The relationship between firms and physicians is also regulated, for example, in the USA, a firm cannot mention off-label use to physicians, while a physician is free to use the drug for whatever purpose he or she sees fit. In other countries, the number of detailing calls the firm can make to a doctor or the number of samples it distributes, may also be capped. Many other restrictions may apply. In almost all countries, governments play the role of both regulator and largest payer.

Drug price is also heavily regulated in various ways, such as ex-manufacturer price regulation (i.e., direct capping of prices by the government), cross-country reference pricing (i.e., restricting the price based on an international comparison of the prices of the drug in reference countries), or therapeutic reference pricing (i.e., restricting the price based on a comparison of drugs with similar therapeutic potential). Several governments (e.g., the UK, as discussed in Verniers et al. (2011)) also restrict the total profits a pharmaceutical firm can make. Even in the USA, the

price of a drug is indirectly regulated through the government's role as the largest payer (Medicare). For a review of the regulation of pharmaceutical markets around the world, see Stremersch and Lemmens (2009) and Verniers et al. (2011).

In sum, a successful pharmaceutical firm must implement a marketing plan that builds upon the complex patient–physician decision-making process and the multi-faceted role of a third-party payer, while at the same time adhering to the rules set by regulators.

1.2 Challenges to Firms in the Pharmaceutical Industry

In the last 2 decades, the pharmaceutical industry has faced numerous changes and finds itself in an increasingly challenging environment for sustaining past profits. We discuss several of these changes and the challenges they impose on firms.

1.2.1 The Number of New Treatments That Are Approved for Commercial Use Continues to Decrease Substantially

The chapter in this book by Petrova shows a consistent decline in the number of new drugs that received regulatory approval. In 2010, only 21 molecular entities were approved, a historical low (Jack 2011). Consequently, because new products typically generate a higher margin than mature products, the sales generated from relatively new drugs also substantially decreased, which resulted in a quite negative profit outlook for the industry. The following are some of the cited reasons for the decline in the approval of new drugs.

1. The industry does not invest enough in R&D. According to some, this is because of declining prices and thus declining returns on innovation. This reason is questionable, because statistics on R&D investments by firms show that those investments have consistently increased over time.
2. The regulator follows increasingly strict approval procedures that are partially triggered by an increasingly suspicious general public and heavily publicized withdrawals such as Vioxx. Events of the latter kind drive up the clinical testing costs for firms and suppress the success rate.
3. Many diseases have been satisfactorily addressed, which limits the space for big medical breakthroughs (even though the number of deaths from cardiovascular disease, cancer, or hard-to-treat diseases such as neurodegenerative or autoimmune diseases, is still large).
4. The industry has not yet developed the right competences to be successful in developing new treatments that are biological rather than chemical in nature.

The decline in the number of new molecules approved generates several main challenges for firms. How can firms optimize portfolio management to improve their risk-return ratio? How can firms use new innovation models, such as grassroots innovation programs or open innovation, to improve their innovation yield? What type of agreements with other firms (e.g., small biotech start-ups or university spin-offs) yield optimal outcomes? What can a firm do to overcome the negative consequences of a dry pipeline if R&D efforts fail? How can it move the innovation model from the blockbuster model to models with a higher likelihood of success, be it of more limited size, such as targeted therapies or orphan drugs? How can firms optimize launch success for the few approved drugs they are launching?

1.2.2 Competition of Generics That Branded Drugs Undergo Increases

The drop in the number of new drug approvals has led to increasingly mature product portfolios in most firms. As drug patents expire, firms increasingly face generic competition. Generics offer the same active ingredient as the originator drug, and typically with no more than 20 % deviation in efficacy but at much lower prices. To lower the pressure on the healthcare budget, governments and insurers have increased the pressure on the healthcare system to transition to a higher generic drug use instead of branded drug use. Various countries have implemented policies such as promoting or enforcing generic prescription by physicians, prescription budgets of doctors, promoting or enforcing generic substitution by pharmacists, and public tendering for preferred molecule supply have become increasingly popular as well. Often patients are more informed about the equivalence between generic and branded drugs, potentially making patients less brand-loyal and more price-sensitive. Given the business value in generic drugs, the number of firms that supply generic drugs has increased. This is true even among the conglomerates that also supply branded drugs, several of whom have generic divisions (e.g., Pfizer). Among an increasing number of generic firms, generic competition itself has intensified, putting even more pressure on branded drugs at the end of the life cycle.

The increased competition from generics has generated several challenges for pharmaceutical firms. Should a firm have its own generic division? If yes, to what extent should it focus on generics business vs. branded business? How can the two be made compatible? If patents expire, what are the firm's optimal patent expiration strategies? Can it reengineer the molecule for improved efficacy (e.g., new administration methods)? Can the firm develop a follow-on drug (e.g., a new molecule in the same molecule class)? Should it develop combination drugs with increased convenience or efficacy? How can it sustain or strengthen its brand to retain brand-loyal physicians and patients? How should it adjust its price? Should the firm price on par with generics or higher, and if higher, how much higher?

1.2.3 Price Pressure Increases Even for Drugs Under Patent Protection

Even for new drugs that still enjoy life years under patent protection, price pressure is increasing. The main reason for this is that payers—be it insurers or governments—are increasingly under pressure from ageing. Older patients typically bear higher costs than young patients because a great number of older patients suffer from chronic diseases (e.g., diabetes), neurodegenerative diseases (e.g., Alzheimer, Parkinson), rheumatic diseases or cancer. Thus, in developed countries where much of the population is ageing (such as in the USA and Europe), the payers in these countries are increasingly pressured to attempt to lower healthcare expenses. Drug costs are an ideal target for such efforts since saving on drug prices seems to hurt only large multinational pharmaceutical firms, which typically does not concern the public at large. Attempts to lower prices for drugs that are under patent protection take many forms.

Many countries have a system in which prices are regulated, i.e., the government first needs to approve the price that a pharmaceutical firm will charge before the latter is granted market access. Often governments examine the prices of the same drug in reference countries and determine that local prices cannot rise above those reference prices. Alternatively, governments may determine a therapeutic reference, for instance drugs that bring similar benefits, and demand that prices should be comparable to that of therapeutic equivalents. Drugs that according to payers demand too high a price may be "punished" by several methods: they may be put in a lower prescription tier, thus depressing sales volumes; they may be excluded from the reimbursement system; or they may even be denied market access altogether.

Price pressure has significantly complicated the task of pharmaceutical firms. The elaborate use of cross-country reference pricing systems has led to a very complicated optimization problem for firms: they need to decide which countries to enter first and at what price, and which countries they should possibly not enter so as not to spoil global pricing levels. Pricing models have shifted, so firms need to develop competences with very new pricing models. For instance, pay-for-performance models, in which firms only receive payment if certain health outcomes are achieved in the target population, are becoming increasingly popular. Tendering has also become more popular, even for branded molecules, if multiple options exist within a category.

1.2.4 The Pharmaceutical Industry Has Experienced a Serious Deterioration in its Corporate Image

The corporate image of the pharmaceutical industry has deteriorated. Global firms, such as those from the tobacco, finance, energy and pharmaceutical industries, are increasingly under societal pressure. In the case of pharmaceutical firms, the

populist belief is that these firms try to gain financial benefit from the misery of diseased people. Several shocks to its confidence have not helped the image of the industry. Think about withdrawals of drugs such as Vioxx, which displayed the unethical behavior of firms in their sales messaging. Also the tactics of firms when threatened by generics have been scrutinized by the public, especially the ethically questionable practices, such as "evergreening" (milking a patent life cycle by extending it through dubious "innovations"), cornering the supply of the active ingredient, bribing the generic company not to supply generics, and suing generic makers over dubious patents. Much of the pharmaceutical industry was investigated by the European Commission over such practices, and class action law suits have been filed (e.g., consider AstraZeneza's marketing practices in the PPI category, in which its two drugs, (Pri)Losec and Nexium, are now being challenged by both regulators and consumers).

The weaker corporate image of the pharmaceutical industry is in desperate need of repair. Rather than focusing on the short-term, the pharmaceutical industry needs to develop long-term policies to maintain long-term trust of the population. In the words of Singh and Jayanti later in this book, the industry needs to transition from a logic of conflict (with payer, patient, or healthcare provider) to a logic of cooperation, to align itself in a win–win cooperation with the entire healthcare value chain.

1.2.5 The Pharmaceutical Industry Needs to Rethink its Policies Towards Sales Representatives

Multiple changes challenge the common way of detailing for pharmaceutical firms. First, with decreased margins, less money is available to be spent on sales representatives. This seems to finally be a trigger for rethinking the arms race in detailing that has been going on between major pharmaceutical players. Second, more and more healthcare providers are turning their backs on pharmaceutical sales representatives for behaving unethically in the past. Sales representatives' influence on prescription behavior is less and less socially tolerated. With fewer product introductions, less news is informative enough to warrant time investment by the healthcare provider to listen to a sales representative. Third, technology has entered into the detailing visit. Sales teams use iPads to present their pitches to doctors, and the virtual detailing visit (i.e., a detailing call over an electronic connection) is making its entry as well. Moreover, an increasing number of doctors network online, increasing the need for information provision by manufacturers on such online platforms.

Many firms still struggle with estimating the return on investment (ROI) of sales calls and adjusting their sales allocation to such ROI estimates. This involves questions about the efficacy of virtual sales calls, about getting into doctor's practices when such entry is increasingly discouraged, how to make sure doctors get the required information, and how to make sure that the sales representatives comply with the firms' normative and ethical guidelines and messaging, especially, say, in developing markets.

1.2.6 The Pharmaceutical Industry Faces a Changing Media Landscape in a Heavily Regulated Environment

Digital and social media have strongly affected many industries: publishing, entertainment, and grocery retailing. They are also starting to have an increasingly dramatic effect on the pharmaceutical industry. Pharmaceutical firms are used to communicating directly with the patient under strict regulatory conditions (in the USA, New Zealand, and Canada) or to being prohibited from doing so (in the rest of the world). Today's global social media challenge this regulatory environment. Online and in social media, patients speak freely about their experiences with pharmaceutical treatments. Some early efforts by firms to get engaged in social media (e.g., think of Sanofi's VOICES program) have shown this engagement not to be trivial for pharmaceutical firms. Sanofi's attempt to delete and then preempt, on its online platform, the entries of a cancer patient, who was being treated with a Sanofi drug and who consequently experienced permanent baldness, has shocked public opinion.

At the same time, the context is so complicated that the FDA has been notoriously slow in releasing clear guidelines on how pharmaceutical firms should behave online. Consequently, there is continuous discussion online about pharmaceutical brands, while pharmaceutical firms are struggling with such questions as whether they should get online or not; how much resources they should pour into it; which platforms to use (Facebook, Patients Like Me) or to build one themselves; how communication should be handled on such platforms: whether to do it themselves or outsource to either an independent supplier or a subcontractor; what the goals are to begin with; whether they should only listen, or only speak, or both; if they speak, what will it be about; and, if and when they agree on clear goals, how they will measure if they are getting a good ROI. It is complicated for any firm to start with calculating ROI on Facebook investments, but it is even more complicated for pharmaceutical firms.

1.2.7 The Patient Has Turned into an Empowered Consumer

Consumers have become more vocal in general. Call it a general trend in society. Pharmaceutical firms cannot escape this trend. The consumer takes a more dominant role in the economy. Online medical diagnosis and information has enhanced a consumer's confidence to become more involved in treatment decisions, in some cases even to take control. The cartoon where a patient tells his doctor "Doctor, I diagnosed myself online, I am just here for a second opinion" is a well-known abstraction of the reality of today's medical practice. In areas such as oncology, increased involvement of patients is welcomed. For instance, after explaining the pros and cons of different treatment options, patients are often asked if they desire to make the final choice about which treatment to pursue. This can tilt to a complete consumerism of healthcare, where consumers shop around to obtain the prescriptions

they request from their doctors, and where patients stop treatment or choose their own drug regimen out of their own initiative. While welcomed by some, this increased role of consumerist patients may be a serious worry for doctors. For instance, consumerist patients, by not completely adhering to the prescribed therapy, endanger the efficacy of the treatment. This was already anecdotally illustrated in the consumerist behavior towards Prozac, with patients going on and off Prozac at will, often with limited medical guidance. Camacho et al. (2012) quantitatively documented that more consumerist patients often do not adhere to therapy. Keeping therapy adherence on track either by introducing reminder devices or by developing customer relations management (CRM) processes gets more attention among firms.

Moreover the centrality of the patient puts pressure on the typical way in which pharmaceutical firms market their drugs. Firms are used to the physician taking a prominent role, thus much of their marketing is aligned with the physician. In today's market, pharmaceutical firms need to become substantially more consumer-centric, and this poses a formidable challenge. Together with consumer empowerment comes increased influence of the pharmacist. An increasing collection of over-the-counter (OTC) medication in pharmacies makes the pharmacy more of a retailer, with similar factors of importance as in grocery retailing. Moreover the pressure towards generic prescription gives the pharmacist more power over which manufacturer's drugs get dispensed.

1.3 Overview of the Chapters

The book provides state-of-the-art reviews of various relevant themes written by experts in the field. These reviews cover the topics from different perspectives: analytical/empirical models, behavioral research, case studies, and more, making the materials accessible to a wide range of audiences. Given the rapid changes the pharmaceutical industry is experiencing, all chapters conclude with suggested areas for further research. The book is organized along the following three aspects: innovation and the product life cycle of pharmaceuticals, patient and physician behavior, and marketing of pharmaceuticals.

1.3.1 Innovation and the Product Life Cycle

The chapter by **Petrova** provides a comprehensive overview of the drug innovation process. The chapter reviews various mechanisms of intellectual property protection pertinent to the pharmaceutical industry. It addresses issues related to me-too and follow-on drugs, to the fundamental types of organizations that operate in the industry, as well as issues related to the modes of collaboration that have emerged in drug innovation, with a particular focus on alliances.

Ding, Dong, Eliashberg, and Gopalakrishnan provide definitions of portfolio management, review relevant facts and evidence about the pharmaceutical industry, and examine current portfolio management practices. They then probe deeper into specific managerial issues within portfolio management in the pharmaceutical industry.

Betz, Camacho, Gerards, and Stremersch provide a detailed conceptualization of grassroots, or bottom-up, innovation and show how it can be applied in the pharmaceutical industry. They anchor their conceptualization in self-determination theory. They describe principal drivers of motivation and success for employees in pharmaceutical companies to come up with and develop innovative ideas into new business lines. They share their experiences in developing *innospire*, a grassroots innovation program at Merck KGaA, Darmstadt, Germany.

Wuyts' chapter focuses on three important issues: competing perspectives on why firms benefit from portfolio diversity; how the differences among firms in their commitment of managerial resources to portfolio management and in their internal R&D strategies can help explain why some firms benefit more than others from portfolio diversity; and why technological developments, such as the rise of nanotechnology and institutional developments like healthcare reforms, change the very nature of collaboration and alliance portfolios in the pharmaceutical industry.

In their chapter, **Chan, Narasimhan, and Xie** address the innovation theme through an evaluation of the effectiveness and side-effects experienced by firms in the pharmaceutical industry as their innovative drug goes through clinical trials data. They argue that there are several important issues that cannot be addressed with clinical data alone and propose how researchers may benefit by supplementing such data with post-marketing prescription choice data.

Taking the perspective of the launch and diffusion decision chain, **Landsman, Verniers, and Stremersch** provide a review of both the sequence of decisions that managers must make, as well as the analytical tools pharmaceutical firms can use to improve their decision making. The rich set of decisions includes decisions regarding the specific methods for the assessment of a treatment's commercial potential, decisions aimed at optimally extracting the new treatment's potential, and decisions regarding the strategy that will be used to leverage the new treatment's potential across countries.

Kappe focuses on innovation strategies available for a drug that is already on the market and is approaching its patent expiration. This scenario is of interest to different parties: branded drugs/generic manufactures, physicians, patients, insurers, pharmacists, and the government. This chapter focuses on the consequences of patent expiry for branded manufacturers, and discusses the regulatory environment for prescription drugs, the determinants and impact of generic entry, and various life cycle extension strategies.

The innovation section is concluded by **Jain and Conley**'s chapter. It summarizes a broad list of patent extension and market exclusivity options and pricing of pharmaceuticals both pre- and post-expiry, analyzes how promotional activities and newer product branding actions such as advertising and product configuration impact the behavior of patients exposed to such innovations, and it closely examines two distinctly different pharmaceutical cases: the markets for gastro-esophageal reflux disease and neurological medicines.

1.3.2 Patient and Physician Behavior

How do consumers assess their own risk and that of others? Are their own risk estimates biased upwards or downwards, merely inaccurate or normative? How do biases in underestimating or overestimating risk affect consumers' behavior, and what are the implications of under- or overestimation of risk on pharmaceutical companies, medical establishments, the economy, and society in general? These represent the critical questions needed to gain understanding of patient behavior. These and more are addressed in the chapter by **Raghubir and Latimer**.

Patient adherence represents another important issue in the pharmaceutical industry. Consistent with the accepted definition of adherence as conformity to, or adoption of marketers' recommendations about medication acquisition (purchase) and correct usage, **Ilyuk, Irmak, Kramer, and Block** discuss factors that lead to poor adherence. These factors are categorized as: medication-related, patient-related, prescriber-related, pharmacy-related, and condition-related. Focusing on medication efficacy, they review different biases and heuristics that influence patients' perception of it.

Miron-Shatz, Doniger, and Hanoch provide a related and complementary review of factors affecting adherence to governmental warnings against the use of household products previously perceived to be safe. Their discussion starts by examining the psychological decision-making literature on such factors as trust of the source issuing the warning and safe experience with the risk-causing agent. They then go into the basic requirements of awareness and understanding of the message, review the marketing literature on message design, and discuss natural cognitive and emotional consumer biases that may reduce adherence and how these may be counteracted. They proceed with an evaluation of the specific case of the 2008 US Food and Drug Administration (FDA) warning against administration of over-the-counter cough and cold medication (OTC-CCM) to children under the age of 2 years (FDA 2008), and conclude with recommendations for optimizing the design and dissemination of similar warnings in light of the literature reviewed.

Arguing that preventive vaccines differ from therapeutic pharmaceuticals in a number of ways, **Angelmar and Morgon** suggest that consumers' and other party's behavior in this context are quite different, and hence they deserve special attention. They provide a review of the vaccine industry including its structure, entry barriers, and threats from substitutes. They then discuss the behavior of the parties involved (i.e., patients, physicians, and payers), and highlight the marketing implications.

A recent patient-related phenomenon is the emergence of the empowered patient, a topic **Camacho** addresses. He reviews key trends that precede patient empowerment such as modernization and self-expression, demographic and lifestyle changes, technological evolution, and regulatory changes. He then analyzes the consequences of the patient's new role for the patient–physician relationship and for pharmaceutical marketing. Parallel to new trends observed in patients' behavior, we also witness new trends in physicians' behavior.

An important one is the emergence of peer-to-peer networks, a theme addressed by **Bhatia**. The chapter provides an overview of the network structure and draws a distinction between physicians who prescribe high volume and those who are connected to many other physicians. It then reviews how physician social networks are built through social links, job and location links, and professional links. This leads to the emergence of opinion leaders who should be of great interest to pharmaceutical firms. The chapter concludes with the managerial implications involved in identifying and targeting the opinion leaders in the peer-to-peer network.

The chapter by **Shankar and Li** also examines recent trends that indicate how the proliferation of electronic communication through social media is reshaping the pharmaceutical industry. They note that both physicians and patients actively use online information and social networks. The emergence of social media poses several important questions for pharmaceutical firms, such as how to engage in social media within the regulatory framework; how to integrate social media into traditional marketing strategy; how and where to start a social media campaign; and what the ROIs are of social media efforts. The chapter provides a framework for analyzing the effects of social media on patients, physicians, and marketers. It offers actionable implications for pharmaceutical companies, and provides pointers to successfully develop and implement an integrated social media marketing strategy. This chapter provides an essential link to the next section.

1.3.3 Marketing of Pharmaceuticals

Pharmaceutical marketing strategies and their effectiveness is the main theme of this section. Pharmaceutical marketing strategies range from sampling to detailing, to journal adverting, to DTCA, and to various promotional efforts. These and more are covered in this section.

Starting with sampling as a promotional tool, **Dong, Li, and Xie** provide an overview of common practices in pharmaceutical sampling in the USA. They discuss various data sources that can be used for drug sampling research, and present a literature review on the effects of samples on pharmaceutical sales from both academic literature and empirical studies in the industry.

Sridhar, Mantrala, and Albers study the following questions: How effective is personal selling or detailing to physicians? What is a generalizable quantitative estimate of detailing effectiveness? How does detailing effectiveness vary by product life cycle stage and geographic region? They provide evidence based on a meta-analysis of 373 econometric estimates of pharmaceutical detailing elasticities that appeared in 48 papers. The authors suggest that optimal detailing spending-to-sales ratios today should (1) be in the region of 6–7 % over pharmaceutical product life cycles, (2) involve judicious shifts from higher to lower detailing emphasis as products age, and (3) be larger in Europe than in the USA.

Fischer examines various marketing spending models: physician-oriented, patient-oriented, and ones that are oriented towards other stakeholders. This chapter

summarizes insights obtained from managerial surveys and econometric models, analyzes demand for pharmaceuticals, and then concludes with recommendations for setting optimal marketing budgets.

With a similar focus on multiple strategic marketing variables, **Wieringa, Osinga, Ruiz-Conde, Leeflang, and Stern** address the following questions: How do marketing variables affect the diffusion pattern of newly introduced pharmaceutical innovations? How do dynamics influence pharmaceutical marketing effectiveness? Focusing on aggregate demand for prescription drugs, they present an overview of papers that investigate the effectiveness of pharmaceutical promotion, and discuss the significance and relevance of pharmaceutical promotional effects, distinguishing between effects on product category level demand and effects on brand level demand. They review the applications and findings of studies that investigate how marketing efforts affect the diffusion of new pharmaceutical innovations, and provide an overview of studies that examine how dynamics impact the effectiveness of pharmaceutical promotion.

Liu and Gupta review the history of DTCA, claiming that expenditure on prescription drugs in the USA have been growing explosively. They survey next various methodologies designed to assess the effectiveness of such expenditures, considering patients, physicians, and governments as audience. They conclude with a summary of findings related to the short- and long-term elasticities of these marketing efforts—suggesting that these are in the lower half of the distribution of advertising elasticities.

The direct-to-consumer advertising and direct-to-physician advertising are also the main topics addressed by **Vakratsas and Kolsarici**. They provide a review of studies addressing marketing-mix efforts directed towards patients and physicians and discuss the relative effects of these marketing activities. Based on the evidence they survey, they conclude that the elasticities of DTCA are smaller than those of direct-to-physician, rendering the physician as the primary decision-making agent in the prescription process.

Desiraju and Tran's chapter deals with spillovers and related externalities in the industry. A spillover may arise, for example, in the Canadian market since much of the Canadian population lives relatively close to the US border and has access to the US television broadcasts. Surveying the extant literature on spillover effects, they address in particular questions such as: Does DTCA in the USA influence sales in Canada due to spillover from a variation in government regulation? In case it does, what is the magnitude of return from such spillover?

The section concludes with **Singh and Jayanti** who adopt an institutional theory perspective and examine the dominant logic that underlies pharmaceutical marketing strategies, contrasting it with the organizing logic of the value chain partners. Two key questions are discussed in this chapter: What specific marketing strategies do pharmaceutical companies use to engage medical practitioners, and how do these strategies relate to particular tactics? And, under what conditions, and why, do pharmaceutical marketing strategies amplify (or diminish) the aversive (approving) response from its value chain partners? The analysis suggests that the pharmaceutical value chain reveals dynamics that are consistent with several aspects of

institutional theory: (1) system conflict due to coexistence of competing logics, (2) institutional failure in resolving conflict of logics that are amplified by pharmaceutical marketing practices, and (3) continued escalation of conflicted logics that invite regulatory intervention that constrains and restricts marketing efforts.

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Chapter 2
Innovation in the Pharmaceutical Industry: The Process of Drug Discovery and Development

Elina Petrova

Abstract Continuous innovation is one of the pharmaceutical industry's most defining characteristics. New medications can be crucial for maintaining the quality of human life, and may even affect its duration. The sales potential is staggering: the global pharmaceutical market is expected to reach $1.1 trillion by 2015. The pressure to succeed is tremendous. Yet, pharmaceutical innovation is hardly an orderly, predictable process. It follows a technology-push model dependent on a meandering path of scientific breakthroughs with uneven timing and hard to foresee outcomes. Technological competency, decades of rigorous research, and profound understanding of unmet customer needs, while necessary, may prove insufficient for market success as the critical decision for commercialization remains outside the firm.

Drug innovation as a business process requires savvy strategic, organizational, and managerial decisions. It is already enjoying intensive research coverage, giving rise to abundant but relatively dispersed knowledge of the mechanisms driving drug discovery and development. In this chapter, we present a comprehensive overview of the process of drug innovation from a business and academic perspective. We discuss the evolving organizational forms and models for collaboration, summarize significant empirical regularities, and highlight differences in market positions related to firms' strategic orientation, innovation emphasis, attitudes to risk, and specialized resources. As a guide to future research, critical drivers and modes for drug innovation are systematized in a unifying framework of characteristics and process decisions, and multiple areas in need of further scrutiny, analysis, and optimization are suggested. Because of its rich potential and high significance, research on drug innovation seems poised to gain increasing momentum in the years to come.

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2.1 Introduction

The pharmaceutical industry is essentially defined by innovation. Research on the forefront of science, the creation of new knowledge bases, the invention of new medicines, and the improvement of existing drugs constitute the fuel that propels the firms in this industry. The occasional triumph of creating a novel therapy in an area with no prior treatments counts among the pharmaceutical industry's most defining hallmarks. This is the only industry whose output can make a difference by affecting the very molecules we are made of.

Modern era medications can influence the quality and the duration of human life in ways that were never possible before. As recently reported by the Pharmaceutical Research and Manufacturers of America (PhRMA), over the last 25 years prescription drugs have successfully improved the wellbeing of arthritis and Alzheimer's sufferers around the world, and have significantly reduced deaths from heart disease, several types of cancer, and HIV/AIDS. The death rate for cardiovascular disease has fallen by a dramatic 28 % between 1997 and 2007, while the average life expectancy for cancer patients has increased by 3 years since 1980. Most of these gains are attributable to new medicines. In the USA, since the approval of antiretroviral treatments in 1995, the death rate from HIV/AIDS has dropped by more than 75 %. As predicted by IMS Health, innovative treatment options for stroke prevention, arrhythmia, melanoma, multiple sclerosis, breast cancer, prostate cancer, and hepatitis C are also imminent.

Successful and continuous new drug introductions constitute the source of sustainable competitive advantage for the firms in this industry. The sales potential is gigantic: the global pharmaceutical market was estimated at $837 billion in 2009 and was expected to reach $1.1 trillion by 2015. As reported by the IMS Institute for Healthcare Informatics (www.imshealth.com), in the USA alone, a total of $307 billion dollars, or $898 per capita, was spent on ethical drugs in 2010, representing 2.1 % of the GDP. The USA is poised to remain the single largest pharmaceutical market, with four billion dispensed prescriptions and a total revenue of $380 billion expected by 2015. Some estimates indicate that 46 % of the people living in the USA take at least one prescription drug.

Not only is the USA the largest market for ethical drugs, but it is also recognized as the world leader in drug discovery and development, as well as a global hub for scientific and medical research. The pharmaceutical sector is the second largest US export sector, just behind the aerospace industry. It is also a major employer, estimated to provide jobs to 655,000 people. In total, directly and indirectly, the sector supports over 3.1 million jobs nationwide. It is also one of the few industries that are projected to keep adding jobs in the years to come despite the recent slowdown in the economy (PhRMA and the Bureau of Labor Statistics).

Although innovation is the lifeblood of any industry, the discovery and development of new medicines is accompanied by a host of unique challenges, ethical implications, and social responsibilities. One will be hard pressed to think of another industry where meticulous research, rigorous testing, and stringent product standards (or the lack thereof) can have such a profound impact on human wellbeing.

The fundamental role of the pharmaceutical industry in maintaining and enhancing human life is further reflected in the magnitude of its R&D activity. By some accounts, pharmaceutical R&D holds an impressive 19 % share of *all* business spending on R&D worldwide—an impressive financial commitment for a single industry. The USA is accountable for the lion's share of pharmaceutical innovation as it finances about 36 % of the global expenses in pharmaceutical R&D.

In 2010, the US-based pharmaceutical firms had a total budget of about $67 billion designated for research. Another $31 billion was earmarked by the National Institutes of Health (NIH) to fund research in public sector institutions (primarily government labs and universities).[1] The total pharmaceutical R&D spending in the USA has been steadily rising at an average rate of about 12 % a year, not adjusting for inflation (Cockburn 2007).

PhRMA members allocate about 20 % of their domestic sales to R&D, which makes the pharmaceutical industry the most research-intensive one in the USA. The industry's R&D spending per employee is estimated at $105,430, which is 40 % higher than the second highest research-intensive industry (communications equipment), and 60 % higher than other technology-driven industries such as semiconductors, computers, and electronics.

PhRMA companies currently boast rich pipelines of drug candidates. In the USA there are nearly 3,000 different medicines in various stages of product development, representing a whopping 45 % of all drugs in development worldwide. Of those 3,000 new drugs in the pipeline of the US-based firms, an assortment of anticancer drugs holds the lead with 861 medicines in development, followed by 334 for respiratory diseases, 300 for rare diseases, 299 for cardiovascular disorders, 252 for mental and behavioral disorders, 235 for diabetes, 100 for HIV/AIDS, 98 for Alzheimer's disease and dementia, 74 for arthritis, and 25 for Parkinson's disease.[2]

Despite the ubiquitous presence of medications in our lives, to many of us laypersons, the actual drug innovation process seems arcane. As customers or patients, we tend to focus on the end outcomes, just like we do with other high-tech, increasingly complex and specialized fields of innovation. And yet, as human beings, we are often fascinated by the possibilities the latest advances in life sciences (e.g., genomics, molecular biology, neuroscience, biotechnology) open to us. Drug innovation converts these new opportunities into drugs that can directly impact our physiology. This realization prompts a closer examination of the methods, steps, and processes associated with the genesis of ethical drugs.

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[1]The National Institutes of Health (NIH), part of the U.S. Department of Health and Human Services, is the nation's leading medical research agency. It is also the largest source of funding for medical research in the world. More than 80 % of the NIH's funding is awarded through about 50,000 competitive grants to more than 325,000 researchers at over 3,000 universities, medical schools, and other research institutions across the USA (*Source*: NIH website, www.nih.gov).

[2]It is hardly surprising that the innovation pipeline of the US pharmaceutical firms is primarily composed of drugs corresponding to the therapeutic categories with the largest sales in the USA: oncologics ($22.3 billion), respiratory agents ($19.3 billion), lipid regulators ($18.8 billion), antidiabetes ($16.9 billion), and antipsychotics ($16.1 billion). *Sources*: IMS Institute for Healthcare Informatics, Adis R&D Insight Database, PhRMA Pharmaceutical Industry Profile 2011.

Surely, some aspects of the drug innovation process are well-known and widely discussed. The industry is perhaps less of an enigma these days due to the unfaltering attention given it in the media. But creating efficacious drugs is also a multibillion dollar business, and there is a need to integrate the abundant yet rather compartmentalized extant knowledge about drug innovation. Such synthesis can enable us to view the process systematically and discuss it in more depth, richer detail, and with a clear emphasis on its business aspects.

It is well known that drug creation finds itself on the leading edge of the latest scientific and technological breakthroughs. Revolutionary discoveries in various disciplines are often employed to assist in the selection among myriads of naturally occurring compounds, in the design of new ones, or in the transformation of existing ones. The economic aspects related to the colossal amounts of effort and dedication germane to drug innovation are no less deserving of attention.

Drug innovation emerges at the confluence of state-of-the-art discoveries in the life sciences, aided by cutting-edge advancements in other fields such as engineering, informatics, and optimization. Thriving in the wake of the latest achievements in these disciplines, it often brings them together to intersect and interact in a way geared to ultimately improve human health and extend human life. In the process of finding the most effective structures and the most efficient strategies, novel decision opportunities and challenges arise, and new organizational forms and arrangements emerge to address them.

Inventing novel drugs is ultimately a business process in need of strict fiscal discipline and effective strategic, organizational, and managerial decisions. Various aspects of pharmaceutical innovation have been the object of intense scrutiny in diverse fields such as economics, business strategy, and marketing. Still, the obtained findings and inferences have remained somewhat insular, limited to the originating discipline despite their broader applicability and significance. There are many areas that warrant further analysis and optimization. This is why a comprehensive overview of the business processes, strategies, and practices related to pharmaceutical innovation seems necessary and timely. A compilation of this kind can be a useful reference source for various future streams and areas of research.

Hence, the intention with this chapter is to present recent findings related to the organization and the outcomes of the innovation process in the pharmaceutical industry, and concisely yet systematically review them from a business perspective. We hope that a more integrated and informative picture of the currently dispersed fragments of knowledge will arise in this process. Such an outlook will be of interest to business students, fellow researchers, and pharmaceutical executives alike, as well as to anybody with a keen curiosity about the exciting domain of drug innovation.

We start by presenting some facts and figures related to the economics of drug innovation, and briefly describe the evolution of drug discovery from a historical perspective. We proceed with a comprehensive overview of the modern process of drug innovation. To highlight the nature and the sources of its inherent complexity, we provide succinct but hopefully informative descriptions of some of the latest technologies involved. Next, we discuss the mechanisms of intellectual property protection pertinent to the industry, and outline the distinction between patents and market exclusivity.

Then we move on to discuss me-too and follow-on drugs. The foray of generic drugs, the market conditions most conducive to their entry, and the drastic market changes triggered by such entry are detailed next. This discussion is followed by a review of theoretical arguments and empirical findings related to economies of scale and scope in the pharmaceutical industry. We then proceed by presenting the fundamental types of organizations that operate in this industry and discuss the modes of collaboration that have emerged in drug innovation, with a particular focus on alliances. Next, we present a summary of recent findings and insights from the academic literature. We touch upon the precursors to the current industry structure in the USA, the synergistic and preemptive benefits of investing in own R&D, the implications of early and late timing for market entry, the dynamics of market adoption in the case of pent-up demand, and the key factors that affect the market diffusion of a new drug. Then we outline the most recent trends related to pharmaceutical innovation. We conclude the chapter by suggesting directions for future research.

2.2 An Overview of Innovation in the Pharmaceutical Industry

The nature of the pharmaceutical industry makes it a veritable standout compared to others. Profound understanding of market needs is necessary but woefully insufficient for a firm to succeed. Even when finding effective medications is vitally important for the wellbeing of millions of patients, decades of painstaking research may still fail to produce a satisfactory new product.

No other industry is expected to affect how long people can live or how fast they can recover from an illness. No other industry is focused on relieving the physical pain and other discomforts everyone gets to experience in life. Consequently, no other industry is under such tremendous pressures to innovate. Still, no other industry can burn through billions of dollars and man-hours only to end up empty-handed, with not much to show for its vast expenditure, dedication, and effort.

Unlike many other market-driven industries, the pharmaceutical industry follows the so-called technology-push model. Life sciences are at the center of its endeavors to alter or reverse the processes in the human body. The onus of creating value for patients is squarely dependent on a meandering path of scientific advances and technological breakthroughs with largely unpredictable results and uneven timing.

From a business perspective, the positive momentum created by successful innovation can have dramatic, long-lasting implications for the pharmaceutical firm. The impact of a new drug launch often goes beyond the hefty profits associated with patent protection and first-mover advantage. Incremental, follow-up improvements involving greater efficacy, fewer or less severe side effects, a more convenient dosage regimen, changes in the application method, modified formulations, or new indications can significantly expand the market potential for the firm by making the drug appropriate for new patients (e.g., patients who can benefit from different dosage protocols). Notably, more than half of the new brands of drugs introduced in

2010 were not novel chemical entities or biopharmaceuticals, but improved versions and altered formulations. Incremental drug modifications of this type can ensure improved treatment, may induce better patient compliance (by interfering less with the patients' routines or lifestyle), or enable a more convenient drug delivery (e.g., weekly instead of daily regimen). Importantly, newly released improved versions of a drug can ensure cash-flow continuity, bring in additional streams of revenue for the firm, and increase shareholders' returns.

Besides, the options for making incremental drug modifications or the chance to manufacture bioequivalent low-cost generics present coveted new opportunities to scores of eager industry rivals seeking to enter a new market. Thus, in addition to the creation of new product value affecting millions of patients, there is also the immense social and economic benefit from the thousands of new job positions created to handle the research, manufacturing, and marketing of novel drugs in multiple formulations and variations. This realization highlights the role of drug innovation as a powerful engine of economic progress.

But the creation of new drugs is hardly an orderly, predictable process. There are enormous difficulties associated with the making of a safe and efficacious drug. Despite unprecedented recent advances in science and technology, serendipity and chance still play a role in the discovery and synthesis of effective compounds. There is practically no way of ensuring that years upon years of intense R&D efforts and huge costs will pay off handsomely in the end as the rates of success in drug discovery remain steadily low. Importantly, the performance uncertainty is amplified by the presence of stringent regulations and intense scrutiny over the entire development process. The critical decision to go to market is essentially outside the control of the firm. The market approval for a new drug ultimately rests with the Food and Drug Administration (FDA), the government agency entrusted to exercise regulatory and control functions over the pharmaceutical industry. These idiosyncrasies combine to make the development and the life cycle of drugs different from the innovation process in any other technology-intensive industry.

2.2.1 The Economics of Pharmaceutical Innovation in Facts and Figures

Creating new drugs is a complex, laborious, lengthy, and costly process with very uncertain outcomes. For instance, in the USA, the total number of new drugs approved between 2000 and 2010 was only 333, which seems surprisingly low given the colossal effort and cost expended by large pharmaceutical companies and numerous biotech firms alike. To explore the economics of drug innovation more closely and to size up the gravity of the issue, we will focus on the USA as the leading powerhouse in pharmaceutical research worldwide.[3]

[3] Some estimates indicate that 64 % of all research on new drugs approved in the last 10 years was done in the USA, making it the most relevant target of scrutiny.

The odds of creating a marketable drug are minuscule: only 1 in every 5,000–10,000 potential compounds investigated by the US-based pharmaceutical companies is granted FDA approval. Even if the initial screening and testing have shown favorable indications, the chances of a promising drug candidate to make it through the sequential stages of the drug development process remain around one in five. About 30 % of the failures are associated with unacceptable toxicity. Another 30 % stem from lack of efficacy, while the remaining failures can be related to issues with the drug's rate of action, the duration of its effects, or problems with the absorption, distribution, metabolism, or excretion of the drug by the human body.

On average, obtaining FDA approval and the rights to market a drug take about 15 years, with the majority of that time dedicated to clinical trials. In 2005, the average cost of a new drug successfully introduced in the USA was estimated to be $1.3 billion—a hefty 62 % increase over the last known estimate of $803 million in 2000. The opportunity cost of capital, related to the time the drug is winding its way through the discovery and development process, accounts for about 50 % of the total cost. Hence, the estimated out-of-pocket R&D expenditure for a new drug is approximately half of the amount mentioned above (DiMasi et al. 2003). Also, it must be noted that these frequently cited cost estimates are the fully capitalized cost per *approved drug*, which includes the cost of investigating compounds that fail to make the cut.

2.2.2 A Brief Historical Perspective on Drug Innovation

Before WWII, the link between the pharmaceutical industry and the life sciences was relatively tenuous. Most new drugs were derived from natural sources (herbs) or were based on existing compounds, mostly of organic origin. Little formal testing was done to ensure their safety or efficacy. The war instigated an extraordinary need for antibiotics worldwide. Fueled by surging market demands, pharmaceutical firms invested in unprecedented R&D programs that changed forever the process of drug discovery and development. In addition to acquiring technical and managerial experience along with the organizational capabilities to produce massive drug volumes, pharmaceutical firms emerged from the war with the clear realization how highly profitable drug development could be. Large-scale investments in R&D followed suit.

After the war, the industry faced a vast set of diseases and disorders with no known cures. There was little detailed knowledge of the biological underpinnings of many ailments. The pharmaceutical companies had to resort to *random screening*, trying tens of thousands of diverse natural or chemically derived compounds in test tube experiments and on laboratory animals in search for potential therapeutic effects. This process resulted in the compilation of enormous libraries of chemical compounds with known structure and studied properties. Random screening was generally inefficient—serendipity played a major role in finding a promising substance as the various action mechanisms (the biochemical and molecular pathways responsible for the therapeutic effects of drugs) were not well understood at the time.

Through the mid-1970s, significant advances in physiology, pharmacology, enzymology, and molecular biology, stemming mostly from publicly funded research, had propelled the understanding of the biochemical and molecular mechanisms of many diseases and the action pathways of existing drugs (Cockburn and Henderson 2001a). Yet, as most of the drugs at that time were derived from nature or through organic synthesis and fermentation, they were not suitable for the production of complex macromolecules such as proteins, which consist of genetically encoded long chains of amino acids. In the late 1970s to early 1980s, the advent of biotechnology and the technological breakthroughs made possible by the more versatile tools of genetic engineering marked a second watershed moment for the industry.[4]

2.2.3 The Genesis of a Drug: From Inception to Market

2.2.3.1 Creating a Drug by Discovery or Design

Human physiology is vastly complex, and there is a lot that is not known about the onset, the triggers, or the pathways of many diseases and disorders. For these reasons, interdisciplinary research spanning various scientific domains has become essential for modern drug discovery. Input from scientists competent in a broad range of disciplines is required in the process, e.g., skills and expertise in molecular biology, physiology, biochemistry, analytic and medicinal chemistry, crystallography, pharmacology, and even more distant areas such as information science and robotics. Advanced interpretative and integrative capabilities are critical for success. Collaboration transcending organizational, departmental, or therapeutic category boundaries has grown increasingly important for drug discovery (Henderson and Cockburn 1994). Thus, the combination of interdisciplinary competencies and openness to knowledge generated outside the firm can become the source of enduring competitive advantage for pharmaceutical firms.

Importantly, creating new drugs in the twenty-first century is no longer a series of accidental, serendipitous breakthroughs. Instead, a long and systematic process requiring steadfast commitment, diligence, and meticulous work has taken the place of the previous haphazard experimentation. The majority of modern new drugs have completed an involved and strictly regulated process to reach the market. We discuss the phases of this process next.

[4] Two key events have come to be recognized as critical for the revolutionary union of genetics with biotechnology. One was the 1953 discovery of the structure of DNA by James D. Watson and Francis Crick, and the other was the 1973 discovery by Stanley N. Cohen and Herbert Boyer of a recombinant DNA (rDNA) technique by which a section of DNA from one organism (e.g., bacterium) could be transferred into the DNA of another, so that the latter could be induced to produce a specific protein. Popularly referred to as genetic engineering, this technique has come to define the foundations of modern biotechnology.

Prediscovery: *understanding the disease and choosing a valid target molecule*. In contrast to the old trial-and-error routines, nowadays the process starts with a clear understanding of the disease on a molecular level. Based on studies showing associations between biological mutations and disease states, pharmaceutical researchers formulate hypotheses about the action mechanisms involved—they study how genes have changed, how these changes affect the proteins encoded by the genes, how those proteins interact with each other in living cells, how the affected cells change the specific tissue they are in, and how all these processes combine to affect the patient.

Once scientists develop a good understanding of the underlying causes and pathways of a disease, a *biological target* for a potential new medicine is chosen. A biological target is most often a biomolecule (e.g., a gene or a protein), which is involved in that particular disease and can be modulated by a drug. For example, the focus in understanding autoimmune diseases such as cancer and HIV/AIDS is on discovering the proteins that affect the human immune system. The latest advances in *genetics*, *genomics*, and *proteomics* (studies of human genes and proteins) are employed in the process. Complicated experiments in living cells as well as tests on experimental animals are conducted to demonstrate that a particular target is relevant to the studied disease.

Drug discovery: *finding promising leads for a drug candidate*. Having developed a good understanding of the disease and its mechanism, scientists start looking for a drug. They search for a *lead compound* (an organic or other drug molecule) that may act on the target to alter the disease course, for example by inhibiting or stimulating the functions of the target biomolecule. If successful, the lead compound can ultimately become a new medicine.

Scientists turn to *nature* (plants, animals, or microorganisms) to find interesting compounds for fighting the disease. Microbes or bacteria, cells, tissues, and substances naturally produced by living organisms, or existing biological molecules can be used as a starting point, and then modified. An increasingly promising and flexible set of possibilities is furnished by the advancements in *biotechnology*, whereby scientists can genetically engineer living systems to produce disease-fighting biological molecules.[5] Rich drug source options are also provided by *combinatorial chemistry*, or the rapid actual or virtual synthesis of a large number of different but structurally related molecules. It enables the quick generation of new molecules to augment the chemical diversity of known molecule libraries. The method of *high-throughput screening* is the most common way for screening the already existing vast libraries to find those compounds that can modify the chosen target without affecting any off-target molecules. Advances in biorobotics, bioinformatics, and

[5]If the medical drugs are created by biological processes, rather than being chemically synthesized, they are referred to as *biopharmaceuticals or biologics*. Recombinant DNA technology (*rDNA*), whereby scientists are bringing together genetic material from multiple sources to create sequences that may not otherwise be found in biological organisms (e.g., joining plant DNA with bacterial DNA), is often the technology used to derive them. Pioneered by Genentech, this is the main method for obtaining insulin nowadays, having replaced the animal sources previously used in the process. The technology has found many other applications—e.g., in HIV diagnosis, for the creation of growth hormones or blood-clotting proteins.

increased computational power allow researchers to test hundreds of thousands of compounds against the target to identify those that might have good potential.

Of late, thanks to advances in chemistry and pharmacology, scientists can abandon the generally inefficient method of systematic screening of existing molecules for a novel approach known as *rational drug design*. Applying analytical methods to figure out the genesis of the disease from its onset to chronicity, they come up with prototypes of a drug molecule designed from scratch. The structure of the target biomolecule can be identified with the assistance of X-ray crystallography or nuclear magnetic resonance. This information can then be used in computer modeling and simulation to predict the characteristics of potential drug candidates so that they can not only exhibit affinity and selectivity to the target biomolecule but also affect its biological and physical properties in the desired way. Designed drug molecules can be synthesized by researchers once they understand the molecular characteristics necessary for binding to the biological target. The designed drug molecules are then tested on the target biomolecule.

Next, scientists must learn how the generated compounds are absorbed into the bloodstream, if they are distributed to the proper site of action in the body, whether they can be metabolized efficiently and effectively, if they are being successfully excreted from the body, and whether they appear to be toxic in any way. Lead compounds that survive the initial testing can be optimized further or altered to make them safer and more effective. By changing the structure of a compound, scientists can change its properties to make it less likely to interact with other processes and mechanisms in the body, thus reducing the potential side effects. Hundreds of different variants of the initial leads are made and tested. Teams of biologists and chemists work closely together: the biologists test the effects of these variants on biological systems, while the chemists use that information to make additional alterations that are then retested by the biologists. After many iterations, the final compound becomes a *drug candidate*.

Even at this early stage, researchers attend to practical issues, considering the drug formulation (e.g., its right concentration as well as the inactive ingredients that will hold it together and make it dissolve at the desired rate), the administration route (e.g., oral application, injection, inhaler), even the details regarding the transition to large-scale manufacturing. Techniques for making the drug in the lab may not translate easily to large volume production. Still, before clinical trials can start, sufficient quantities of the drug will be needed.

Preclinical testing. With one or more optimized compounds in hand, researchers turn their attention to extensive preclinical testing. Before any human subjects can be involved in the trials, a safe starting dose must be established. Scientists carry out in vitro and in vivo tests to check the safety profile, the toxicology and the efficacy of the studied compounds.[6] Starting with approximately 5,000–10,000 lead compounds, scientists winnow them down to between 1 and 5 molecules (candidate drugs), which then enter a series of clinical trials.

[6]In vitro tests are experiments conducted in the lab, usually carried out in test tubes and beakers. In vivo studies are those in living cell cultures and experimental animals, conducted to gauge the effects of the drug candidate on the metabolism and the systems of intact living organisms.

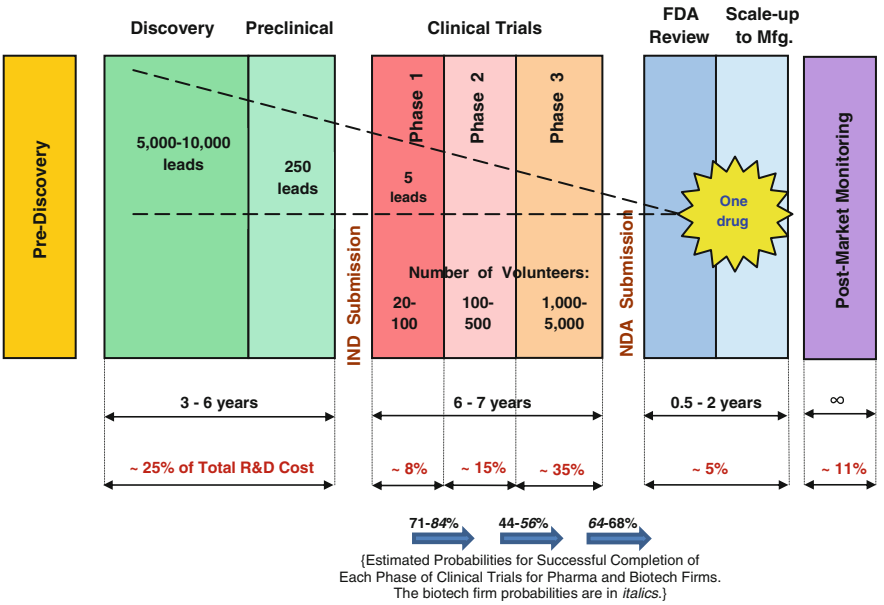

Fig. 2.1 The research and development process for new drugs (compiled from data in PhRMA Pharmaceutical Industry Profile 2011; DiMasi and Grabowski 2007)

2.2.3.2 Drug Development and Clinical Trials

Upon completion of drug discovery, pharmaceutical firms prepare for the next critical stage in the innovation process—drug development through clinical trials on humans. Before clinical trials can begin, the researchers must file an *Investigational New Drug* (*IND*) application with the FDA. As part of the submission, the drug sponsor must provide clinical evidence in support of claims about the primary drug indication (the targeted medical condition).[7]

Drug development is structured as a linear sequence of several phases (Fig. 2.1). The transition to each next phase is conditional on a favorable outcome from the one preceding it. Each phase of the clinical trials could end up with a decision to proceed, suspend, or terminate the testing. The firm may decide to halt or withdraw its application on financial or commercial grounds, or choose to stop the trials in the light of adverse new information. The FDA can mandate that the trials be terminated at any time if problems arise. In addition, in some cases a study may be stopped because the

[7]The IND application outlines the results of the preclinical work, the candidate drug's chemical structure and how it is thought to work in the body, a listing of the expected side effects, and information about the manufacturing process. The IND also contains a detailed test plan specifying how, where, and by whom the clinical studies will be performed.

candidate drug is performing so well that it would be unethical to withhold it from patients receiving a placebo or an inferior drug for comparison purposes.

Clinical trials Phase 1: *initial human testing on healthy volunteers to establish safety*. In Phase 1 trials the candidate drug is tested in people for the first time. These studies are usually conducted with about 20–100 healthy volunteers. The main goal of Phase 1 trials is to discover if the drug is safe in humans and to determine the range of safe dosage. Researchers look at the pharmacokinetics of a drug: how it is being absorbed, metabolized, and eliminated from the body. They also study the drug's pharmacodynamics: whether it appears to produce the desired effects and if any prominent side effects may occur. These closely monitored trials are designed to help researchers determine if the drug is safe to use with actual patients.

Clinical trials Phase 2: *testing in a small group of patients to demonstrate efficacy*. In Phase 2 trials researchers evaluate the candidate drug's effectiveness in about 100–500 patients who have the investigated disease or disorder. Possible short-term side effects and risks associated with the drug are noted. Researchers strive to understand if the drug is working by the expected action mechanism and whether it improves the condition in question. The optimal dose strength and the appropriate application regimen are being established. If the drug continues to show promise, it can proceed to the much larger Phase 3 trials.

Clinical trials Phase 3: *testing in a large group of patients to establish safety and efficacy*. In Phase 3 trials researchers study the drug candidate in a large number of patients (about 1,000–5,000) to generate statistically significant data about safety, efficacy, rare side effects, and determine the ultimate tradeoffs between benefits and risks. This phase of the research is crucial for determining whether the drug will be both effective and safe. For establishing drug efficacy, comparative testing against placebo options or against other standard treatments can be performed. Phase 3 trials are both the costliest and the longest trials (Fig. 2.1). Hundreds of sites around the USA and throughout the world participate in these trials to get a large and diverse group of patients. Coordination and monitoring of this activity can get rather challenging.

Upon the completion of clinical trials, if the analysis demonstrates that the experimental drug is both safe and effective, the company files a *New Drug Application* (*NDA*) or *Biologic License Application* (*BLA*) with the FDA, requesting approval to market the drug. The NDA/BLA includes all of the information from the previous years of work, as well as the proposals for manufacturing and labeling of the new medicine, and can run 100,000 pages or more. The FDA studies the data to determine whether the benefits outweigh the risks, what information must be included in the drug label, whether the proposed manufacturing process is adequate, and if there is any need for certain prescription criteria or special physician training.

Scaling-up for manufacturing. The transition from producing small drug quantities for testing purposes to large-scale manufacturing by the ton is not a trivial task: new manufacturing facilities may have to be built, equipment will need to be installed and processes must be calibrated. Meticulous planning and coordination are necessary to ensure smooth operations.

Post-market monitoring and Phase 4 trials. Research on a new medicine continues even after the FDA approval is obtained and the drug has been launched. As a much larger number of patients start taking the drug, companies must continue to monitor it carefully for newly found adverse effects. Periodic reports to the FDA are submitted on a quarterly basis for the first 3 years, and annually thereafter.

Sometimes, the FDA requires additional studies on the already approved drug in what is known as Phase 4 trials. These trials can be set up to evaluate the long-term safety of the new medicine. The company itself may also choose to conduct such studies to assess the drug's potential benefits in other disease areas or for more specific patient populations (e.g., children, the elderly), leading to extended uses and indications.[8]

The distinct phases of the drug innovation process with their characteristics are presented in Fig. 2.1.

2.2.4 Protecting Intellectual Property: Patents and Market Exclusivity

Pharmaceutical organizations can file for a patent on a new drug molecule they have synthesized. In addition, they can obtain market exclusivity for the drug. Although both patents and market exclusivity confer protection from competition for a specific molecule, they are conceptually and functionally distinct from one another. A *patent* protects the intellectual property of the firm from the time of its invention and is unrelated to the drug's eligibility for commercialization. In contrast, *market exclusivity* adds more years past the FDA approval for market launch and is meant to hold off the entry of generic drugs. Patents and market exclusivity may or may not run concurrently and may or may not encompass the same claims. While some drugs have concurrent patent and exclusivity protection, others may have either type, or none whatsoever.

Patents are typically issued on novel pharmacological compounds quite early in the drug development process. They cover the active compound in a specific formulation and for specific indications. Firms can file several patents associated with a single drug, the first of which typically protects the key compound (the core of the drug as a specific new biomolecule or a new chemical entity [NCE]), while the subsequent ones can be related to different indications or new formulations. In the USA, patents can be granted by the Patent and Trademark Office (PTO) anytime along the development lifeline of a drug. Regardless of where the firm is in its clinical trials or with the FDA approval process, patents expire 20 years from the date of filing.

[8]This was the case with Vioxx®, the anti-inflammatory drug developed by Merck, which was voluntarily taken off the market in 2004 because of findings about elevated risks for a heart attack or stroke. The unexpected risks were unveiled during a follow-up study designed to test the efficacy of its active ingredient for the prevention of colorectal cancer (Cockburn 2007).

In contrast, market exclusivity pertains to the marketing rights granted by the FDA upon its approval of the drug, and is conferred on the actual product, inclusive of its quality, indications, and dosage. The rationale for having FDA-mandated exclusivity that is separate from the patent protection mechanism stems from the independence between the patent status and the timing of the FDA approval. As the development process leading to an FDA approval is long and uncertain, patents can expire before the drug approval, can be issued after the drug approval, or anywhere in between. Still, firms need assurance that their products will not be reproduced by competitors soon after the market launch, which can happen if the patents have expired by the time FDA approval is granted. Market exclusivity is the tool that provides such assurance. Hence, although market exclusivity does not directly extend patent life, it prevents competitors from entering the market with the exact same formulation, quality level, indications, and dosage.

Essentially, both patent protection and market exclusivity are designed to place the firm into what is a temporary monopoly situation so that it can recoup the hefty costs incurred in drug discovery and development. In the USA, firms that manage to get patent protection and exclusivity rights stacked up in the most favorable way can obtain a window of protection lasting more than 23 years. The duration of market exclusivity for new drugs can vary with the type of the drug. For an NCE, the exclusivity horizon is 5 years. If the drug is redesigned for children, additional 6–12 months of pediatric exclusivity can be obtained upon the submission of specific pediatric studies. Orphan drugs (drugs for rare disorders or for diseases that affect a small percentage of the population) get 7 years of exclusivity. For them, the extended exclusivity horizon is intended to compensate for the small market. Original biopharmaceuticals can obtain 12 years of exclusive market rights pursuant to the Patient Protection and Affordable Care Act of 2010.

If the original drug is reformulated for a different indication or for another dosage regimen, or if a modified version can demonstrate clinical superiority (e.g., greater safety, tolerability, or convenience of administration), an additional 3 years of exclusivity may be granted. However, this extension is contingent on the approval of a new application by the FDA, which requires reports on new clinical trials conducted to investigate the new formulation, indication, or dosage.

The clock on market exclusivity starts ticking at the time of obtaining FDA approval. In the USA, 74 % of all new drug sales tend to occur in the 5-year exclusivity window following drug approval, with additional 15 % of sales realized in the 3 years following the loss of exclusivity when cheaper generic versions enter the market (Higgins and Rodriguez 2006).

2.2.5 Late Entrants: Me-too and Follow-on Drugs

Despite patent protection and exclusivity, many pioneer, or first-in-class drugs do not remain the only “game in town” for too long. Even before generic alternatives enter the market, other branded drugs, also known as *me-too* and *follow-on* drugs,

can make an incursion, essentially curtailing the uncontested reign of the pioneer drug over the market.

Me-too drugs. Typically, me-too drugs are minor variations of the original drug as they employ the same or similar action mechanisms, or have a related (although not identical) chemical structure. Compared to the pioneer drug, a me-too brand is a market follower, a late entrant offering a therapeutic solution that is very close to that of the pioneer drug. These drugs either replicate or provide a minor improvement over the breakthrough products in their class. Typically, they are priced at levels close to, or slightly lower than the price of the pioneer drug (reports place them in the range of 14 % below the price of the pioneer drug).

In reality, the vast majority of me-too drugs are not the product of brazen, deliberate imitation. Most of them have been in clinical development prior to the approval of the pioneer drug (DiMasi and Paquette 2004). By providing numerous viable leads, biomedical sciences create new opportunities for drug development. It stands to reason that different avenues can be simultaneously pursued by multiple firms.

The pharmaceutical industry is attractive to entrepreneurs because of its open access to fundamental knowledge, rapid information dissemination, opportunities for specialization, and connectedness to scientific networks. With the industry's shift away from heuristics and random screening, and owing to the capabilities offered by targeted rational drug design, the discovery process has become more systematic. As a result, lots of new ventures, drawn by the alluring rewards and undaunted by the inherent risks, choose to enter. Inevitably, they engage in a race with a slew of competitors who are already working on compounds targeting an essentially finite set of publicly known diseases. As rivals get to work in parallel on similar targets, often applying the same fundamental knowledge sourced from open science, the solutions they come up with may not be all that different. Inevitably, when one of them is the first to obtain market approval, the successful rival products are going to fall in the me-too category as their market entry will be subsequent to that of the pioneer drug.

Vigorous efforts to win the innovation race are the norm as the first drug to reach the market will not only induce a significant reputation boost for the firm, but, in the absence of other alternatives, will be poised to dominate the market. For late entrants that are not well differentiated from the pioneer drug, this is no longer the case. While desperately needing to recoup their huge R&D costs, they can be left with a difficult choice: switch patients away from the pioneer drug, uncover new niches to tap into, or resort to an overall market expansion. To be lucrative, me-too brands need sufficient differentiation (actual or perceived) from existing alternatives in the market. If their market launch is at a price lower than that of the pioneer drug, price competition will ensue. Barring that, there is little reason why a patient happy with their treatment would want to switch to a me-too brand if it offers no extra therapeutic value. Moreover, prescription inertia may persist if physicians fail to perceive differential value in the me-too product, or are reluctant to interfere with an already successful therapy. Thus, marketing to physicians and direct to consumer advertising (DTC) tend to become the main battleground for share of mind and share of market for the me-too brands.

Me-too brands have been criticized primarily on the grounds of offering little or no additional advantages relative to the pioneer drug. However, clinical responses to different drugs in the same class can vary significantly by individual patient. Traditionally, physicians have adopted a trial-and-error process for finding the drug that works well for each patient. The availability of extra therapeutic options is not only clinically advantageous in case of adverse side effects induced by the pioneer drug, but is also economically and socially beneficial.

To the pioneer drug, the impending entry of me-too drugs is a threat that diminishes the incentives for costly breakthrough innovation. Despite the regulatory protection conferred upon FDA approval, the market dominance of the pioneer drug can be curtailed by the entry of closely positioned, yet differently formulated me-too alternatives. Due to relatively minor differences in formulation or action, me-too drugs can circumvent the mandated exclusivity that deters the generics, and can place the pioneer drug under intense competitive pressures much sooner, diluting its sales and eroding its market share.

Recent studies show that the effective period of marketing exclusivity enjoyed by the pioneer drug in a specific class has declined dramatically—from a median of 10.2 years in the 1970s to a mere 1.2 years in the late 1990s—due to the market entry of me-too alternatives (DiMasi and Paquette 2004). Insufficient value differentiation by the me-too brands is perhaps the worst case scenario: it can undermine the intent of patent protection and market exclusivity, and may effectively split the market without offering additional therapeutic benefits or lower price to patients. In this case, the vast resources firms have spent on R&D may never be recouped as the market proceeds are divided among multiple firms. Patients are not generally better off either except for those intolerant to the pioneer drug, as they will have extra options.[9]

Follow-on drugs. In contrast to me-too drugs (the product of parallel development but belated launch, the timing of which can be beyond the firms' control), the inception of follow-on drugs is rather deliberate and their launch is timed to occur after the pioneer drug. Even drugs that have gained FDA approval may have clinical shortcomings that are just not serious enough to terminate the project, but can nevertheless be improved upon by introducing minor alterations to the chemical structure of the breakthrough drug. Such incremental improvements are called follow-on drugs, and they constitute the majority of new drug introductions.

Developing breakthrough drugs that are safe and efficacious is very costly while the outcomes are unpredictable. In this case, another firm might see a modestly lucrative option in the incremental improvement of an existing drug. There is assurance that comes from exploiting an effective, tried-and-tested method of therapy. Besides, even the residual returns from a very large market can be rather substantial.

Overturning the conventional first-mover advantage, an improved follow-on drug may even surpass the pioneer drug through enhanced effectiveness, greater

[9]For at least one therapeutic category (antibiotics), there is definite value in the presence of more drug diversity per se. It is well known that bacteria mutate and can become resistant to the most common existing drugs, necessitating a wide variety of medication choices.

convenience, or weaker side effects, as done by Zocor®, Lipitor®, Symbicort®, and Xyzal® in their respective markets (Stremersch and van Dyck 2009). Still, the size of the market is essential as evidenced by the fact that late-market entry is less common for orphan drugs. The markets for orphan drugs are typically quite small and cannot support multiple treatments of a generally similar nature.

In some cases the opportunities for incremental changes (e.g., altered formulations, new combinations, different dosage, or novel administration routes) are well-known to the manufacturer of the breakthrough drug. If there are no compelling reasons to delay the launch, the firm can press on with the market release while simultaneously undertaking the development of improved follow-on versions to be launched soon thereafter.

It has been suggested that these two strategies—breakthrough invention with relatively short-lived first-mover advantages, and late entry with differentiated or incremental innovations—can be equally effective when examined over a 10-year horizon from their respective market introductions. Over time, breakthrough drug innovations are known to undergo drastic changes in market share—they tend to start with a systematic above-average growth, may even create a new market that they can effectively dominate for a while, but will experience a steep decline not too long after their release as other alternatives emerge. In contrast, the sales of their follow-on counterparts can be more stable overall and may quickly reach their long-term market position (Bottazzi et al. 2001). In Sect. 2.3.6.3, we outline additional findings from recent academic research on the benefits accruable to first and late market entrants.

If me-too drugs are sufficiently well-differentiated, and if follow-on drugs present incremental innovations, they can cumulatively raise the standard of patient care in the category, yield substantive treatment benefits, and enhance the value to patients.[10] The presence of multiple drugs in a category may not only address the increasing price sensitivity in the market, but can enable greater choice and thus, foster intense rivalry. The availability of alternatives can also provide leverage to health insurance companies to extract higher rebates from the drug manufacturers.

To branded drug manufacturers, though, a considerable downside of operating in a therapeutic category populated with me-too drugs is that collectively, they all become more vulnerable to each other's fate: the loss of patent protection or market exclusivity by one member in the category can have a ripple effect on all competitors if their brands are close substitutes in terms of indications, applications, side effects, and dosage. These dynamics are discussed in more detail in Sect. 2.2.7.

[10]There is an ongoing argument about raising the standards for late entrants so that a demonstration of performance superiority, or at least, non-inferiority compared to existing therapies is demanded before obtaining market approval (Angell 2004; Hollis 2004). However, such changes might considerably complicate and prolong the development process, and are likely to be fervently opposed by the industry. Essentially, adopting them will place the innovation race contenders in a position to chase after a moving target. The front-runner will be the only exception as it is competing against a placebo, or in some cases, against the conventional treatment.

2.2.6 *Watch Out: Here Come the Generics!*

Patent expiration or the end of the exclusivity period (whichever comes last) is the dreaded moment for every pioneer brand. Although in practice market exclusivity can extend past the loss of a patent, for brevity purposes hereafter we refer to the loss of all regulatory protection collectively as patent loss.

When the market opens up to generic entrants, aggressive price competition ensues and the original brand quickly loses market share. It is worth noting that by then, the brand might have been competing with me-too or follow-on drugs for some time. However, the competition with branded alternatives is likely to be more quality-based than price-centered. If marketing efforts emphasizing differentiation have been effective in expanding the market, the loss of market share for the pioneer brand might have been relatively limited. But when the drug patent expires, exact generic clones appear promptly at prices that can be as much as 50 % lower than those of the original brand (Griliches and Cockburn 1994).

Generally, the average price of the first generics to enter the market is about 25 % lower than that of the original brand. Over time and with increases in generic entry, generic drug prices stabilize at levels close to the long-term marginal cost of production and distribution, which is about 20 % of the original brand's price. For example, in 2006 the average price of a brand name prescription in the USA was $111, whereas the average price for a generic prescription was $32 (Kanavos et al. 2008). Given that two-thirds of the global pharmaceutical market, currently valued at about $1 trillion, consists of molecules that are already subject to generic competition or whose patents have already expired (Kanavos et al. 2008), generic drugs offer an option for significant savings and cost-containment. Yet, generics represent a formidable threat to incumbent brands and their entry introduces a major turbulence in the markets they enter.

The selection of new markets for entry by generic drug manufacturers is driven primarily by economic factors and considerations. Empirical findings demonstrate that markets of large revenue potential, markets with a greater proportion of hospital sales relative to pharmacy sales, markets defined by chronic conditions, markets offering high profit margins to incumbents, and treatment forms or therapeutic areas with which the generic drug manufacturer has prior experience constitute the most attractive conditions for entry by generics (Morton 1999, 2000; Hudson 2000; Magazzini et al. 2004). Therefore, product/market characteristics conducive to greater price elasticity of demand, in conjunction with provisions associated with functional efficiency (scale and scope effects, experience, concentration of effort, business sustainability) have a preeminent role in the market entry strategies of generic drug manufacturers.

Brand-name manufacturers typically eschew price competition with the generic drugs. The price competition is left to the generics, which, due to insufficient differentiation, tend to experience a strong downward price pressure over time. By contrast, the price of the original brand remains higher and may even rise in nominal terms after the generic entry. This counterintuitive move is justified by the strategic

decision to focus on its most loyal segment and harvest the market by maintaining premium pricing (Grabowski and Vernon 1992). However, the average market price for the *molecule* with the lost patent will decrease over time as the lower-priced generic alternatives achieve significant gains in market share.

Generic drugs are required to have the same active ingredients, strength, safety, quality, route of administration, and dosage form (e.g., capsule, tablet, liquid) as the brand name product, but may or may not contain the same inactive ingredients as the original brand (e.g., binders, coating, fillers), and must differ in appearance (most often, by shape or color). As the company that makes the original drug has already proved during extensive clinical trials that the drug formula is both safe and effective, the FDA approval process may not require the same rounds of clinical trials from the generic candidates, but will nevertheless demand evidence of sufficient *bioequivalence*.

The complex biomolecular and chemical processes involved with the action of a drug suggest that often, demonstrating identical active ingredients and concentrations may not be sufficient for a generic alternative to be approved by the FDA. With the more common small-molecule drugs, an exactly identical generic drug can be reliably produced and marketed, and minor differences in inactive ingredients may be largely inconsequential. But this is not the case with biopharmaceuticals (macromolecule drugs produced with the complex tools of biotechnology). Even a slightly different manufacturing process may result in large variations in the effects of biopharmaceuticals. The generic drug manufacturer may not have the same cell bank or compound library as the brand name manufacturer. Nearly undetectable differences in impurities and/or breakdown products have been known to incur serious health complications. This is why the generics must show that they are, within acceptable limits, bioequivalent to the original brand.

A bioequivalence test is a study to determine whether the administration of the same dosage of the generic brand will result in the same release pattern, i.e., whether, over time, it will produce the same levels of concentration in the bloodstream as the original brand. Although acceptable deviations are not disclosed by the FDA, many experts seem to believe that the generic drug must fall within an 80–125 % range of bioequivalence to the original brand.[11] Besides, all manufacturing, packaging, and testing sites for the generic drugs are held to the same quality standards as those of the original drug.

Often, generic drug manufacturers can reverse-engineer the original brand, or reproduce it by getting access to its patent documentation that discloses the active ingredients. If generic drug manufacturers choose to press on with filing for approval

[11] Although such a range of variation seems perfectly acceptable for many treatments and conditions, there are situations where severe adverse effects can occur if the drug concentrations exceed or fall below those ruled as safe and efficacious—for instance, when a precise calibration of a process is necessary (e.g., in the treatment of seizures, for regulating blood pressure, blood clotting and blood thinning, heart rhythm, thyroid activity). FDA will find it necessary to apply much stricter standards in these cases, which can explain its reluctance to publicly acknowledge the often-cited 80–125 % bioequivalence range.

from the FDA before the expiry of the exclusivity period for the original drug, they would have to carry out *all* requisite clinical trials. For obvious economic, practical, and ethical reasons, generic entrants are often unlikely to attempt to reproduce the entire set of test data. The costs associated with replicating the rigorous clinical trials seem prohibitively dissipative and the wasted time would only extend the monopolistic reign of the original drug.

In 1984 new legislation enabled the extension of the original NDA process to all generic drugs, effectively allowing generic drug manufacturers to gain marketing approval by relying on the safety and efficacy data from the original drug's NDA, but only after the expiration of the 5-year exclusivity period and any further extensions granted by the FDA. Thus, the mechanism of exclusive rights bestowed on the original drug prevents generic drug manufacturers from relying on its clinical data, or denies them the so-called right of reference for the duration of the exclusivity period, effectively deterring their entry.

If generic drug manufacturers can get access to the results of the original brand's clinical trials, all they would need to do is demonstrate that the generic alternative is released in a similar way in the human body. In that case, the testing of the generic drug is performed on a sample of healthy volunteers, which is far less costly than conducting the full cycle of clinical trials. The results are then compared to those obtained in the original brand's Phase 1 trials. For the generics, this approach represents a shortcut to market that is sanctioned by the FDA as it demonstrates the criteria for safety and efficacy are met. Formally, the generic drug manufacturer submits an Abbreviated New Drug Application (ANDA). When it is approved, the FDA adds the new alternative to its Approved Drug Products list (also known as the Orange Book), and annotates the list to show the equivalence between the original brand and the approved generic. The *first* generic drug that obtains FDA approval may be granted 6 months of market exclusivity.

2.2.7 Market Changes Following Generic Entry

The FDA reports that 70 % of all filled prescriptions are presently filled with generic drugs. However, the overall cost of dispensed generic drugs is only about 20 % of the total drug spending in the USA (Kanavos et al. 2008). The cumulative annual savings from generic drugs bought instead of their original branded counterparts are estimated to be in the range of $8–10 billion in the USA alone. These facts suggest that generic entry triggers dramatic shifts in the competitive landscape of a therapeutic class.

2.2.7.1 Changes in the Within-Molecule Competitive Dynamics

Upon patent expiration and in the presence of generic alternatives that replicate its formulation on a molecular level, the original brand starts losing market share relatively fast. Brand name recognition and the secured loyalty of patients or physicians

remain its only sources of leverage. In the USA, drug formularies (lists of drugs that are covered by the health insurance companies) would only include the cheapest bioequivalent drug, which is typically a generic. The difference to the original brand's price is not reimbursed by insurance companies and has to be paid out-of-pocket by patients who want to retain their original treatment. Although the vast price differential causes the original brand to lose much of its market share, it may still retain a decent stream of revenue from prescriptions to patients who perceive its quality as superior. On occasion, physicians can refuse to allow substitutions to generic drugs for fear that switching medication may interfere with their patients' treatment, or apprehension that the cheaper alternatives may contain inactive ingredients that can cause allergies or other unwanted side effects.

It is precisely because of their bioequivalence to the original drug that, when finally given access to the market, generic drugs have a limited set of marketing tools to differentiate themselves. The lack of unique identity can prevent a generic brand from vertical differentiation based on quality, as the ANDA process has proven it equally effective and safe, but not superior to the original brand. This results in predominantly horizontal product differentiation. Parity in quality, however, seems to be questioned by some patients and physicians, and these qualms give rise to the segment that remains loyal to the original brand.

The most prominent characteristic of a generic brand is its low price relative to the original brand.

Offering a huge price advantage relative to the much more expensive branded drug is not problematic for the generics as they don't need to recoup the significant R&D cost associated with the discovery and the development of the original molecule, and can get by on a fairly limited marketing budget. Besides, generic drugs can take a ride on the coattails of the existing market awareness for the pioneer drug they replicate, and often set out to exploit its brand recognition. Some generics openly reference the original brand on their product labels, trying to gain from favorable price comparisons and direct associations with an already familiar brand name.

Yet, overreliance on low price in a fairly competitive market can trigger a price war that can quickly annihilate the profits for the generic drug manufacturers. Occasionally, to remain viable, generic drug manufacturers turn to offering preferential arrangements and better terms to distributors (Kanavos et al. 2008). Branding their products in an effort to enhance recognition and build credibility can be an alternative strategy. *Branded generics* are prescription products that are either novel dosage forms of off-patent products, or a molecule copy of an off-patent product with a trade name. In either case, branded generics are produced by a manufacturer that is neither the originator nor is licensed by the originator of the molecule. By dispensing with the anonymity often associated with such products, generic drug manufacturers can create recognition and differentiation through a perception of better quality, which can also translate into higher prices.

In some countries, the original drug manufacturer may resort to a multi-branding strategy and introduce what is essentially a fighting brand by licensing its own

subsidiary or an independent third party to sell a generic drug, sometimes known as a *pseudo-generic* or *authorized generic*, under the original patent. Sometimes the pseudo-generic drug is still manufactured by the originator firm, but is marketed under a different brand name. The introduction of pseudo-generics is usually a pre-emptive strategy originator firms may undertake pending the invasion of true generics (Hollis 2002, 2003). The intention is to ward off the significant loss of market share upon patent expiry and to retain greater market control by being the first firm to offer a generic option. However, the practice of introducing pseudo-generics is sanctioned differently across countries. As national regulators may find it objectionable enough to challenge it, it has not become routinely used yet.

As the differentiation value of generics is associated with their low price, the first generic entrant in a market seems poised to capture a considerable part of the price-sensitive segment and can essentially lock it in, ensuring long-lasting market domination. Late generic entrants would have to overcome pharmacy inertia and patient switching costs to displace the first generic entrant. Therefore, if a pseudo-generic is the first generic drug to enter a market previously dominated by the originator firm, the firm can retain more of its market power, although its sales revenue will inevitably plummet. Hollis (2002) points out that in Canada, where the practice of originator firms offering pseudo-generics is legal, it may cost about $1 million to introduce the first generic drug in the market. Still, the benefits are certainly worthwhile as the first generic can reach a sustainable market share advantage of 20–35 % relative to late generic entrants (Hollis 2002).

2.2.7.2 Changes in the Between-Molecule Competitive Dynamics

The incursion of generic drugs in the wake of a major patent loss will almost certainly affect the sales of the other branded, non-bioequivalent drugs in that class, even if they are still under patent protection. *Price-sensitive* physicians may increase the prescription incidences of generic drugs to the detriment of most branded drugs in a therapeutic class, regardless of their patent status. Moreover, the branded drug that has lost its patent will often scale back on its detailing efforts, enabling the drug representatives of rival non-bioequivalent brands to more easily switch *detailing-sensitive* physicians to their own brands. Gonzalez et al. (2008) find empirical evidence that with generic entry, the ensuing within-molecule price competition and the reduced marketing support of the firm losing its patent can also affect the between-molecule, non-bioequivalent competition in the same class. The overall effect on the sales of patent-protected non-bioequivalent drugs in that class will depend on: (a) their own marketing response in the wake of the patent loss; (b) the size of the price-sensitive and the size of the detailing-sensitive physician segments; and (c) the already established patient loyalties to the brand that is under attack because of patent loss.

In summary, the competitive landscape will get irreversibly altered when a major pioneer brand loses its patent protection, giving rise to interesting dynamics within the affected therapeutic class. In addition to the within-molecule rivalry instigated

by the bevy of generic drugs, the between-molecule competition can also intensify, fostered by changes in the marketing efforts of rival non-bioequivalent brands. Over time, as incumbent firms or new entrants release novel and improved branded alternatives in the same class, physicians and patients will gradually move away from the older active molecules and the associated branded or generic drugs. Thus, the market share of an old molecule (regardless of its branding) will gradually decline over time at the expense of new active molecules launched in the same class.

2.3 Business Models in Drug Discovery and Development

2.3.1 Scale and Scope Effects in Innovation

The lengthy, costly, unpredictable, and research-intensive process of drug innovation calls for organizational settings that can help streamline operations, defray part of the costs, and enhance process efficiency. Two concepts from economics are often invoked to address such issues.

Economies of scale refer to reductions in unit cost as the size of the firm's operations and the usage level of inputs increase. In contrast, *economies of scope* arise when, due to diversification in the product portfolio of the firm and in the presence of synergies across processes and activities, the same set of outcomes can be attained more *efficiently*, i.e., with less resources such as time, effort, or expenditure.

Economies of scale in drug discovery. Pharmaceutical companies typically organize their R&D efforts by therapeutic category based on the key systems in the body (e.g., respiratory, cardiovascular, digestive, central nervous system), then by research program (disease area), and ultimately, by specific project. Large research efforts tend to become less costly per program (and consequently, by project) in the presence of economies of scale from a large portfolio of research programs. In this case, the enormous R&D cost of drug discovery can be spread over a greater number of related research programs and projects.

Large pharmaceutical firms often invest in 10–15 distinct research programs run simultaneously. Several programs in the same therapeutic category can tap into the same pool of knowledge about the pathways related to particular biotargets or molecular processes. The new findings can be applicable across multiple programs. The more intensive use of the firm's research talent and resources, the shared lab facilities and expertise, along with the enhanced rates of equipment utilization and reduced downtime can ensure reduction in the marginal cost of R&D. In turn, the declining marginal R&D cost of the firm makes the undertaking of risky new projects more affordable because of lower incremental costs.

Long-term market presence and cumulative experience in a therapeutic category can bring about strong learning and reputation effects. Researchers have found that firms focusing on drug discoveries in therapeutic categories in which they already have expertise (e.g., Merck with cardiovascular and cholesterol problems, Eli Lilly

& Co. with psychiatric disorders, or GlaxoSmithKline with infectious diseases) are more effective than the relative novices in the category at converting R&D efforts into approved drugs (Chandy et al. 2006).

Scale effects can accumulate over time. Specifically, the firm's cumulative technological experience in a therapeutic category has been associated with increases in the first year sales of a new drug from that category (Nerkar and Roberts 2004). It remains to be examined whether: (a) technological experience confers market advantages due to measurable improvements in drug quality, safety, or efficacy; (b) the effects are reputation-based and largely perceptual (and if so, if it is the physicians'-, the pharmacists'-, or the patients' impressions that are of greater consequence); or (c) the positive impact stems from largely intangible firm assets, e.g., tacit knowledge about the category, special expertise with the core technologies, effective professional contacts and network leverage, or greater familiarity with the market gained during the firm's previous launches in these categories. As this is an area of immense significance to drug manufacturers, more research disentangling the possible determinants of an experience-based sales boost for a new drug will be rather welcome.

Economies of scope in drug discovery. Competent deployment of integrative knowledge spanning different therapeutic categories may give rise to a richer set of novel ideas. It can also foster ingenious approaches and problem solutions. Internal spillovers of new know-how may galvanize the process of drug discovery by leveraging the inimitable asset of tacit knowledge that is proprietary to the firm.

Substantial economies of scope can ensue if the same amount of R&D in one therapeutic class produces valuable findings with favorable implications for *another* therapeutic class or category. Such positive crossover effects can emerge when knowledge acquired in the course of studying one disease can propel the research done in another program. Cross-fertilization between therapeutic categories can also occur—e.g., research programs focused on cardiovascular issues have brought about therapies related to the central nervous system (Henderson and Cockburn 1996). Internal spillovers of know-how will depend, however, on the presence of sufficient breadth of knowledge at the firm. Such proficiency will facilitate the recognition of diverse opportunities for asset redeployment stemming from the new discoveries.

Developing the foresight to identify therapeutic potential outside of the focal research area can be of immense value to the firm. First, drug candidates can be repositioned and projects can be redirected instead of terminated.[12] Second, even if a project fails or gets terminated, the accumulated specific knowledge will not simply vanish. Such knowledge remains within the firm and can be internalized or assimilated in subsequent work, potentially aiding other innovation projects. Competencies, experience, and insights developed during failed projects can be as important as those

[12]Pfizer discovered the key compound in what was to become the blockbuster hit Viagra® during Phase 1 of clinical trials for two totally different indications—high blood pressure and ischemic heart disease. When its efficacy for erectile dysfunction became apparent, Pfizer was quick to change research directions and made Viagra® one of the most successful drugs in history.

associated with successful drug outcomes. Besides, it is no small feat if the pursuit of unproductive research trajectories can be detected early and avoided in the future.

Mitigating the uncertainties associated with the success or failure of any specific investigational project is another advantage of research efforts that are broad in scope. With sufficient project diversification, the individual project risks get attenuated. As this may lower the overall credit risk associated with the firm, it can improve its access to capital.

Abundant and varied research experiences can contribute to effective learning, and may strengthen the capacity of the firm to adopt external know-how. For example, experience with diverse projects can foster more discerning capabilities for evaluating the applicability of emerging technologies, and may ease the process of integrating those technologies within the firm's own technological stock.

A firm with a fairly diverse portfolio of research programs is also in a position to build an extensive compound library, which in itself becomes a valuable proprietary asset of a certain market value. Large libraries can assist in generating the leads in drug discovery and, thanks to high-throughput screening, have become much easier to work with. Meanwhile, smaller firms with no extensive libraries of their own may need access to the information accumulated in existing libraries. In fact, large pharmaceutical firms have started to trade access to their chemical libraries in exchange for access to new technologies, highlighting the growing significance of a more open market for information and technology in the pharmaceutical industry (Thomke and Kuemmerle 2002).

Yet, there can be a significant downside to excessive diversification in drug discovery. For example, research has shown that the simultaneous pursuit of too many project ideas can exert a negative impact on the probability of converting them into successfully launched drugs (Chandy et al. 2006). Also, with too many leads in discovery, the suggested economies of scope can be squandered due to heightened coordination and monitoring costs. Therefore, lest they spread their resources too thin, firms might be better off focusing on a *moderate* number of promising ideas.

Economies of scale in drug development. Economies of scale in drug development can arise from expertise that is easily transferable across different therapeutic categories because of its more fundamental nature (e.g., knowledge in biostatistics, experience with organizing large-scale clinical trials, or with obtaining regulatory approval in foreign countries). Increasingly efficient operations can result from the availability of such portable expertise. The project-related cost of having it in-house (as opposed to seeking it outside the firm on an as-needed basis) will decline if the company plans to engage in multiple development projects requiring the same areas of expertise.[13]

[13]For instance, Hoffmann-La Roche's Pharma division has established a department called International Project Management. It is entrusted with the coordination of a resource pool of about 50 highly qualified project managers overseeing the firm's dispersed R&D sites around the world, with the purpose of maintaining quality standards and ensuring consistency in procedures (Gassmann and von Zedtwitz 1998). Upon project completion, these project managers can be immediately reassigned to projects in other locations, thus enacting fast and seamless transfer of managerial experience, knowledge, and expertise within the firm.

Economies of scope in drug development. Economies of scope can be expected in drug development too as it relies on a wide range of diverse skills—from clinical pharmacology to biostatistics and metabolic chemistry. The participation of scientists and technicians whose focus is to determine the best way to manufacture and deliver the new compound (e.g., process chemists, operations engineers, or packaging experts) is also required at this stage (Cockburn and Henderson 2001b). Hence, enhanced productivity can be attained if the firm has developed diverse yet synergistic competencies, has installed the needed infrastructure (systems, technology, equipment, software), has invested in inimitable resources shared across the firm's various programs (specialized centers and units, expert knowledge, physician networks, sales contacts), and has established the right coordination mechanisms to efficiently manage a multitude of research activities and processes.

Just as with drug discovery, a diversified research portfolio can reduce the variation in firm's procedures and outcomes and, through learning and experience effects, increase the likelihood of successfully completing clinical trials. For example, a firm might learn to better recognize projects that, based on initial test results, signal low probability of conversion into successful drugs, and terminate or modify them early in the process to save time and costs. Experience gained through numerous NDA filings may prompt the firm to institute organizational changes to facilitate the navigation of the FDA approval process. In result, key routines can be optimized and streamlined, while the high standards and rigorous procedures required by the FDA can be carried out expertly and more efficiently.

The advantages of a solid track record of successful innovation outcomes can in turn translate into steady cash flows and help the firm attain better visibility and credibility, bolstering its position in the market. The acquired market power and enhanced professional clout can make the firm more attractive for strategic alliances and partnerships, which can essentially perpetuate its advantageous position.

The empirical evidence largely supports the presence of economies of scale and economies of scope in drug discovery (DiMasi et al. 1995; Henderson and Cockburn 1996). However, there is some ambiguity regarding measurable scale and scope effects in drug development. Economies of scale effects in drug development have remained elusive. One possible explanation is that firms have only recently started to enact coordinated project management practices to facilitate smooth transfers of tacit knowledge across dispersed research sites. With the greater deployment of such practices, data will become available to better test the premise of economies of scale through coordinated project management.

Performance advantages associated with economies of scope in drug development have been found in Cockburn and Henderson (2001b). The analysis of Sorescu et al. (2003) also supports these findings. Specifically, Sorescu et al. (2003) demonstrate that maintaining a greater scope of products (measured by the entropy in the product portfolio) enhances the value of radical innovations launched by a firm. In contrast, Danzon et al. (2005) find that more focused firms are more likely to reach successful completion of Phase 3 clinical trials. They explain their result with *diseconomies of scope*.

This divergence in the empirical findings can be indicative of differential patterns in scope effects depending on capacity-related organizational characteristics such as firm size. Smaller firms may need to focus on fewer therapeutic areas as their limited resources can stymie effective diversification. For them, specialization and narrow focus could be the most effective strategies. Large firms, however, can afford to develop expertise in multiple categories as their greater resources enable more successful diversification.

Still, even the largest and the best-funded pharmaceutical firms do not invest in *all* therapeutic categories (Henderson and Cockburn 1996). Instead, most seem to prefer to invest heavily in a few large programs, while also sustaining some involvement in various small programs. Finding the right balance in the research program portfolio and judiciously allocating the R&D budget across the right mix of diverse projects can be crucial for successful drug discoveries attained in the most efficient way.

In sum, discovery and development programs initiated within more diverse investigation portfolios can enhance the efficiency of the innovation process and increase the likelihood of getting FDA approval. The odds are stacked in favor of large pharmaceutical firms that can afford to maintain diverse portfolios and take advantage of the accrued benefits. Still, firm size is inherently scalable; organizational structures can be changed. Identifying possible regimes of size-related impact and detailing other boundary conditions that can modulate the process of drug innovation and enhance its efficiency would be a fertile ground for R&D portfolio optimization. Besides, firm reorganizations through mergers, acquisitions, spin-offs, and split-offs are frequent in this industry. They provide natural experimentation settings for examining various configurations of firm governance and size. Future research can elucidate their effects on innovation in finer detail.

2.3.2 The Changing Landscape in the Pharmaceutical Industry

2.3.2.1 Times of Transition for Big Pharma

The pharmaceutical industry is science-driven and technology-dependent in the extreme. For decades, the discovery of the next blockbuster drug (a drug likely to reach global sales of more than $1 billion) was seen as the golden grail at the end of the tortuous process of drug innovation. Creating novel drugs was deemed mostly the prerogative of large pharmaceutical firms as they were the ones best equipped to succeed.

The pressure to be first-to-market with a drug that offers unique value to millions of consumers has led to the so-called blockbuster mentality. It has propelled many a quest for drugs that can address widespread disorders and diseases, generate sky-high profits for the originating firm, cement its position as a market leader, and establish its reputation of a trailblazer and formidable rival. The appeal of creating a sustainable, lucrative, world-renowned franchise out of a single drug molecule has been too strong to resist.

To succeed in the ambitious pursuit of blockbuster hits, in their formative years most of today's large pharmaceutical firms saw it fit to build an organization that could carry out functions encompassing all stages of the innovation process: from creating fundamental science to drug commercialization and post-market monitoring. For these Big Pharma firms—the powerhouses on the Fortune 500 list—this legacy business model has driven them to the top and kept them there for decades.

But the blockbuster mentality is essentially opportunistic. It is a costly gamble with high stakes, prone to generating many more "misses" than "hits." Given the long time for drug development, the shorter exclusivity periods, the decrease in expected returns, and the constantly increasing costs of commercialization, the strategy of sourcing all the skills and knowledge necessary to create a new drug from within the firm, through a fully integrated business model, may have run its course.

Besides, the frequent breakthroughs in life sciences, combined with high-paced advances in technology and the ever-expanding toolsets for drug synthesis and design, suggest that fully integrated firms straddling all aspects of drug innovation might quickly fall behind in the race to invent fast and well. Highly specialized skills aligned with the constantly evolving technologies are becoming essential. The current proliferation of state-of-the-art technologies can steer the pharmaceutical industry toward more decentralized business models. This transition has already started, and its onset was marked by the emergence of a rather unprecedented new venture type—the biotech firm.

2.3.2.2 The Foray of Biotech Firms

The 1980s brought about a surge of entry into the pharmaceutical industry by small, research-focused, entrepreneurial firms that positioned themselves between the incumbents (the already large for-profit pharmaceutical companies) and the public sector research institutions (Cockburn 2007). The rise of these independent centers of vigorous R&D and invention, primarily in the area of biotechnology, was facilitated by a range of institutional and legal changes at the time. Widely known as biotech companies, these firms focus on the discovery and development of biopharmaceuticals (proteins, DNA, RNA, and other biomolecules created by means other than direct extraction from a native biological source).[14]

[14]Nowadays, the US biotech firms account for 80 % of the world's R&D investment in biotechnology. The US culture of encouraging entrepreneurship and innovation has been conducive to the creation of such firms. This tendency can be traced back to several noteworthy factors identified in Cockburn and Henderson (2001a): (a) strong intellectual property protection; (b) favorable financial climate with robust and vigorous venture capital industry (both of which are relatively uncertain in many European countries); (c) regulatory climate that is not restrictive of genetic experimentation; (d) strong scientific and medical establishment with developed infrastructure and access to the latest technologies to supplement the limited resources of fledging small firms; and (e) the existence of strong and facilitating academic and cultural norms that permit the rapid translation of academic results from the originating institutions (often in the public domain) to the private sector, with commercial purposes.

Biotech firms are often credited as the engine of innovation in the pharmaceutical industry (Wuyts and Dutta 2008). They generate drug discoveries by maintaining a narrow focus on the latest knowledge in the life sciences and are dedicated to mastering leading-edge technology. However, the majority do not have easy access to large amounts of capital and could be severely underfunded or understaffed. Their limited resources may prevent them from attaining the critical mass or the diversity in R&D projects necessary for the realization of significant economies of scale or scope in drug innovation.

For example, recent research has found that although the out-of-pocket R&D costs for the development of an approved drug do not vary greatly between small biotech and large pharmaceutical companies, those originated by small biotech firms take about 7.5 months longer to reach FDA approval, which raises their capitalized cost (DiMasi and Grabowski 2007). Efficiencies in operations are hard to attain for these firms. Even if they manage to successfully take their innovative products through clinical trials, small biotech firms may not have the requisite commercialization capabilities to go to market. Therefore, the stages of the innovation process that need large-scale efforts combined with access to considerable capital, infrastructure, and proprietary assets (e.g., clinical trials, manufacturing, or marketing) might be the stages best delegated to other industry participants.

If the strategic preferences of biotech firms are more in line with building competencies in the life sciences and performing on the forefront of biotechnology, they may seek to outsource clinical trials to better equipped organizations (e.g., hospitals, university research centers), or form strategic alliances with firms that already have the necessary competencies, e.g., large pharmaceutical companies. Outsourcing the later stages of clinical trials to larger, better funded and well-staffed organizations can be not only the more effective but also the more efficient strategy to rapidly bring drug development to completion and, contingent on FDA approval, commercialization (Grewal et al. 2008). Partnerships and strategic alliances constitute a vehicle that can provide biotech firms with a shortcut to what they need the most—fast access to capital, infrastructure, or market knowledge. Delegating these concerns to those more adept to handle them enables biotech firms to remain focused on invention and discovery, and frees their resources to react swiftly to the latest scientific information needed for sustaining a technological edge. The attendant division of labor might be an efficient collaborative outcome stemming from existing competencies and the desired domains of expertise in the pharmaceutical industry.[15]

[15]In an exploratory study of biotech firms (Khulji et al. 2006), their managers—mostly scientists-turned-entrepreneurs—reveal the conflicting tensions they most frequently grapple with: the desire to retain leverage, control, and confidentiality by keeping the invention close to their chest for as long as they can, and the realization that to advance and be effective, they need to collaborate and attract partners who have greater access to capital, more business contacts, better organizational capabilities, and understanding of marketplace dynamics. Trust issues, insufficient alignment of interests, and coordination problems in asset deployment are some of the areas that introduce challenges in such arrangements.

If biotech companies need assistance with the organization of clinical trials, they have the option of outsourcing to independent Contract Research Organizations (CRO). Yet, many biotech firms may decide to license their products to large pharmaceutical firms despite the CRO option because of the greater marketing knowledge and experience large pharmaceutical firms can also bring in. For the originating biotech firms, the downsides of relinquishing market control can be more than offset by the infusion of vast amounts of capital and the massive advertising and sales effort large companies can deploy before and during the market launch.

2.3.2.3 Public Sector Research Institutions as Centers for the Creation of Open Science

The extraordinarily science-intensive process of innovation in the pharmaceutical industry is critically dependent on state-of-the-art technologies. The prediscovery phase of drug innovation starts with basic research, fundamental knowledge, and understanding of the mechanisms of pathology. By nature, such broadly applicable research is germane to the mission and the interests of research institutions operating in the public sector. The most active institutions in this regard are universities, hospitals, and government labs.

In the USA, public sector institutions, funded mostly by NIH, are an essential contributor to drug innovation. Their involvement comprises knowledge accumulation through fundamental research, participation in clinical studies, and training of future healthcare professionals. Public funding for fundamental science is predicated on its expected value: basic research creates fundamental knowledge, whose future applications and commercial potential might be presently unclear.

Unlike their counterparts in the for-profit sector, most public sector institutions are not inordinately governed by commercial considerations. For them, the scientific curiosity, the broader societal interests, the recognition by a community of peers, the wide range of implications, or the gratification of doing novel research can be among the most compelling drivers. Self-guided, replication-focused, regulated by publication measures and often sanctioned by a peer review system, the science created by public sector institutions generates the data, ideas, tools, and paradigms that push the scientific and technological frontiers in the pharmaceutical industry and chart its future trajectories. The expectation is that many of the advances in fundamental science are going to be utilized by applied researchers working on specific projects at for-profit firms. It is their job to eventually convert the fundamental knowledge generated by public institutions into specific, marketable drugs.

Because of the more general nature of fundamental science created in public research institutions (e.g., understanding metabolic processes and biological mechanisms), its ultimate benefits are contingent upon the open dissemination of results (e.g., through publications or presentations) to downstream firms and the industry at large. Fundamental scientific advances generated by public sector institutions are likely to be relevant to a broad range of fields. Open access to the latest basic

discoveries, mandated by the public goods nature of this knowledge, makes them promptly available to all industry participants.

Scientific discoveries of great social value can transcend any private firm interests. This rationale dictates that they be kept in the public domain for maximum social returns.[16] Still, the widely accessible knowledge generated by the public sector creates a strong and positive externality for the private sector. This unconstrained availability of new fundamental knowledge is called *open science* (Cockburn 2007). The expected rapid diffusion of open science serves to stimulate distributed, decentralized research efforts and essentially prompts innovation. However, it can also make the returns on investment in fundamental science generally hard to attribute or appropriate (Cockburn and Henderson 1996).

However, the notion of the public sector as a designated entity for creating and disseminating fundamental knowledge is a simplification of its actual involvement and contribution. Many public sector institutions engage in building molecular libraries by screening compounds that can directly benefit private firms. The training of a vast pool of qualified personnel for the pharmaceutical industry is also in the hands of publicly funded organizations. They are often tasked with providing the necessary infrastructure for drug discovery and conduct clinical trials for commercially oriented, for-profit firms.

The distinctions between the roles assumed by the public and the private sectors can easily blur. Private firms sometimes straddle the boundaries between creating fundamental science and applied know-how. On occasion, pharmacologists working at for-profit firms may have to conduct basic research. Many academic institutions file for patents and retain exclusive rights on their innovations, underscoring the shifting roles the industry participants go through. Such practices notwithstanding, the current trend seems to be toward greater mutual dependence among autonomous organizations, which we discuss below.

2.3.3 Maps, Engines, Vehicles: The Trifecta Model for Navigating Drug Innovation

The traditional blockbuster model based on genuine breakthrough innovations has become increasingly hard to maintain. The majority of new drug launches are those of follow-on or next-in-class compounds that may not provide highly differentiated therapeutic value, but are released at short intervals. In fact, only about 20 % of firms' R&D budget associated with clinical testing is for drugs categorized by the FDA as offering significant improvement over marketed products (Angell 2004). New innovation opportunities are associated mostly with segmentation strategies: niche markets, combination drugs addressing related or concurrent disorders, drugs tailored to specific

[16]For example, the eradication of the smallpox virus was made possible, thanks to the efforts of the World Health Organization, which mounted a global vaccination program.

genotypes, and ultimately, mass customization in the form of strictly personalized medications or therapy (Gassmann and Reepmeyer 2005). A new generation of blockbusters driven mainly by breakthrough innovation is still likely to emerge, but may need a more specialized business model (Gilbert et al. 2003).

What are the factors that have brought about greater specialization and decentralization pressures to the previously highly centralized, vertically integrated industry? The answer might be found in the specifics of the drug innovation process, its inherent modularity, and the "ticking clock" of patent protection and market exclusivity.

Commercial considerations still reign supreme in the pharmaceutical industry, as they do in any other high-tech industry. Yet, the considerable uncertainty related to a drug's future may prevail. An important point of divergence from other industries is that in the pharmaceutical industry, decisions to terminate projects are rarely made on economic grounds. Although the direction of R&D efforts may be guided by stark commercial reasons (e.g., large markets associated with common diseases or chronic disorders are most attractive for investors in drug innovation), project outcomes are driven by modern science and technology and remain constrained by their limitations. Ultimately, the candidate drug's safety and efficacy are the true deal-breakers on the route to market in this industry. Nevertheless, no firm can forecast or control them too well.

Furthermore, the drug innovation process can be disassembled into distinct stages with clear inputs, outputs, and objectives, which can be carried out by the same firm (provided it has the necessary resources), or distributed across different organizations. The act of invention, which is central to drug discovery, rests on fundamental knowledge that can be sourced from various organizations or disseminated as open science. Drug discovery produces a certain biomolecule, a tangible and finished product in its own right. Thus, it can be separated from the subsequent stages of clinical development, large-scale manufacturing, and commercialization, each one of which is also self-contained, with distinct and well-defined outcomes.

In line with this notion of modularity in the drug innovation process, a naturally occurring division of organizational focus and research effort has come to the forefront. Considerable efficiencies can be realized if tasks can be divided across different firm types based on their idiosyncratic competencies and strengths. As timing is critical under a limited window of patent protection and market exclusivity, arrangements that can streamline and expedite the innovation process, lower its costs, and diversify the inherent risks become increasingly attractive.

Hence, a multi-tier system of organizations supplementing each other's competencies might be best equipped to handle the complexities of modern drug innovation both efficiently and effectively. In fact, it has already emerged. Three organizational tiers are involved in pharmaceutical innovation: *public sector organizations* provide the fundamental science that essentially maps out the landscape for subsequent innovations, *small biotech firms* serve as a veritable innovation engine, conducting cutting-edge research and supplying novel biomolecules, while *large pharmaceutical firms*, ambidextrous and multifunctional, are particularly

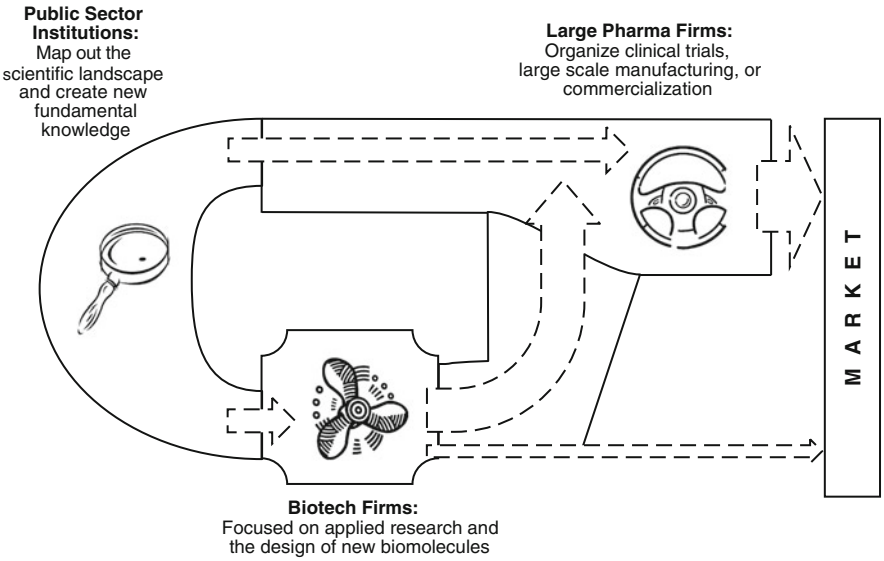

Fig. 2.2 The Trifecta model of innovation in the pharmaceutical industry

adept to serve as a vehicle for advancing scores of drug candidates through clinical trials to FDA approval, and then to commercialization. These three organizational types complement each other's strengths and can operate in symbiosis to advance biomedical research in a *trifecta model of innovation* (Fig. 2.2).

Note that these three types of organizations are not, by nature or by articles of incorporation, accustomed to be "chummy" with each other. They can be bona fide rivals, competing for market share, racing for patents, or vying for the position of a market leader in their field. And yet, they have come to coexist in a mutually agreeable way, gaining from synergies and benefiting from occasional acts of cooperation. The occurrence of *drug-centered partnerships* appears to be the new business model increasingly gaining prominence in the pharmaceutical industry.

Throughout the life cycle of a drug, the output of public institutions (i.e., universities, government labs, hospitals) benefits the private sector in at least two major ways. First, the created fundamental biological and chemical knowledge generated by the public sector is often used as groundwork for drug discovery as it maps out promising avenues for applied research. Second, the public sector can assist with clinical trials, e.g., by contributing practical knowledge for trial design, by carrying out the actual testing of new drugs, or by collecting and processing post-market information following the market launch.

Close connections between the private and the public sector can enhance the performance of private firms. Participation in the construction of publicly available research data and findings, as well as joint publications or presentations with leading researchers from the public sector are precursors to more effective drug discovery in private firms (Cockburn and Henderson 1998). Some evidence suggests a

30 % return on investment for research done in the public sector, when measured by its effects on the private sector (Cockburn and Henderson 2001a). This estimate is 2.6 times higher than the average return on innovation in this industry, assessed to be about 11.5 % (Grabowski et al. 2002). Positive externalities like open science and free information exchange help private firms overcome the boundaries of specialization, and make specialization itself more feasible and desirable. Immediate access to leading edge, publicly funded science bestows a competitive advantage on large pharmaceutical firms, but is particularly vital as a source of new knowledge, information, and intellectual stimulation for the emerging biotechnology sector with its small, research-focused private firms.

Notably, the open-science model underpinning interorganizational interactions and cooperation is sustained by a veritable bidirectional flow of information. The collaboration between the public and the private sector can be mutually beneficial: private firm researchers, too, can contribute practical experience and expertise, as well as knowledge (applied or experimental), to their counterparts in the public sector. The vibrant culture of applied science and the specific challenges encountered in drug innovation can stimulate the publication-driven public sector and reenergize its efforts by suggesting new research directions.

The ongoing shifts in the industry landscape and the increasing prominence of new types of organizations can be unsettling for large pharmaceutical firms which, because of their considerable resources, networks, and marketing prowess, are used to having an uncontested advantage in the complex and expensive process of drug innovation. After all, outspending, outlasting, or displacing poorly funded small rivals should come easy for them. Vast intangible assets like experience and reputation, tacit knowledge, contact networks, or proprietary know-how from years of intensive and diverse research should have been sufficient to sustain their dominance as the leaders in innovation productivity. Their capacity for economies of scale and scope should be indispensable as efficiency gains can be enormous in this highly research-intensive industry. And yet, the emergence of a specialized market for biotechnology, in conjunction with the multitudes of agile and inventive small firms drawn to it, has fostered vertical disintegration in the pharmaceutical industry.

The exigencies of rapidly changing modern technologies stemming from the life sciences may prompt large firms, too, to carve out specialized niches for themselves. Recent specialization tendencies, added to the constant pressures to perform on and beyond the ever-shifting frontiers of science, have increased the value of network externalities and the need for more open information exchanges. What remains to be seen is whether large pharmaceutical firms, accustomed to being ambidextrous in drug innovation, might shift gears and opt for efficiencies through tighter research focus, exploitation of existing assets, and aggressive pursuit of partnerships, so that they start scaling back on the range of scientific and technological areas they invest in.

Specialization by therapeutic area, disease pathway, target molecule, drug candidate molecule, method of drug synthesis, or even by patients' pharmacogenomic profile seems to be the way of the future for pharmaceutical firms. Such streamlining

and narrowing of their exploratory focus can free resources for obtaining greater scientific and technological proficiency and help develop unique experience and expertise in a few therapeutic areas. The acquired in-depth knowledge and know-how can still be shared with selected partners through various forms of collaboration and controlled information exchanges so that functional synergies and cross-pollination of ideas can occur.[17]

Large pharmaceutical firms seem particularly well-equipped to serve as expedient platforms to market. Owing to their vast scale of operations, professional networks, and experience, they are adept at designing and overseeing extensive clinical trials, and can organize and conduct them faster. In addition, their sizable marketing prowess and already established sales forces can ensure more effective end-product commercialization. Researchers have already found empirical evidence in support of this premise. For example, products developed in interfirm partnerships turn out to have a greater probability of success, particularly if the licensee is a large firm (Danzon et al. 2005).

In summary, the pharmaceutical industry seems to have embarked on a gradual transformation away from the vertically integrated model with the strong blockbuster orientation. The emphasis is shifting to incremental innovations, greater specialization, and focused R&D in an effort to capitalize on established competencies, realize greater efficiencies, and benefit from synergies. In turn, these tendencies have brought about new business roles and practices that have supplanted the earlier vertically integrated model of self-sufficient firms with more distributed, collaboration-intensive models. Public sector research institutions, large pharmaceutical firms, and small biotech ventures seem to have found a way to flourish side by side and balance bouts of rivalry with forms of interdependency and collaboration. We examine these forms next.

2.3.4 Modes of Collaboration for Innovation in the Pharmaceutical Industry

The high stakes associated with exclusivity rights, unpredictable outcomes, fierce competition, and first-to-market races in the pharmaceutical industry have given rise to a multiplicity of business models and interfirm arrangements to choose from or gravitate between. The industry is evolving fast, mixing-and-matching from a smorgasbord of options based on fluctuating demands and environmental shifts. Large vertically integrated firms coexist and collaborate with organizations with a strictly narrow focus, alliances and partnerships are frequently formed and dissolved, new

[17]For example, a firm that has serendipitously made a discovery in a non-focal area can partner up with a company whose research focus matches the discovery in question so that they can jointly take the new drug to market.

entry of small specialized firms is common, mergers and acquisitions are a familiar fixture, and the occasional spin-offs of divisions into autonomous ventures are no surprise either. Pharmaceutical innovation is no longer a stand-alone activity undertaken by individual firms in total isolation.

An increasing practice of technology transfers and know-how diffusion across firms builds upon the positive momentum created by the openness of fundamental science. In addition to staying alert to the intellectual output of public sector institutions, firms seek to lower the total costs of new drug creation and shorten the time to market through strategic alliances and licensing agreements. Calculated knowledge exchanges introduce system efficiencies by exploiting synergies between various assets and resources held or developed by the individual firms. Sharing know-how can facilitate and accelerate the innovation process and would explain the ever-increasing number of licensing deals, partnerships, and strategic alliances among pharmaceutical firms. Besides, the industry remains prone to occasional consolidations through mergers and acquisitions. The persistence of such tendencies indicates that economies of scale and scope may be too valuable to forgo despite the benefits of specialization.

There is evidence that drugs developed in a partnership are significantly more likely to succeed in Phase 2 and 3 of clinical trials. In a sample dominated by small- and medium-size firms, Danzon et al. (2005) find that interfirm cooperation in Phase 3 of clinical trials produces a 15 % greater probability of approval compared to independent efforts. These odds may actually be old news to the industry as indicated by current business practices, which show that compared to large pharmaceutical firms, biotech firms are less likely to take drug candidates to clinical trials on their own (Arora et al. 2007).

Large pharmaceutical firms are in a position to enjoy the vast awareness, credibility, and the brand equity that small firms find lacking. Owing to their sizable budgets and greater scale of operations, large firms are poised to have easier access to capital. They are also more likely to possess the necessary marketing resources small firms may find hard to acquire. Also, inimitable assets like a steadfast reputation for process rigor and product quality might turn out to be critical for sustaining a competitive edge in crowded therapy markets. Such intangible assets could be more easily accruable to large firms because of their vast drug portfolios and long track records of market presence and innovation.

Although they tend to operate on a smaller scale, the intellectual output of biotech firms has made them as significant to the US pharmaceutical industry as powerhouses like Merck, Pfizer, or Eli Lilly. However, biotech firms in general may not have the resources to maintain a diverse project portfolio and would often lack the downstream assets to take new drugs to market. Many seem inclined to specialize in advanced research, the outputs of which are licensed out to others. One implication of this practice is the lack of public visibility for their achievements, which may become a strategic deterrent in case of future plans for market entry.

Still, for all the entrepreneurial drive and agility of biotech firms, a narrow focus and concentration of efforts in a few therapeutic areas could be both more effective and more efficient given their limited resources. It is the combination of their

in-depth knowledge and the willingness to tap into risky cutting-edge research that comprises biotech firms' chief contribution to drug innovation. In fact, in some cases, licensing out newly developed technologies may be their only viable route to market, as the majority have no significant sales structure or marketing capacity in place. Thus, licensing fees may constitute their main source of revenue.

As biotech companies assume the role of renowned drivers and suppliers of innovation, those that succeed can enjoy a rather favorable business outlook. There is empirical evidence that firms investing more in research tend to obtain more licensing deals. In turn, having a wide portfolio of licensing deals translates into more new licensing deals (Wuyts and Dutta 2008). Thus, investment in focused R&D efforts can create a self-perpetuating momentum that bolsters firm viability and brings in sustainable revenue streams from licensing. Increased innovation output, learning effects, the accumulation of valuable R&D stock, or a growing reputation for creativity and novelty can explain these linkages.

Dedicated biotech firms investing in narrowly focused drug research can find themselves on a lucrative spiral of growth.[18] Developing specialty drugs for *niche* markets can be profitable as no large-scale marketing efforts are involved, and competitor entry is less likely due to the small market potential. There are indications that the stock market, too, regards small firms of a sharp research focus (i.e., those with small research portfolios) more favorably by boosting their stock prices, essentially acknowledging the greater likelihood that they can be successful if they sustain a narrow specialization (Grewal et al. 2008).

Still, too narrow a specialization in innovation can become risky as economies of scope might be hard to come by. Moreover, overreliance on partnerships and excessive dependence on collaboration, necessary to overcome the constraints of narrow specialization, can turn precarious. Disagreements between partners may occur, leading to delays. The incurred R&D costs can be difficult to allocate and recoup. A more detailed examination of licensing dynamics and their impact on performance is necessary to further elucidate the associated mechanisms, the drivers and the moderators, the boundary conditions and the most likely process outcomes under different conditions.

Generally, small firms would find large firms attractive to partner with because of their considerable resources and intangible assets. Yet, in a partnership, large firms will have to share the eventual market proceeds with another firm. If small firms can benefit from the immediate access to funding, downstream assets, and experience that alliances with large pharmaceutical firms make possible, what are the advantages from in-licensing agreements and other forms of cooperation for the large firms?

[18]Prior to its acquisition by Roche in 2009, Genentech, the company considered to be the first biotech firm, remained focused almost exclusively on large molecules, using partnerships to augment its core research and to increase its access to capital. Other companies have also chosen to restrict their R&D to few carefully selected areas, e.g., Biogen Idec Inc. is specializing in drugs for neurological disorders, autoimmune disorders, and cancer.

For them, in-licensing is a shortcut to quickly fill their product pipelines and extend their research portfolios. As continuous innovation is imperative in the pharmaceutical industry, replenishing drug pipelines on a regular basis is crucial for maintaining a strong competitive standing. Large pharmaceutical firms are under constant pressure to maintain full and promising project portfolios, which makes them appealing to shareholders and can affect these firms' access to capital. As shown by Grewal et al. (2008), shareholders tend to support the large pharmaceutical firms that have broad research portfolios, and are particularly interested in firms with drugs in the later stages of development. In view of such considerations, publicly traded firms will look to sustain a reasonable number of ongoing investigative drug projects and will try to quickly replace those that have been concluded or terminated. Besides, maintaining large research portfolios can lead to economies of scale and scope, resulting in better resource utilization.

It is hardly a surprise that the largest pharmaceutical companies are the ones advancing most new chemical entities to market.[19] These firms can leverage superior integrative capabilities, tacit knowledge, and abundant experience to improve the chances of in-licensed drug candidates to get to market. For large firms, in-licensing is a rather desirable business strategy geared for the realization of synergies, reduction in effort duplication, and ultimately, more efficient use of firms' resources. These arguments explain why taking products discovered by their smaller brethren—the biotechs—and bringing them to market seems like a reasonable and savvy move for many large pharmaceutical companies.[20]

It is worth noting that although large firms are typically drawn to in-licensing, they may occasionally opt to out-license some of their own compounds. Even a large firm may have insufficient capacity to handle too many projects. If a large firm has a number of candidate drugs all approaching clinical trials, it may prefer to retain those with the greatest market potential, and license out the rest. The projects that get licensed out could be the riskiest ones or those with the lowest expected sales, although the firm will still keep a stake in their future performance. However, Danzon et al. (2005) find no evidence of such a "lemons" problem.

Of course, partnerships may occur between large pharmaceutical firms too. A compelling reason for such partnerships is the intention to diversify the risk and share the huge marketing costs for an impending market launch. In such cases, strategic alliances are created for the express purpose of marketing a specific drug jointly.

[19]In fact, by the late 1990s, the large pharmaceutical firms were marketing seven out of the ten top-selling biotech drugs, although *none of the drugs had been developed by them*. Those seven drugs accounted for two-thirds of the revenues from the top ten drugs at the time (Rothaermel 2001b). In 2000, more than half of the drugs in the pipelines of Schering-Plough, Bristol-Myers Squibb, and Johnson and Johnson were products of in-licensing agreements (Simonet 2002).

[20]The first firm to apply biotechnology in drug discovery was Genentech. Using recombinant DNA technology, it created synthetic human insulin, heralded as the first-ever approved genetically engineered therapeutic product. But Genentech didn't take that revolutionary product to market. Instead, it licensed Eli Lilly to navigate the FDA approval process.

Typically, the partner firms employ carefully coordinated pricing and communications strategies and, by pooling their sales forces together, can obtain broader access to markets.[21]

Licensing has an immediate impact on the size of the firm's project portfolio. It also affects the resource allocation of the firm. Simonet (2002) identifies three types of large pharmaceutical firms based on the prevalent sourcing of their project portfolios: (a) *development-oriented* firms choose to maintain a project portfolio dominated by in-licensed products, for which the focal firm conducts clinical development (e.g., Johnson & Johnson, Bristol-Myers Squibb); (b) firms with *well-balanced portfolios* strive to maintain a set of self-originated products that match or slightly exceed the number of in-licensed products in their pipeline (e.g., Eli Lilly, Pfizer, Roche, Novartis, GlaxoSmithKline); and (c) *research-oriented* firms operate with a relatively small number of in-licensed products in their portfolio, and place strong emphasis on self-originated products that they take into development (e.g., Merck & Co., Bayer, Boehringer Ingelheim, Novo Nordisk).

Regardless of their revenue, it is the firms experiencing a decline in new drug productivity (measured as depletion in their research pipeline) that are more likely to engage in R&D-focused alliances, in-licensing agreements, or consolidation through mergers and acquisitions (Higgins and Rodriguez 2006). The examples studied in Simonet (2002) seem congruent with this conclusion—two of the four development-oriented firms in that review were subsequently acquired.[22] Nonetheless, tempting as it is to make causal inferences about a precipitated downfall associated with too much dependence on in-licensed products, anecdotal and isolated cases like these are not sufficient for generalization. Besides, an acquisition can be a springboard to faster growth under a different identity instead of a death knell for the acquired company. Data including information on the retention of management and R&D teams and on the fate of projects initiated before the acquisition may shed more light on these issues.

The assimilation of external ideas, knowledge, technology, or know-how can determine the future market options for the firm, and can be an instrument to quickly balance a temporarily weakened pipeline. Given the uncertainty in gaining FDA approval with a single drug candidate, a richer portfolio will increase the firm's chances to take at least one drug to market. The success of a business model with a stronger leaning toward external innovative input through in-licensing may be contingent on the current state of the firm's R&D portfolio, as well as its capacity to attract, select, and carry out projects of greater potential for success.

[21] A recent example for an international alliance of large pharmaceutical firms is that of Boehringer-Ingelheim and Pfizer for the joint manufacturing and marketing of Spiriva®, a treatment for chronic obstructive pulmonary disease.

[22] In 2009, Schering-Plough got acquired by Merck, while American Home Products was taken over by Pfizer.

Firms looking for licensing or acquisition targets may need to find the right balance between leveraging specific competencies and attaining pipeline diversity. Evaluating the knowledge-based assets of other firms can be rather challenging. Only firms actively engaged in certain therapeutic areas may have the confidence and the capabilities to accurately assess the potential of others' R&D efforts, the expertise to manage the development process more efficiently, or the marketing experience and the sales contacts to execute the launch effectively. On the other hand, acquiring a firm with a rather *different* pipeline might be advantageous in its own right as it will contribute to the acquiring firm's project diversification. Maintaining focused or diversified research portfolios may be differentially conducive to small vs. large firms or to upstream vs. downstream organizations. Therefore, large pharmaceutical and small biotech firms alike may need a clear recognition of the combination that could be optimal in their setting.

Collaboration assists firms by supplementing their own R&D activity. Licensing, strategic alliances, mergers, and acquisitions can invigorate firms' internal research efforts and extend their research pipelines (Chan et al. 2007). Promising drug candidates can be brought forth for clinical investigation at a much higher rate, building a valuable momentum in the competitive race to market. Ding and Eliashberg (2002) find that firms underspend on drug development during clinical trials, suggesting that optimization of their pipelines could be necessary. The infusion of external know-how and the adoption of candidates from new therapeutic categories will lead to more diversified research programs, opening up options for more efficient utilization of resources. Besides, diversification through assimilation can create new strategic advantages and translate into greater gains for the firm.

Of course, there can be exceptions and variations from the business models and practices discussed heretofore. For example, not all biotech firms are small, nor are they solely confined to highly specialized research with a narrow focus. Some, like Amgen, are sufficiently vertically integrated to take promising drug candidates from prediscovery to market. Biotech firms can learn to successfully manage diverse R&D programs, too. The modes of collaboration in the pharmaceutical industry are abundant and multifaceted, and hold great potential for more in-depth analysis and continued empirical research.

Considerable differences in productivity across pharmaceutical firms might be associated with variability in their strategic decisions about the scope, the focus, or the coordinated timing of their innovation efforts. In the academic literature, two likely scenarios have been explored in more detail: overflowing project pipelines and shortages in the project pipeline. We sketch out some of the analytical inferences below.

Cassiman and Ueda (2006) analyze the conditions under which an established firm might be advised to spin off some of its newly conceived technologies to start-up ventures. Such spin-offs are typically headed by former employees (scientists) proven to be essential for the development of the said technologies at the incumbent firm. The authors conclude that firms will spawn off such ventures, and occasionally even partially subsidize them, if: (a) the firm undertakes a lot of successful

R&D projects and has no free capacity for commercializing them all (that is, a capacity threshold has been reached); (b) the firm is already operating close to its commercialization capacity and thus, becomes increasingly selective about the market value of additional projects; (c) the spun-off technology is considered to be of low complementarity value to the firm (e.g., it is misaligned with the firm's prevalent know-how, requires large investment in new co-specialized assets, or has a poor fit with the existing core markets); and (d) the new technology represents a low cannibalization threat for the incumbent firm's other products. The assertion in (d) is based on the premise that potential cannibalization can be best controlled when the technology in question is kept in-house.

In case a firm has its R&D pipeline running low on projects of high expected value, the decision to "purchase" new projects may depend on the firm's risk aversion. The potential trade-off between *adjustment costs* (the forgone returns from co-specialized investments if they become underutilized or must be downsized in the face of diminishing activity—e.g., the thinning out of a specialized sales force), and the candidate project's *transaction costs* (the transfer and the assimilation costs for a licensed-in candidate) should be evaluated before a new project is brought in from outside the firm (Chan et al. 2007).

Analytically, it can be shown that even if entrant firms are more risk-seeking than incumbent firms, for sufficiently high adjustment costs relative to transaction costs, the entrants may choose to specialize in R&D and would rarely seek to commercialize projects (Chan et al. 2007). Knowing this, established firms may consider raising their own adjustment costs (by making a greater investment in co-specialized assets) as a preemptive strategic move aimed to lower the transfer cost (e.g., the license fee) of future projects offered by entrants. Although current practices in the pharmaceutical industry appear broadly consistent with the implications suggested by this analysis, targeted empirical research can help illuminate the related strategic interplay between entrants and incumbents in more detail.

2.3.5 Strategic Alliances as a Shortcut to Market in the Pharmaceutical Industry

The earlier and the later stages of the drug innovation process differ by nature. Accordingly, the tasks and the required skills, competencies, and resources would change along the innovation pathway of a drug. The specific objectives of each investigative phase enable tasks to be performed by different organizations so that the ones most adept in certain functions get to carry them out.

Strategic alliances represent a propitious ground for symbiotic collaboration between the small biotech and the large pharmaceutical firms. They provide for a closer interfirm relationship than licensing, yet are safer than outright acquisitions.

Such alliances are intended for the commercialization of science and aim to exploit complementary competencies residing in different organizations.[23]

Many of the earlier studies on strategic alliances in drug innovation have been largely case-based. The industry is fairly young and volatile, and there is a relative paucity of tractable measures on the partner selection process, the structure, governance, and evolution of alliance modes, or the way innovation value is created and appropriated in such partnerships. Due to space considerations, we briefly outline recent empirical findings from the academic literature that relate to alliance-related decisions. These studies have used large samples to enhance generalizability.

Rough estimates point to biotechnology as the industry with the highest rate of alliance formation and the one with the highest growth rate in new alliances (Hagedoorn 1993). This is hardly surprising given the advantages of strategic alliances as well as their considerable signaling value. For the generally less visible biotech firms, participating in alliances with large pharmaceutical firms can be seen as a tacit endorsement. Such partnerships can bestow special clout on small, relatively unknown ventures.

A study by Stuart et al. (1999) demonstrates empirically that alliances can boost the stock market valuation and expedite the IPO of the biotech partner. In addition, as shown by Danzon et al. (2005), in the late stages of clinical trials a new drug developed in an alliance has a higher probability of success, especially if one of the partners is a large pharmaceutical firm. A strategic alliance between a biotech firm and a large pharmaceutical firm can also be a precursor to the pending acquisition of the biotech firm by its large partner.

However, alliances in the pharmaceutical industry are not limited to biotech-pharmaceutical dyads and can also occur between peer biotech or peer pharmaceutical firms. Public institutions (e.g., universities) can also partner with biotech or pharmaceutical firms. Many organizations tend to engage in multiple alliances simultaneously. Tracking all alliances of a firm is difficult as firms are not expected to disclose their interfirm arrangements (but may choose to publicize them nevertheless). Also, some agreements could be rather informal (e.g., handshake deals).

The rationale for alliances in the pharmaceutical industry. The incumbent large pharmaceutical firms, vertically integrated and well-funded, already in command of considerable sales forces and embedded in vast networks of industry contacts and

[23]The onset of extensive interfirm cooperative arrangements in the pharmaceutical industry in the early 1980s coincides with the time of its sweeping transition from chemical to biological compounds, which had also triggered the emergence of biotech firms in the late 1970s. The confluence of several critical factors created favorable conditions that fostered such cooperation: the Supreme Court passed a decision that live forms could be patented, the Patent and Trademark Act allowed universities to patent discoveries funded with federal dollars, and the first biotech firm, Genentech, went through a very successful IPO, drawing the industry's attention to the creative potential of such firms (Hoang and Rothaermel 2005). The trend toward strategic alliances got an extra boost in the 1990s in the wake of several biotech firms' stock market failures that underscored the advantages of partnering with large pharmaceutical firms. Around the same time, drastic healthcare reforms curtailed the growth potential of large pharmaceutical firms and sent them scrambling for faster innovation. This precipitated the need for cooperation on their part.

relations, have essentially become efficient vehicles for drug development and market access. They offer synergies to both public sector institutions and biotech firms, the majority of which may lack the requisite assets to carry drug discoveries to commercialization. In the absence of steady cash streams, the long horizon to market launch places biotech firms in a particularly vulnerable position to sustain operations and highlights the likely benefits of their partnerships with the incumbent large pharmaceutical firms.

The value of large pharmaceutical firms' downstream assets (manufacturing, marketing, sales) can be crucial to biotech firms working in the same or similar therapeutic areas. Most of the dominant incumbents have developed valuable firm-specific competencies and market familiarity regarding certain types of disease. The competitive advantage conferred by such specific, in-depth knowledge could be strengthened with the ties between the firm's drug representatives and the physicians specializing in certain therapeutic areas. The repeated visits of a pharmaceutical firm's sales representatives with dedicated healthcare specialists may foster better rapport and increased credibility as the two sides get to capitalize on highly relevant pools of idiosyncratic, specialized knowledge. Good personal relationships with key decision makers in healthcare, reinforced with compelling sales presentations by the firm's drug representatives, can become an inimitable co-specialized asset for the firm. For the dominant pharmaceutical firms, this can translate into considerable downstream leverage. It also provides an option for significant innovation rents to be extracted through target-specific alliances.

The leadership role of the established and profitable pharmaceutical firms in commercializing technological breakthroughs (pioneer drugs) and market breakthroughs (follow-on and me-too drugs) has been documented empirically in Sorescu et al. (2003). The findings show that such firms launch more new drugs, and that being backed up by such a firm boosts the value of newly released medications as measured by their net present value. The increase in market value is particularly pronounced in the case of pioneer drugs. Yet, as Sorescu's et al. (2003) study had no controls for alliance activity, follow-up work could illuminate the share of drug innovations that large firms have sourced from partnerships. Such scrutiny can shed light on the contribution of strategic collaboration to both partners, essentially measuring the returns from alliance participation.

Alliance modes for large pharmaceutical firms. In a study of 889 strategic alliances between incumbent pharmaceutical firms and new biotech companies, Rothaermel (2001a) finds evidence that the large pharmaceutical firms prefer *exploitation alliances* (alliances that leverage their downstream assets, for example in the areas of clinical trials, FDA regulatory management, marketing, sales) to *exploration alliances* (alliances that build their upstream, technology-based competencies—e.g., discovery, R&D). The preference for exploitation alliances can be explained by efficiency considerations: exploitation alliances can leverage the already existing specialized downstream assets of large pharmaceutical firms, help them capture significant amounts of new revenue, as well as sustain their reputation as innovators, while limiting the amount of extra risk involved.

Alliance modes for biotech firms. Using a different nomenclature of alliance modes (upstream, horizontal, and downstream), Rothaermel and Deeds (2006) examine the new product output of 325 biotech firms participating in 2,226 alliances. *Upstream alliances* are defined as those with research universities or nonprofit institutions, when the goal is to tap into leading-edge scientific discoveries and develop them for commercial purposes; *horizontal alliances* are those with biotech peers or other technology ventures, whereby firms intend to combine complementary assets, realize economies of scale, and advance products to clinical trials or to the early stages of new drug commercialization; *downstream alliances* are those with established pharmaceutical firms, with the purpose of gaining access to manufacturing, regulatory, and marketing knowledge (Rothaermel and the Deeds 2006). Consequently, the three alliance modes differ by partner type, goals, and the nature of transferred knowledge.

The results of that study show that the biotech firms' limited capability for alliance management is exhausted the fastest with upstream alliances, followed by horizontal, and then by downstream alliances, in this order. Upstream alliances, with their intrinsic transfer of tacit, complex, ambiguous knowledge of uncertain value, are the most taxing on a biotech firm. A firm's potential to simultaneously engage in a number of upstream alliances is fairly low. In contrast, with downstream alliances, the drug formula has been discovered and the drug has been created, so the level of transferred knowledge ambiguity and complexity is at its lowest. Hence, downstream alliances are the least taxing on a firm's alliance management capacity, and a firm can afford to handle a higher number of these. This suggests that a biotech firm can participate in a greater number of downstream alliances relative to upstream alliances. Horizontal alliances hold the middle ground—with them, the knowledge shared between the partners is more specific, application-oriented, and easier to assimilate compared to fundamental science, although it remains less structured than the knowledge necessary for commercialization. Hence, in this case the burden on a firm's alliance management resources is lower compared to upstream alliances, but higher than that in downstream alliances.

Diminishing marginal returns in innovation output associated with high levels of alliance activity are found in all three alliance types, but the locations of the turning points differ. The tolerance threshold is the lowest when the firm has multiple upstream partners. It is higher with numerous horizontal partners, and is the highest in case of multiple downstream ones. Consequently, firms can afford to engage in more horizontal alliances compared to upstream ones and can manage an even greater number of downstream alliances (Rothaermel and Deeds 2006).

Selection of partners. In a study of 69 alliances between pharmaceutical and biotech companies, Lane and Lubatkin (1998) contend that the overall performance of an alliance is best explained not so much by the absolute absorptive capacity of the downstream partner (the pharmaceutical firm), but by the downstream partner's relative absorptive capacity that is idiosyncratic to the partnership dyad and stems from similarities with the biotech partner's: (a) basic knowledge—scientific, technical, and academic; (b) knowledge-processing systems; and (c) commercial objectives (the dominant logic in new product development). In other words, to be effective in interorganizational learning, the alliance partners must share similar theoretical and

technical backgrounds, as well as have proximate organizational processes and common research communities. Such symbiotic partnerships would result in more successful innovation outcomes from the alliance (Lane and Lubatkin 1998).

Diminishing returns from excessive alliance activity. Simultaneous participation in multiple alliances can be conducive to prolific product development, but may incur significant transaction costs, manifested in increasing burden on the firm's management. The heightened complexity and the specificity of information exchange with multiple partners, the need to monitor diverse relationships and to abide by multiple agreements can overextend the firm's managerial capability. The scrutiny with which it selects new partners may wane, or the selection pool may shrink significantly once the most promising partners are already on board, rendering additional alliances less well-fitting or less productive. Diminishing marginal returns will eventually set in and may even transition to negative effects. The firm's innovation performance may decline when the firm extends beyond a certain critical threshold of alliance connectivity.

Entering too many alliances opens up the venture to risks of coordination problems, mismanagement, opportunism, and expropriation. Yet, participation in too few can place the firm at a competitive disadvantage. The implied inverted-U effect of the number of alliances on a firm's innovation performance has been supported in the empirical studies of Deeds and Hill (1996) and Rothaermel and Deeds (2006).

Network effects, *experience effects and partner diversity*. Exploring the alliance networks of a panel of 225 biotech firms in a dynamic setting, Powell et al. (1996) find that the majority of firms establish multiple alliances over time. The interfirm connectivity in the industry grows rapidly. Collaborative practices with *diverse partners* contribute to learning effects, which enhance firm growth. Hoang and Rothaermel (2005) propose that alliance experience obtained from a firm's joint activities with a portfolio of diverse partners aids knowledge codification, brings about new intra- and interorganizational routines, and may even prompt the formation of new structures within the firm. The new routines or structures can be mutually beneficial: they may facilitate the functional cooperation between the partners, enhance the assimilation of new knowledge, and boost the information exchange between them. The locus of learning can be the development of alliance experience among dedicated *alliance managers*. Eventually, however, diminishing marginal effects from coordinating too many partnerships may set in.

The impact of experience obtained from the *same set of a few long-term partners* can be less effective. Having only a few partners leaves less room for organizational learning. The variation in new experiences will be limited. Complacency, process inertia, or functional rigidities between the partners may set in. The empirical results of Hoang and Rothaermel (2005), obtained from a study of 158 collaborative new product development projects, support these propositions. For the biotech firms in that study, the impact of diverse prior alliance experience has a positive but diminishing effect on the success probability of joint R&D projects, while the cumulative partner-specific alliance experience is rendered insignificant. The same pattern was subsequently demonstrated by Rothaermel and Deeds (2006) in another, larger sample.

Interestingly, these findings have failed to replicate with large pharmaceutical firms. Having a diverse alliance network does not exert a positive impact on their project

success probabilities, suggesting some inherent deterrent in their harnessing of a rich experience from multiple alliances (Hoang and Rothaermel 2005). The authors' explanation invokes an argument from organizational behavior: in the relatively small biotech firms, diverse alliance experiences can be easily concentrated in the hands of one key individual (often the founder or a top-level manager), who is also more motivated to learn from these experiences as alliances are particularly critical for the survival of small firms. In large firms, the management of multiple alliances is often distributed across the organization and is handled by different individuals. Such dispersion in the alliance experiences makes the cumulative benefits harder to materialize.[24]

In general, the consensus in the academic literature is that for pharmaceutical and biotech firms alike, interfirm cooperation has a positive impact on innovation outcomes, particularly for a small number of alliance partners (Shan et al. 1994; Deeds and Hill 1996; Rothaermel 2001a). For biotech firms, access to public equity markets and a well-embedded network position exert additional positive effects on innovation outcomes (e.g., Shan et al. 1994).

The industry can benefit tremendously from a more fine-grained understanding of the rationale employed by different firms in their strategic choices regarding various forms of partnership activity. Insights about the evolution of alliances and assessment of the direct and indirect extra value they bestow on the partners can be rather informative for future strategic decisions. It will be illuminating to examine the interactions between different alliance types, to analyze the latent discrepancies in the partners' interests, their reconciliation or resolution, and to study in detail the impact of relevant environmental, organizational, managerial, or structural factors. A better understanding of the potential synergies in the collaboration strategies of pharmaceutical and biotech firms, along with a clear recognition of the potential pitfalls, can guide firms toward systematic improvements in their partnering decisions for innovation—a win–win situation all around.

2.3.6 The Business of Drug Innovation from an Academic Perspective: Findings and Insights

Inventions are by default disruptive, which makes them relatively impenetrable to attempts to explain or predict. Yet, examining the process of drug innovation for pivot points that can introduce extra efficiencies, along with studying the various business models that arise in the industry are attractive areas for academic scrutiny. Detailed datasets present new opportunities for testing complex model frameworks; advanced estimation techniques enable the disentangling of interdependencies; the

[24]Eli Lilly has established a dedicated function called Office of Alliance Management to serve as an "integrator, intermediary, and catalyst for best practice performance" (Hoang and Rothaermel 2005). This move is consistent with the suggested need for intraorganizational streamlining of diverse alliance experiences.

amassed conceptual understanding gives rise to reasonable data proxies and avenues for data augmentation; previously arcane mechanisms and procedures are made more transparent through case studies and open discourse.

Most of the academic papers cited in this chapter have focused on capturing the drivers behind successful innovation outcomes while accounting for factors germane to the pharmaceutical industry. Now that the readers are more familiar with the complex landscape in the industry, we will briefly discuss other academic findings illuminating additional aspects of the drug innovation process. Of course, we are limited by space considerations so this review will be somewhat sketchy, but we hope that even a brief exposition will incite the curiosity of more researchers to focus on this domain. Readers interested in a good summary of strategic marketing decision models in the pharmaceutical industry are referred to the detailed compilation by Shankar (2008).

2.3.6.1 Risk-Taking + Investment in R&D + Good Luck = Business Viability and Market Dominance

The sources of today's strategic and performance heterogeneity in the pharmaceutical industry were examined by Lee (2003). In a historical study on the development trajectories of the US pharmaceutical firms from 1920 to 1960, he traces the current powerhouses back to their origins, and most importantly, to the decision to embrace large-scale manufacturing of antibiotics in the 1940s despite the uncertainties prevalent at the time. Considerable investments in R&D made this possible, although the risks were substantial. Also, those early innovators were able to charge premium prices. The most successful of them have managed to sustain their dominance in drug innovation by investing the market proceeds into hiring biologists and scientists at an increasing rate, which ultimately enabled them to branch away from antibiotics (Lee 2003).

Other pharmaceutical firms (imitators) chose not to commit considerable resources to R&D and survived for a while by selling existing, known products at low prices, thus remaining peripheral to drug innovation. The initial choice of product strategy, perhaps influenced by the risk adversity of the firms' management teams at the time, has acquired irreversible momentum over the years, persistently widening the gap between these two groups (Lee 2003). A third group of less successful early innovators, constrained by modest market returns, could not sustain the high levels of R&D investment needed for risky innovation, and have either morphed into imitators or vanished altogether. This study demonstrates the stickiness in early strategic choices, as they get reinforced and perpetuated by their own consequences.

2.3.6.2 The Importance of Investing in Own R&D

Synergies between biotech firms and large pharmaceutical companies seem natural given their co-specialized assets. Indeed, the multiple licensing agreements and the numerous alliances in existence nowadays can certainly attest to the significant

expected benefits from such partnerships. But if complementarity based on co-specialized assets prevails in the industry, the ensuing division of labor should have already eradicated the need of large pharmaceutical firms to invest in in-house R&D. After all, they could source numerous new projects from symbiotic relationships with research-focused firms (e.g., biotech ones). Yet, no such development has materialized. Private firms recognize the importance of investing in R&D bases of their own so that they can build and maintain the skills, the knowledge, and the organizational routines to identify and utilize the research output of others (Cockburn and Henderson 1998). Investing in leading edge research to stay current with the advancements of open science would also enhance the firms' *absorptive capacity* (Cohen and Levintal 1989, 1990).

Firms that underestimate the importance of conducting internal R&D would not only curtail their own capability to originate novel drugs but may also relinquish their ability to benefit from the innovations of others. The theoretical and practical knowledge contained in open science can be adopted more quickly and more easily by firms which have the capacity to internalize it, while adjusting it to their own needs and goals. Virtually no firm in this high-paced industry can afford to sit on the sidelines regarding R&D activities—if it did, it would essentially disqualify itself from the race to market. Therefore, investment in own R&D keeps pharmaceutical firms at the forefront of technological advancements and facilitates the assimilation of know-how obtained through partnerships.

Even the largest pharmaceutical firms have limited financial, technological, organizational, managerial, production, and commercialization capacities. To partner up with other ventures, they need internally cultivated screening capabilities to assess the innovation potential of possible partners before they commit to joining them in collaboration. Conducting R&D in-house can strengthen the firm's ability to recognize promising projects initiated by others. It can also be a strong and favorable signal to the stock market, reasserting the firm's aptitude to generate innovation independently of others.

But there could be another, less apparent strategic reason behind incumbents' reluctance to curtail investments in own R&D. Gans and Stern (2000) advance the argument that there are conditions under which incumbents may consider biotech firms' R&D a strategic *substitute* for their own research, rather than a complementary asset they can easily acquire. In the presence of a market for ideas, incumbents obtain bargaining power if they develop and maintain cutting-edge R&D capabilities of their own. For the biotech firms, incumbents' own R&D constitutes a credible threat of potential competition, particularly if information spillovers can preempt innovation outcomes. In case commercialization is costless and can be handled by biotech firms with no partner participation (i.e., in the absence of a need to engage external platforms to market), own R&D capacity assumes the role of leverage for the large pharmaceutical firms and can raise the share of the innovation rents they capture in strategic partnerships. Gans and Stern (2000) show analytically that in a dynamic bargaining game, incumbents' ability to undertake imitative R&D acts as a negative market externality that can weaken the entrant's position.

2.3.6.3 First or Late Movers' Advantage?

In the neck-breaking race to market, late entrants are generally believed to be placed at a disadvantage. They miss out on a period of uncontested market monopoly and have to fight their way into an existing competitive market. Oftentimes, late entrants need to disrupt established loyalties and displace prescription regimens, which can be rather difficult.

Notably, being a late entrant can have its advantages, too. First, late entrants can gain by monitoring the marketing strategy of the pioneer brand as they learn from its deficiencies. Second, they can benefit from the extra time to improve or differentiate their formulation. Distinguishing between innovative and non-innovative late entrants, Shankar et al. (1998, 1999) set out to examine if innovative late movers may have a competitive advantage. For conceptual consistency and to align the terminology in these studies with the exposition in Sect. 2.2.5, hereafter we equate follow-on drugs and me-too drugs to innovative late movers and non-innovative late movers, respectively.

Being the first of its kind, the pioneer drug is faced with the task of creating awareness for the entire therapeutic class. In contrast, follow-on brands enter an established market. They face a different hurdle: to build brand awareness and differentiate themselves, which might not be too difficult if their superiority is apparent. Me-too drugs' lack of a clear advantage though, places them in the least-favorable position regarding market potential and marketing effectiveness.

Using longitudinal data from 13 brands in two categories of ethical drugs for chronic conditions, Shankar et al. (1998) find that follow-on drugs, typically offering an improvement over the pioneer drug, enjoy an advantage over both the pioneer and the me-too brands. Presumably, follow-on drugs offer sufficient extra value—i.e., they are either superior in quality (e.g., offer greater regimen convenience, higher efficacy, or reduced side effects), or can sustain a lower price point. These distinctions let them expand the market further, while riding on the coattails of the pioneer brand's awareness.

Due to their competitive strengths in positioning, follow-on brands are more effective than the pioneer at converting trials into repeat purchases—a transition that is particularly relevant for the analysis of chronic condition treatments, as in Shankar et al. (1998). More repeat purchases translate into higher sales growth for the follow-on brands. Consequently, they can eventually outsell and overtake the pioneer by slowing its diffusion, while remaining relatively unaffected by other competitors' diffusion and marketing efforts. In contrast, me-too drugs, lacking a clear point of differentiation from the pioneer, are less effective with their marketing spending and attain lower repeat purchase rates compared to the pioneer and the follow-on brands.

Favorable market conditions for innovative follow-on brands will depend on the timing of their late entry relative to the stages of the product life cycle (PLC). If the follow-on brands enter in the growth stage of the PLC, they can benefit from a strong market response. In contrast, market entry in the maturity stage will face an established competitive market. Even superior late entrants may end up with limited

growth prospects as market entry during maturity shortens the proverbial window of opportunity for these brands and pits them against scores of entrenched rivals.

Analyzing sales data and marketing expenditure from 29 brands in six prescription categories, Shankar et al. (1999) find that the market response to total marketing spending by brands in the same therapeutic class steadily declines over the PLC. It is the highest at the time of pioneer entry, then declines through the growth stage and reaches its lowest point in the maturity stage. Market expansion is confined to the early stages of the PLC, which is also when marketing efforts are most effective. The market's reaction to brands' quality, however, follows an inverted U-pattern—it is the highest during the growth stage (when perceived drug improvements can expand the market most effectively given the benchmark set by the pioneer), but is relatively lower in the maturity stage. Moreover, competitor diffusion affects rivals differently: it hurts the pioneer, has no effect on growth-stage entrants, and may even help maturity-stage entrants.

In a model that focuses on competitor reactions in the case of market entry, Shankar (1999) shows that an incumbent will tend to accommodate a new entrant if the entrant is: (a) more experienced (the entrant's marketing is likely to be more effective); (b) entering with a strategy of high marketing spending (an aggressive response by the incumbent can trigger an advertising war), or (c) when the incumbent and the entrant face each other off in multiple markets (the incumbent is exposed to the hazard of retaliatory attacks in those other markets). In addition, small incumbents have limited ability to react, which is recognized by entrants as absence of competitive threats. An entrant would spend more on marketing (advertising and sales force effort) if it is a large firm and if the new drug is of a higher quality (Shankar 1999). Note that these results are also consistent with the arguments advanced in Sect. 2.3.5 to explain the expediency of downstream alliances for small biotech firms seeking the market leverage conferred by large partners.

2.3.6.4 Market Entry in the Presence of Pent-up Demand

If the new drug is indeed so revolutionary that no effective alternative has been available prior to its release, there might be a vast pent-up demand at the time of market launch. With such drugs, an atypical diffusion pattern can occur. Patients diagnosed with severe symptoms will know about the imminent launch and will be eagerly anticipating it. In this case, sales may soar sharply upon market entry, then embark on a steep decline as the wave of critical patients complete their treatment (Vakratsas and Kolsarici 2008). If the condition can be cleared relatively fast and there is no need for long-term treatment, repeat purchases will fail to materialize. However, a second market of less-intense demand can emerge, composed of the purchases made by newly diagnosed or mild case patients. The drug adoption in this second segment may evolve at a much lower rate, with sales growing gradually over time before a slow decline sets in.

Vakratsas and Kolsarici (2008) find evidence of such bimodality in the market adoption pattern for a lifestyle-related drug. The authors posit that such a pattern can stem from an underlying spectrum of treatment urgency. If need intensity can

range from severe to mild, a dual-market diffusion model with a switching regime, which is a version of the Generalized Bass Model, is warranted. Differences in need intensity can essentially create two segments, distinguished by their market potential and by their ability to postpone treatment in anticipation of follow-on drugs of enhanced value.

Subsequent research can systematically examine the market dynamics upon entry of follow-on, me-too, and generic drugs in the presence of differential effects associated with idiosyncratic class characteristics. For example, the gravity and the prognosis of the disease, or the intensity and duration of its symptoms may moderate the repeat-purchase behavior of the market, its price elasticity, or the tolerance for potential side effects, systematically changing the diffusion patterns of pioneers and late entrants alike.

Diseases can range from acute to mild, from genetic to lifestyle-induced, and may run the gamut from life-threatening conditions to brief discomforts. Some are highly contagious, others are exceedingly rare. Some can be cleared once and for all, others occur intermittently, and still others become chronic. Related symptoms can also vary from debilitating to hardly detectable. Important distinctions in market behavior may be uncovered along these dimensions, and future research can elucidate specific diffusion patterns linked to disease type, severity, and trajectory.

2.3.6.5 Factors That Affect the Market Diffusion of a New Drug

Although this volume contains another dedicated chapter on the topic of market diffusion, a brief recount of some notable findings seems warranted here to wrap up our review of pharmaceutical innovation. Rao and Yamada (1988) and Hahn et al. (1994) have developed repeat purchase diffusion models in which drug prescriptions are a function of the firm's marketing efforts (detailing to physicians) and word-of-mouth effects. As the informative role of detailing assumes higher significance with innovative drugs, as well as with drugs that address a broader spectrum of ailments, the effectiveness of detailing is shown to increase for these drug types (Rao and Yamada 1988). The effects of word-of-mouth vary by the type of prescribing physicians and are more pronounced when specialists are the source.

Empirically analyzing the market diffusion of 21 ethical drugs in seven therapeutic classes, Hahn et al. (1994) find that a brand's promotion effectiveness and the corresponding trial rates are linked primarily to the brand's efficacy and dosage, whereas the repeat purchase rate (indicator of the brand's long-term market share) is affected by the drug's side effects and dosage. Greater word-of-mouth effects are found with drugs for acute diseases.

Ding and Eliashberg (2008) examine the influences of physicians and patients on the market adoption of drugs by accounting for dyadic decision-making. Using prescription probability matrices for categories with multiple new brand offerings, the authors find that both patients and physicians can impact the prescription decisions for new drugs, but the effects would vary with symptom intensity. In case of serious symptoms, the patients' influence is limited, and the effect of brands' marketing activities is diminished.

2.4 Trends in Pharmaceutical Innovation

Fewer new drugs—symptom of declining innovation productivity? Despite the rapidly escalating R&D budgets in the pharmaceutical industry (Fig. 2.3), there seems to be a decline in the number of approved New Molecular Entities (NMEs), a trend visualized in Fig. 2.4a. The 2010 Pharmaceutical R&D Factbook, compiled by CMR International (Thomson Reuters), reports that in 2009, new drugs introduced within the last 5 years have accounted for less than 7 % of industry sales.

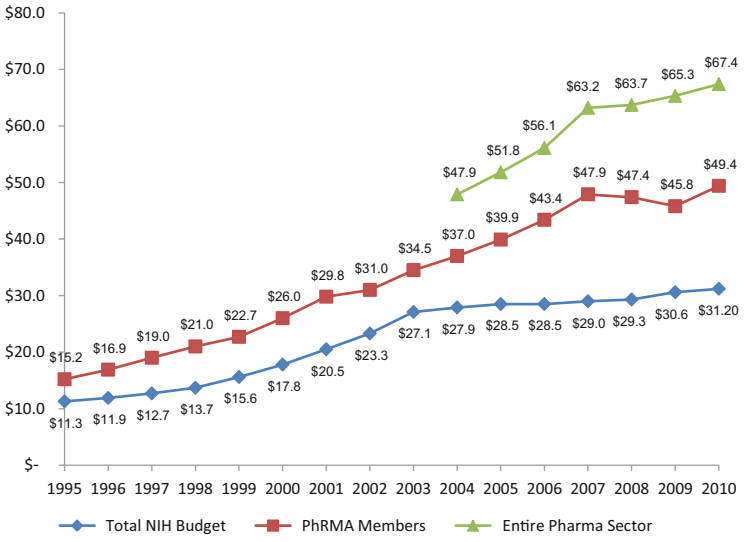

Fig. 2.3 Pharmaceutical R&D expenditure in the USA, in billions of dollars (*Sources*: Burrill & Company, 2011 PhRMA Pharmaceutical Industry Profile, NIH Office of Budget)

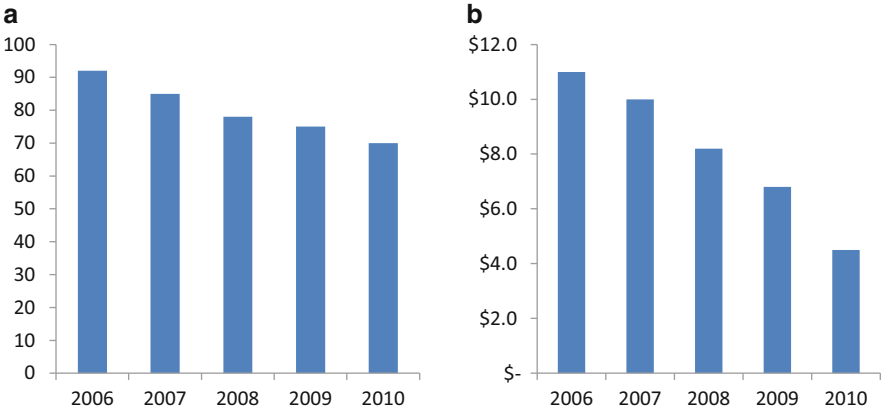

Fig. 2.4 (**a**) Number of new branded drugs in the USA (**b**) Sales of new branded drugs in the USA, in billion dollars (*Source*: IMS Institute for Healthcare Informatics)

Meanwhile, the number of experimental drug projects terminated in the final Phase 3 of clinical development has doubled in the period 2007–2009 compared to 2004–2006.

The decline in revenue from new medications seems particularly puzzling given the extraordinary biomedical and technological advances occurring in recent years: the decoding of the human genome, the transition to molecular biology and biotechnology, the development of advanced R&D techniques (e.g., high throughput screening, combinatorial chemistry, bioinformatics, rational drug design), all of which were supposed to galvanize the process of drug discovery and boost its rate of success.

Noting the dissonance between the ever-increasing R&D costs and the declining innovation outputs, analysts (e.g., Cockburn 2007) have raised the question of a possible productivity crisis in the pharmaceutical industry. The reasons for the presumed productivity crisis can be sought in the following factors noted by Cockburn (2007): (a) the vigorous drug research and successful market introductions over the last couple of decades have already created sufficiently good solutions to the "easy" medical problems, leaving the more challenging and complex diseases (e.g., cancer, HIV/AIDS, obesity, Alzheimer's, Parkinson's, diabetes) to become the focus of most firms' current R&D efforts; (b) the industry appears to have failed to make the necessary investments in human and institutional capacity to quickly turn important biological discoveries into drugs and medical devices; (c) the existing regulatory review process and its standards are not well adapted to the new research technologies; (d) the drug companies are reluctant to bring forward products with low sales potential; (e) firms seem inclined to search for blockbuster drugs, and thus, prefer to seek out candidates with novel action mechanisms and large market potential, which can be more expensive to develop or more likely to fail; (f) the current extent of collaboration in innovation between drug companies could be insufficient. Changes in firms' organizational objectives and strategies, supported by adequate modifications in the respective regulatory policies, can help overcome many of these roadblocks.

However, a more positive outlook challenges the notion of declining productivity in drug innovation by questioning the employed metrics. Properly adjusted cumulative measures (e.g., ones accounting for the increasing quality of follow-on drugs) can be a better yardstick for gauging innovative output than the simple counts of new branded drugs.

It is conceivable that in the absence of great potential for blockbuster drugs, the industry's R&D spending is directed more toward enhancing drug efficacy and safety, or improving the delivery mechanisms of already existing treatments. Therefore, the relevant innovation output might be better assessed not solely by the total number of new drugs qualified as breakthrough innovations, but also by the cumulative value of incremental quality improvements—e.g., by accounting for the relatively minor but frequent drug modifications that create extra customer value (Cockburn 2007). The ultimate measure of productivity seems to require consideration of both drug quality and total impact. Generating fewer successful treatments that are highly efficacious and targeted toward large patient groups might be of greater social and economic value than launching a large number of undifferentiated treatments in already crowded therapeutic categories.

The question of whether the pharmaceutical industry is truly in a productivity crisis, or simply going through a slow growth phase (marked by dramatic shifts toward new knowledge and technologies), is further compounded by the significant delay between R&D spending and the actual drug commercialization. This delay makes the assessment of the relationship between R&D expenses and firm productivity rather difficult. Besides, while basic research performed in government-funded research labs may not result in patentable drugs, it can boost the applied research in the private sector, from which the majority of drug patents originate. The deferred but significant benefits of R&D spillovers from the public sector make the attribution of R&D outcomes in the private sector increasingly difficult. For all these reasons, any assessment of productivity based on simple counts of regulatory approvals is bound to remain a rather crude proxy for the true pharmaceutical output (Cockburn 2007).

Emphasis on more incremental innovations. The competitive dynamics following a major patent loss might be steering the pharmaceutical industry away from its one-of-a-kind, blockbuster orientation and more toward incremental, follow-on innovations. There is a sound economic rationale in the pharmaceutical firms' endeavors to capitalize on their specialized technical knowledge and other existing assets. Most large pharmaceutical firms have invested in vast sales forces. As most of these firms are focused on certain therapeutic categories, their drug representatives would have good contacts and rapport with the physicians specializing in the treatment of a corresponding set of disease types. If the firm has new drugs forthcoming in the same category, the established contacts represent a co-specialized downstream asset that can be leveraged effectively even after the expiry of existing patents.

Besides, incremental drug innovations are easier to generate. Because of their structural proximity to approved drugs, there is a lower risk of failure. Incremental drugs are also more amenable to preplanning than blockbuster drugs. The associated cannibalization hazard or the threat of splintering the market might be more than offset by process efficiencies, reduced uncertainty, and desirable continuities in the product pipeline. By maintaining a stack of incrementally improved drugs in their product pipeline, and by releasing these follow-on drugs on a schedule timed around the patent expiration dates of older drugs, a firm can simply switch its manufacturing and marketing support to the next patent-protected successor drug, with little need for extra costs in production or distribution. A sustainable and smooth flow of new products, brought out by a robust strategy of sequential incremental innovations, can overcome the uncertainties associated with the pursuit of blockbuster drugs and generate steady streams of cash instead.

Influx of generic alternatives. Not only are fewer drugs introduced to market these days but there is also a decline in the sales of new drugs launched within the last 5 years at the expense of a gain in the sales of generics (Fig. 2.4b). The market share of generics has risen from 49 % in 2000 to 78 % in 2010. In fact, the IMS Institute estimates that 80 cents of every dollar spent on drugs in developed markets is spent on generics. Consumer spending on branded and unbranded generics has risen by 4.5 % and 21.7 %, respectively, while spending on branded drugs has declined by 0.7 % in 2010, indicating a shift to lower-cost alternatives.

The competitive landscape in the pharmaceutical industry faces ample changes due to unprecedented numbers of patents coming to the end of their duration. As more than 80 % of the brand prescription volume is replaced by generics within 6 months of patent expiration, the industry seems poised for a series of shocks triggered by a slew of upcoming patent expirations.[25]

Customized drugs. The development of targeted drugs for niche markets, individually designed drugs, or combination drugs (e.g., drugs targeting symptoms or conditions that tend to appear in tandem), is another promising tendency addressing patient needs on a microlevel.[26] Advancements in the life sciences and particularly, the decoding of the human genome, along with the versatile tools of molecular design and biotechnology, offer substantial promise that custom-built therapies will be technically feasible in the not-too-distant future. Still, customized drugs may face considerable regulatory and economic hurdles.

There is potential in the smaller markets. A persistent and salient tendency is that large pharmaceutical markets continue to attract significantly more innovation (Acemoglu and Linn 2004). Economic as well as ethical reasons can explain why R&D spending in drug innovation is prioritized for conditions and ailments affecting large numbers of people (e.g., depression, high cholesterol, diabetes, hypertension, ulcers). Because attractive markets are also likely to be populated with multiple treatment alternatives, FDA scrutiny may tighten for new approvals. New drugs can face steeper hurdles to prove they are market-worthy. In this regard, experts have called for policy regulations that make small markets more appealing, e.g., by reducing the time and the cost of regulatory reviews, maximizing the access to fundamental science and its findings, or encouraging cooperation and collaboration within the industry as a way of supporting the efforts of firms venturing into small markets.

2.5 Conclusions and Directions for Future Research

Drug innovation is not only a multibillion dollar business but also a science- and technology-driven process with exceptionally high stakes that often transcend pure commercial interests. It is a topic that finds itself in the focus of increasing attention

[25] As reported by the IMS Institute for Healthcare Informatics, in 2009–2010 the combined worth of branded drugs set to face generic market competition due to patent loss was estimated as $32.1 billion (an all-time high). Major blockbusters such as Lipitor®, Plavix®, Zyprexa®, and Levaquin®—which have accounted for more than 93 million prescriptions in 2010 and generated a total of $17 billion in sales—may soon lose market exclusivity in the USA. This trend appears to hold worldwide as, over the next 5 years, branded drugs worth a total of $142 billion in sales are likely to see their patents expire in major developed markets. Two-thirds of that loss, or $98 billion, will be from forgone sales in the US market.

[26] For example, the FDA has recently approved Merck's combination drug Juvisync, intended for the joint therapy of type 2 diabetes and high cholesterol. Enhanced patient compliance and better prevention are expected from the convenience of taking a single pill.

from researchers in economics, marketing, strategy, management, organizational theory, and social sciences alike. This thriving interest is fuelled by the unique and challenging issues the industry is facing, along with the ever-shifting opportunities and constraints associated with it. The fascination of the public with the inner workings of the pharmaceutical industry is also growing, and so is the media attention to it.

While new product development always carries a dose of risk, the exogenous locus of control in the approval of new drugs heightens the uncertainties associated with R&D spending in the pharmaceutical industry and introduces a major hurdle on a drug's route to market. Academic researchers should be well aware of the contingencies in drug innovation and properly account for them in empirical work, lest they confound effects caused by process-related externalities with market-related factors that might be more pertinent in other industries. Recognition of the intricacies in the drug innovation process can assist with the interpretation of new empirical results or alert us to specific patterns and dependencies germane to this industry.

The objectives of this chapter were to synthesize some of the existing knowledge about organizational and strategic issues in drug innovation, and to elucidate the prevalent practices, organizational forms, modes of collaboration, and patterns of interdependence that are relevant for its success. Ideally, this summary will give impetus to further research efforts and pave the way toward a more systematic understanding of the determinants and the boundary conditions related to effective and efficient drug innovation.

It is only appropriate to conclude this overview with directions and suggestions for future research. A proposed stylized framework for future study and analysis is presented in Fig. 2.5. Still, while it summarizes the drivers and decisions involved in the process of drug innovation as discussed in this chapter, it is not meant to visualize all plausible interdependencies.

A sound starting point for future examination might be to come up with an appropriate metric for innovation outcomes. Variations in the relevant measures based on differences in total generated value might need to be addressed and resolved. For example, it might be argued that innovation measures can vary across therapeutic categories, or even across disease types (e.g., treatments might be differentially weighed based on indications for acute, chronic, or life-threatening prognosis, infectious disease profiles, symptom severity, and adjusted for side effects, regimen and administration route issues, or other nonmonetary costs).

Besides, there might be a gain in identifying appropriate outcome measures for different firm types based on their likely complementary roles in the drug innovation process—e.g., public vs. private firms, or vertically integrated (pharma) vs. discovery-oriented (biotech) firms. Perhaps researchers can try to develop a more detailed inventory of measures for drug innovation, enabling a more accurate value assessment and sharper attribution of market outputs, performance, and impact. Developing guidelines for the appropriate unit transformations might be needed before a universal scale for gauging innovation outcomes can be deployed.

The already complex and heavily regulated business of drug innovation is under considerable pressures that seem hard to reconcile. Strategic choices made under

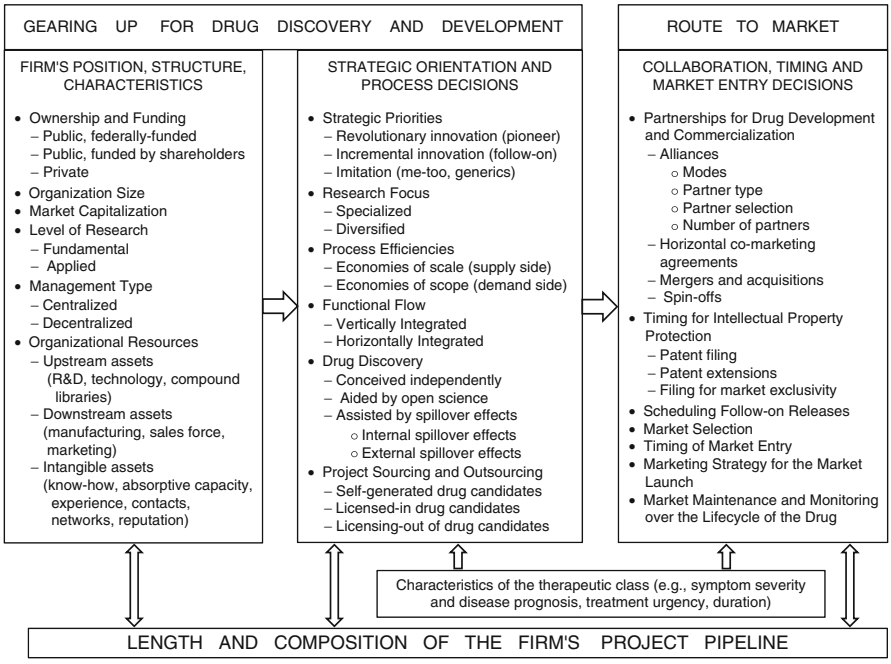

Fig. 2.5 Drivers and decisions in the process of drug innovation: suggested framework for analysis and research

massive environmental strains or in brief windows of opportunity might steer firms toward greater diversification or specialization. Firms may strive to attain process efficiencies from greater economies of scale (e.g., large volumes of production) or from greater economies of scope (e.g., serving niche markets with custom treatments). Conflicting tensions are already afoot and firms often undertake organizational restructuring to modify the scale, the scope, or the focus of their operations. Deliberate or involuntary, such transitions may have considerable consequences for the firm, the duration of its innovation process, its likelihood for success, or its cost and revenue models.

Furthermore, the attendant organizational changes may affect firms' sales and stock market performance, creating a dynamic, evolving ecosystem that would be especially worthy of detailed analysis and possibly, amenable to optimization. Examining the exceptions to the prevalent regularities, in conjunction with studying the environmental, technological, strategic, or structural factors that enable them to emerge and persist, can be illuminating. For example, if specialization can be more closely associated with economies of scale on the supply side while diversification is related to economies of scope on the demand side, then variations in the firms' respective co-specialized assets (e.g., in drug discovery, in development and manufacturing, or in marketing and distribution) might differentially affect the attainable benefits from specialization and diversification, and consequently, the strategic orientation of firms.

Judicious selection of in-licensed products and technologies may increase firms' innovation outputs, lead to greater market power, or create favorable experience and reputation effects. Such positive developments can make a firm more attractive as a potential partner. There is evidence that in-licensing begets more in-licensing. As it starts realizing increasing value from its investments, the firm itself may become more confident and proactive in seeking out additional collaboration arrangements. However, when inputs from multiple sources must be coordinated, potential downsides are overreliance on outside ideas and creative talent as well as the risk of overextending the firm's integrative and managerial capacity. A closer scrutiny of licensing dynamics will make an interesting topic for empirical research.

Researchers can also examine the impact of excessive in-licensing on the future prospects of the firm. How likely is it that a firm may become an easy prey for a takeover bid if most of its products are being sourced from elsewhere? What are the precipitating factors for acquisition compared to other forms of collaboration in the pharmaceutical industry? What are the differential effects of acquisition on the fate of the acquired firm's pipeline of drug candidates? Is there evidence that the rate of FDA approvals for two firms may undergo systematic changes when one gets acquired by the other, and what inferences can be made about the tacit knowledge and the quality of these firms' proprietary R&D before the acquisition? All these questions seem worthy of examination.

The decision to engage in a specific mode of collaboration, the factors behind the choice of a partner, the ultimate impact of that partnership on the individual firms' innovation and market outcomes, as well as the market performance of the drug(s) that are central to the partnership would constitute another fertile area for exploration. Also, it will be interesting to find out what makes a firm appealing as an alliance partner, how alliances evolve, and how they interact within more complex networks where unintended knowledge spillovers can occur. Estimating the costs of an alliance, teasing out its total added value, and understanding how this added value is created and appropriated will also be illuminating.

Future research could also look into the implications of using fundamental knowledge generated by nonprofit research institutions on the secrecy and proprietary rights demanded by private firms, if they are joined in an alliance. The signaling value on industry participants of organizational changes enacted through partnerships such as licensing, co-marketing agreements, alliances, mergers, or acquisitions could constitute another fecund area of study. Elucidating the most common pathway firms follow with the different modes of collaboration, as well as pinpointing directions amenable to optimization, can be worthwhile.

More research is needed to identify the environmental, structural, and strategic determinants that can affect drug innovation outcomes. What are the differential effects associated with firm size? How do the latest state-of-the-art technologies for drug design and discovery affect innovation productivity, FDA approval rates, sales performance, or the firms' market valuation? Are there particular technology-related bottlenecks to be resolved or underutilized process synergies to be considered from an organizational or managerial perspective?

Another line of inquiry could examine if the open science generated by the public sector (i.e., free access to the latest advancements in fundamental biomedical knowledge) affects large and small firms similarly, or whether large firms may have an advantage because of inherently greater absorption capacity. Is it the firms with a more narrow functional focus or the vertically integrated firms, the more specialized ones or those with more diversified project portfolios that are poised to benefit more from open science?

Disentangling the impact of firm-level factors contributing to the sales performance of a new drug is another area that researchers could explore. For example, how does sales performance vary with prior experience in the therapeutic class or category, changes in the marketing budget, the size of the sales force, or embeddedness in vast networks of professional contacts? How does technological experience affect new drug sales for firms with established market presence in certain categories, and what are the underpinnings of these effects? Can the sales effects be attributed to measurable improvements in drug quality or efficacy, or are they largely perceptual, derived from other signals about organizational knowledge and expertise? If the effects are mostly perceptual, does the primary locus of the perceived effect lie with the physicians, the pharmacists, the health insurance companies, or with the patients?

The world is becoming an increasingly more compact place, presenting ample opportunities for dispersed innovation and expedient collaboration. This is particularly evident to global pharmaceutical companies whose subsidiaries and research centers are already spread around the world. The effectiveness and efficiencies of different models of international collaboration in innovation, the impact of policies and laws governing intellectual property across countries, as well as the influence of local cultures and entrepreneurial climate on innovation outcomes or on alliance proclivity can be interesting to explore, too.

In summary, we believe there is an abundance of issues and themes that merit considerable research attention in the field of pharmaceutical innovation. We hope this compilation will be a useful platform for many enthusiastic researchers to join in and contribute to the burgeoning stream of studies related to the discovery and development of efficacious novel drugs.

Databases relevant for research on innovation in the pharmaceutical industry

Database name, provider	Type of data
AC Nielsen	Data on DTC Advertising
Adis R&D Insight Database	Drug pipeline database (reviews, stage, revenue forecasts)
BioScan (American Health Consultants)	Profiles and alliance information on biotech firms
CRSP/CompuStat	Financial and market data on public firms
Datastream (Thomson Financial)	Financial and market data on public firms
Delphi Pharma's Product Trends and Company Trends Databases	Historical and forecast data for top drugs and leading pharma firms
Delphion (Thomson Reuters)	Patent citations

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Database name, provider	Type of data
Factiva (Dow Jones)	Business news and articles on pharma, stock quotes
FDA Orange Book (USA), EMA (Europe)	Drug and treatment approvals data
IMS Formulary Focus	Health plan formularies
IMS Lifecycle New Product Focus	New drug launches worldwide
IMS Lifecycle R&D Focus	R&D pipeline data
IMS LifeLink	Longitudinal prescription information, patient-level metrics
IMS Midas	Worldwide drug sales, trends, market share data
IMS National Disease and Therapeutic Index (NDTI)	Patient demographics, diagnosis, treatment
IMS National Prescription Audit	National prescription activity and payment modes
IMS National Sales Perspectives	Pharmaceutical product sales to pharmacies, clinics, hospitals at actual transaction prices
IMS NPA Market Dynamics	Patient-level prescription data
IMS Pharmaquery	Healthcare systems in key international markets, local pricing and reimbursement regulations
IMS PlanTrak	Managed care plans, sales, co-payments
IMS Plantrak CoPay	Impact of health plan copayments on sales volume and market share
IMS R&D Focus	R&D pipeline data
IMS Rx Benefit Design	Drug sales volume and market share by patients' insurance benefits
IMS Specialty Market Dynamics	Market size by indication, R&D opportunities
IMS Therapy Forecaster	Ten-year therapy-level forecasts in key international markets
Lexis-Nexis	Business news and articles on pharma
Medi-Span (Wolters Kluwer)	Drug sales and price data
NDA Pipeline (FDC Reports)	Drugs in discovery or development
NICE, UK	Independent clinical reviews of treatments
Pharmaprojects (PJB)	R&D pipeline data
PHIND (Informa)	Business news and articles on pharma
R&D Insight (Wolters Kluwer)	R&D pipeline data
Recap (Deloitte)	Interfirm agreements, licensing, alliances in pharma
SDC M&A Database	Mergers, acquisitions, spin-offs, split-offs
SDI (Surveillance Data, Inc.)	Pharmacy audits, physician prescription behavior, dispensing of generics
Thomson Reuters Derwent	Information on patented drugs
Thomson Reuters Partnering	Drugs in development, partnerships, market potential
Tufts CSDD	Databases of pharmaceutical compounds in various stages of investigation
URCH Publishing	Reports and insights related to pharma
USPTO Database	US patents and trademarks
OECD, WHO, CIA World Factbook, World Bank	Economic, demographic data by country

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Chapter 3
Portfolio Management in New Drug Development

Min Ding, Songting Dong, Jehoshua Eliashberg, and Arun Gopalakrishnan

Abstract The pharmaceutical industry leads all industries in terms of R&D spend. Portfolio management in new drug development is extremely challenging due to long drug development cycles and high probabilities of failure. In 2010, a pharmaceutical company like GlaxoSmithKline (GSK) spent over USD 6 billion in R&D expenditure and managed a total of 147 R&D projects across 13 therapeutic areas in different stages of development. There are a lot of challenges in deciding on how to allocate resources to these projects in order to achieve the maximum returns. For example, how to evaluate the value and risk of each project, how to choose new projects for both short-term cash flow and long-term development, how to decide which projects to prioritize and which projects to remove from the portfolio, how to design drug development unit and incentive schemes to maximize the likelihood of success, and so forth.

This chapter reviews both practice and the state-of-the-art research and summarizes the latest insights from both industry and academia. For a manager, it provides a guide to the tools they need in portfolio management in the new drug development context. For an academic, it provides a quick overview of the extant research and points out some promising research directions.

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3.1 Introduction

The pharmaceutical industry stands among a very select set of industries tasked with the dual objectives of improving human health and creating shareholder value, while being under a tight global regulatory microscope. The combination of finite patent shelf life of existing drugs, long drug development cycles of 4–16 years (Rodriguez 1998), high probabilities of failure at every stage of development (Blau et al. 2004), the escalating costs of developing and launching drugs (Munos 2009; DiMasi and Grabowski 2007), and the gargantuan postlaunch market risks (one example being the withdrawal of Vioxx®) make for a volatile landscape that pharmaceutical firms have to navigate. While all of these conditions seem on face value to be deterrents to R&D spending, pharmaceutical firms have in fact continued to invest heavily in new drug development and lead all industries in terms of collective R&D spend (Jaruzelski et al. 2011).

Munos (2009) reports that the number of new molecular entities[1] (NMEs) approved by the US Food and Drug Administration (FDA) since the 1950s has not increased commensurate with the amount of R&D spend. Part of the reason is rising costs of obtaining regulatory approval. DiMasi and Grabowski (2007) estimate that cost of developing an NME (up to approval for marketing) is about $1.3 billion (in 2005 US dollars) when factoring in cash outlays, cost of time, and capitalizing failures, while the cost of biologic drugs is only marginally lower at $1.2 billion. Garnier (2008) acknowledges that the R&D productivity has declined as a result of increasing costs and lack of improvement in output rates, possibly due to the fact that drugs that are "easy to develop" have already been invented, leaving the industry with greater challenges to continually produce a sequence of blockbusters.

There is a broad consensus among pharmaceutical firms that successful portfolio (i.e., "a collection of projects") management of new drug projects is a necessary condition for long-term survival (Munos 2009). The strategic choices for a pharmaceutical firm are to either be a low-cost generics provider or keep generating blockbusters from a portfolio of projects that provide the cash flows to support further R&D investment. Those firms which run out of cash get acquired by firms with deeper pockets, leading to cyclical waves of merger and acquisition activity (DiMasi 2000).

It is estimated that the pharmaceutical industry will lose $90 billion in branded sales over the 2010–2014, a prime example being Lipitor®, the most profitable prescription drug in history, which went off patent in November 2011 (IMAP 2011). Pfizer, which markets Lipitor®, loses a $11 billion annual revenue stream which accounted for about a sixth of its 2010 revenues. Thus, the stakes are high for firms in maneuvering to successfully replace lost revenues with new drugs coming from the R&D portfolio. Pharmaceutical firms are increasing investments in R&D portfolios in lieu of this "patent cliff," evidenced by the growth in the number of new drugs

[1] A new molecular entity (NME) is a medication containing an active pharmaceutical ingredient (API) that has not previously been approved for marketing in any form (Munos 2009). This usually excludes biologic drugs.

under development from 5,995 compounds in 2000 to 9,737 compounds in 2010, an increase of 62 % despite turbulent economic conditions (PharmaProjects 2010).

No shortage of ideas and opinions exist given the scale and stakes of new drug development on how portfolio management should be done (Garnier 2008, etc). However, some of these ideas are beliefs and experiments-in-progress. In this chapter, we present findings of multidisciplinary research on portfolio management in relation to key managerial questions. We believe, upon sifting through the research, that many important managerial questions remain open for new research (as also noted by Stremersch and Van Dyck 2009). Our goal in this chapter is to offer industry practitioners current state-of-the-art know-how that can add to portfolio management practice, and to stimulate researchers to explore topics requiring greater attention.

With the goal of having a self-contained introduction, we organize the chapter as follows. The remainder of this section will provide definitions of portfolio management and how we categorize managerial issues, review relevant facts about the pharmaceutical industry and current portfolio management practices, and close with a summary of what has been explored in the academic literature to date. We then probe deeper into specific managerial issues within portfolio management, detail the key research papers that provide useful perspectives, and summarize the insights that practitioners can take away from research. Finally, we conclude with open questions ripe for further research.

3.1.1 Definitions and Categorization

Portfolio management is at the heart of mapping an organization's innovation strategy to the objective and balanced selection of programs and projects to maximize portfolio value to the organization. We focus on portfolio management methods relevant to the pharmaceutical industry, drawing from both industry-specific and general literature on this subject.

Cooper et al. (1998) define portfolio management as a dynamic decision process which facilitates the evaluation, selection, and prioritization of new projects, and the acceleration, discontinuation, or deprioritization of existing projects in the presence of uncertainty, changing external dynamics and strategic considerations. This definition applies well to the ethical drug industry for which R&D portfolio management holds the key to future survival as existing drugs lose patent rights and market exclusivity.

A typical pharmaceutical firm organizes its R&D portfolio by therapeutic category (Yeoh 1994), with each category containing various medical conditions targeted by research programs (also known as indications). Since each indication can be targeted by multiple projects/compounds,[2] R&D portfolio management in the

[2]The same compound could target multiple indications. Each compound-indication combination is a separate project that follows the pharmaceutical regulatory approval process. In other words, a compound that is approved by a body such as the FDA for one indication can only be marketed for that indication.

pharmaceutical industry requires best-in-class methods to maximize value creation for stakeholders ranging from shareowners to patients.

Portfolio management can be generally classified into two areas: portfolio evaluation and portfolio optimization. Portfolio evaluation is the measurement of the state of a portfolio against specified metrics, such as value and risk. Portfolio optimization comprises the optimal selection of strategies available to the firm to fulfill the given objectives. In this chapter, we summarize the existing practices and research in both these areas and discuss open questions for further research. In addition, we also discuss execution issues that are often faced by firms when implementing portfolio optimization strategies, such as organizational structure and incentive design. We do not, however, focus on the specifics of managing clinical trials with multiple new drugs and refer the reader to Senn (2007) for a comprehensive summary of statistical methods in drug development.

3.1.2 Drivers of Pharmaceutical Portfolio Management

The pharmaceutical industry leads all industries in terms of R&D spend. Jaruzelski et al. (2011) report that four out of the top five global R&D spends and eight out of the top twenty global R&D spends are by pharmaceutical firms. Of these firms, six (Roche, Pfizer, Novartis, Merck, GlaxoSmithKline, and AstraZeneca) increased R&D spend from 2009 to 2010 (ranging from 0.3 to 53 % increase) despite volatile global economic conditions. This suggests that pharmaceutical firms continue to invest heavily in their portfolios with the top eight spending between $5 billion and $10 billion per year, translating to between 11 and 21 % of annual sales.

Two unique aspects of pharmaceutical innovation worth highlighting are the long drug development cycle times (from 4 to 16 years according to Rodriguez 1998) and high probabilities of failure at every stage of development (from Discovery through Phase III). Thus, the impact of last decade's R&D portfolio is felt today, and the impact of the current portfolio will be felt 4–16 years into the future. The reality for R&D leaders in the pharmaceutical industry is that portfolios have to be constructed and evaluated in the face of extreme uncertainty about technological capability, competitive forces, and market potential.

Research using historical data on returns and costs for pharmaceutical firms suggests that both returns (Grabowski and Vernon 1990, 1994; Grabowski et al. 2002) and costs (DiMasi et al. 1991, 2003) have increased since 1970. Additionally, research from the 1970s to 1990s consistently finds a highly skewed distribution pattern of returns and a mean industry internal rate of return (IRR) modestly in excess of the cost-of-capital. Per Grabowski et al. (2002), these findings support a model of intensive R&D-based competition by pharmaceutical firms to gain economic advantage through product innovation and differentiation.

Part of the reason for increasing costs comes from increasingly stringent regulations on clinical trials (e.g., The FDA Amendments Act 2007), such that an

Table 3.1 Number of compounds in therapeutic areas[a] as of Dec 31, 2010 (PharmaProjects 2010)

	Number of compounds	Therapeutic areas
A	1,442	Alimentary/metabolic products (including gastrointestinal group)
B	447	Blood and clotting products
C	800	Cardiovascular products
D	508	Dermatological products
F	1,548	Formulations
G	480	Genitourinary (including sex hormones)
H	166	Hormonal products (excluding sex hormones)
I	543	Immunological products
J	1,710	Anti-infective products
K	2,608	Anticancer products
M	1,093	Musculoskeletal products
N	1,936	Neurological products
P	94	Antiparasitic products
R	601	Respiratory products
S	410	Sensory products
T	2,330	Biotechnology products
Total	16,716	

[a]PharmaProjects (2010) reports a compound which targets multiple therapeutic areas in both areas, hence it should be noted that there are 9,717 total compounds under development, and 16,716 projects which may target the same compound for different diseases

investment close to $500 million may be required just for the opportunity to launch a drug (Blau et al. 2004) provided it successfully passes Phase III trials. Other factors contributing to cost increases include the advent of biotechnology and the shift towards treatments for chronic and degenerative diseases (Yeoh 1994). The investment figure can vastly vary depending on the level of data required by the FDA, which in turn depends on the nature of the innovation. For instance, the costs are dramatically higher for new chemical entities (NCEs) or NMEs which represent more "radical" innovation involving new active pharmaceutical ingredients (APIs) as compared to utilizing existing entities to formulate a new drug.

It is well known that only one in every 5,000–10,000 potential compounds investigated by pharmaceutical companies is granted FDA approval (which is a critical benchmark since the USA forms the single largest market for ethical drugs sales). Thus, portfolios of pharmaceutical firms usually include compounds in diversified therapeutic categories to spread the risk of failure of any given research program or project. The top 25 firms have between 43 and 304 compounds in their portfolio (PharmaProjects 2010), with the largest portfolios coming from Pfizer (304 compounds), GSK (289 compounds), and Merck (249 compounds). It is typical for the top ten firms to source 30–40 % of the compounds in their portfolio from external parties (PharmaProjects 2010).

As of December 2010, there are 9,717 drug compounds corresponding to 16,716 projects under active development or launch (the same compound targeted at different diseases counts as multiple projects). These projects can be grouped into roughly

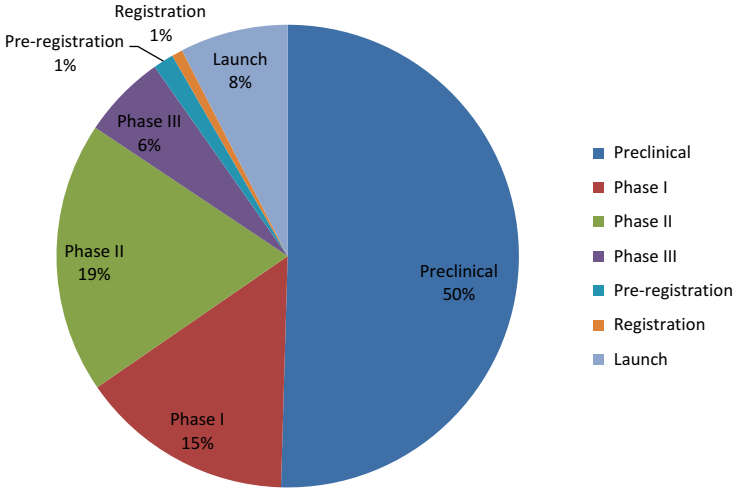

Fig. 3.1 Breakdown of drug compounds by stage of development (PharmaProjects 2010)

16 therapeutic areas/classes/groups (with differing numbers of projects in each area) as shown in Table 3.1.

About 50 % of drug compounds are in the preclinical phase, while the remainder is spread across the more advanced stages of development, as shown in Fig. 3.1.

The uncertainty of success rates by phase can be quantified using historical data. Blau et al. (2004) suggest that roughly 20 % of projects drop out after Phase I, and among the remaining projects, 80 % do not pass Phase II testing. There is no guarantee of success even in Phase III of large-scale clinical trials due to unexpected reasons that did not manifest in earlier trials. For example, from a comprehensive data base across over 200 pharmaceutical companies, Girotra et al. (2007) found 132 Phase III failures in the period 1994–2004. According to their data, a median firm (with annual sales of US$13.26 billion) experienced 6.5 Phase III failures during this time period, and one of the largest firms, Pfizer, experienced 19. Thus Phase III failures are more than infrequent anomalies and are factored into the overall capitalization of drug development costs.

3.1.3 Pharmaceutical Industry Structure

While our discussion thus far has spotlighted large pharmaceutical firms with a strong legacy of chemistry-based drug development, the last 2 decades have seen the advent of small research-oriented biotechnology firms that focus on a narrow range of compounds. These entrepreneurial ventures often partner with larger firms who have more access to capital and have expertise in conducting large-scale trials, under various types of legal structures (profit sharing, acquisitions, joint ventures).

Therefore, an increasing trend in larger firms is to balance self-originated and acquired compounds, leading to several waves of merger and acquisition activity in the early 1970s, late 1980s, and the mid to late 1990s (DiMasi 2000).

Acquisition activity has again picked up in the 2008–2010 period with large deals such as Pfizer's acquisition of Wyeth for $67.9 billion and the $41 billion valued merger of Merck and Schering-Plough. The trend for further acquisitions and licensing deals appears positive, spurred by low interest rates and firms' cash reserves. In particular, therapeutic areas such as oncology, central nervous system disorders, diabetes, and immunology are expected to be target areas for firms to "shop" for mid-to-late stage compounds to add to their portfolios (IMAP 2011).

As R&D productivity levels decline (Garnier 2008; Munos 2009), pharmaceutical firms are expected to pursue a combination of the following options: (1) acquisitions, (2) large horizontal mergers, (3) improve internal R&D effectiveness, and (4) increase alliance agreements (Higgins and Rodriguez 2006).

Public sector research institutions (PSRIs) such as universities, nonprofit research institutes, and hospitals constitute another type of player in the industry. Historically these institutions have focused on fundamental scientific research in drug development, though increasingly the boundary between public and private firms is becoming grey as even PSRIs file for patents to protect their intellectual property as a result of the Bayh-Dole Act of 1980 which allowed such institutes to own the intellectual property from federally funded research. Stevens et al. (2011) quantified the impact of PSRIs, stating that in the last 40 years, 153 new FDA-approved drugs, vaccines. and new indications for existing drugs were discovered from research in PSRIs. The most prolific PSRIs are the National Institutes of Health (NIH), the University of California system, and the Memorial Sloan-Kettering Cancer Center.

The NIH also plays a major role in drug development by allocating its funds across a portfolio, though it does not have the same objective as pharmaceutical firms which seek to profit from their innovation activities. Recently, the NIH has established a new center for advancing translational sciences (NIH 2012) to address bottlenecks in the drug development process, noting that drugs currently exist for only about 250 of over 4,400 conditions with defined molecular causes.

We suggest that the ensuing discussion of portfolio management applies equally well to small firms and public research institutes, though their strategies and resources may differ. In addition, while much of the discussion focuses on self-originated drug compounds, we also specifically address the topic of acquisitions and licensing of compounds.

3.1.4 Portfolio Management Practices in the Pharmaceutical Industry

To value portfolios, pharmaceutical firms use financial tools such as discounted cash flow (DCF) analysis or real options analysis at an individual project level. Through the course of the 1990s, pharmaceutical firms have increasing shifted

towards real options analysis (Nichols 1994), which accounts for the value of managerial flexibility in phase-by-phase decision making in drug development. To simplify the implementation of real options analysis, decision trees (Loch and Bode-Greuel 2001) are often constructed to model the choices and outcomes available, which allows for a flexible representation of risks and uncertainties.

The innovation portfolio dashboard of firms often includes metrics that indicate resource allocation/portfolio balance, process effectiveness, and performance outcomes. For instance, resource allocation can include R&D spend, human capital, distribution of projects from incremental to radical, and ratio of outside to inside sourced ideas. Process effectiveness metrics include time spent in each phase of development, and progress versus budget and target deadlines. Performance outcomes include financial measures that are only usually known after the drug is launched in the market, at which point it is managed in a business unit as opposed to research and development.

These metrics, while useful indicators of overall activity, are still at the discretion of managers who ultimately determine the appropriate portfolio management actions. Management is able to track whether strategic goals match the reality of how the portfolio is executed. Empirical evidence from Vincent et al. (2004) and Tellis et al. (2009) suggest that firm culture may be a strong driver of innovation performance. Interestingly, most of the metrics in a dashboard revolve around "hard" quantities rather than "softer" cultural descriptors.

Portfolio optimization typically involves holding a diverse portfolio of compounds and projects for large pharmaceutical firms. Bubble-chart analysis of risk versus return (Blau et al. 2004; Day 2007), strategic bucketing of various types of innovation programs (Chao and Kavadias 2008), and organizational design (Argyres and Silverman 2004) are typically used as decision levers by firms.

As an illustration, we provide a snapshot of GSK's portfolio at the end of the year 2010 in Fig. 3.2. GSK is a representative, large pharmaceutical firm with over $6 billion in R&D expenditure in 2010, translating to about 14 % of sales. From Fig. 3.2, a total of 147 projects across 13 therapeutic areas are spread across different stages of development.[3]

GSK has 34 projects in Phase I, 56 projects in Phase II, 36 projects in Phase III, 10 projects under application for approval, and 11 projects approved for launch. This totals tens of billions of dollars in investment over several years in GSK's R&D portfolio. Such a portfolio is representative of several other large pharmaceutical firms, such as Pfizer (Fig. 3.3).

To find new ways to boost R&D productivity, GSK has continually explored new organizational structures to facilitate new drug development. In 2001, GSK reorganized its new product development units into Centers of Excellence for Drug

[3]Note that pharmaceutical companies typically report their projects starting from Phase I and do not provide details about preclinical/discovery projects, since these are still in the early stage of development. This is the reason for the discrepancy between the 289 total compounds in GSK's portfolio versus the 147 projects spanning Phase I through launch.

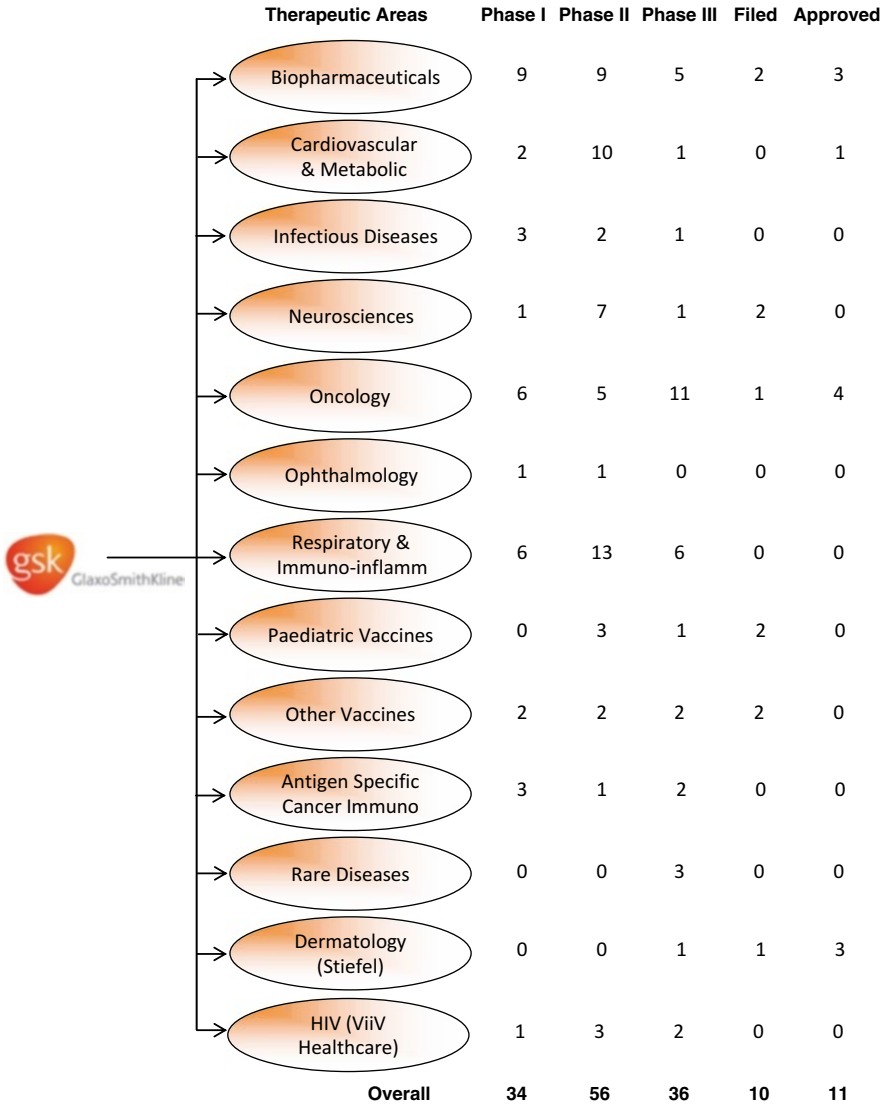

Fig. 3.2 Product development portfolio of GlaxoSmithKline (2011b)

Development (GlaxoSmithKline 2011a). GSK hoped to improve accountability and flexibility by keeping each unit small and focused (outsourcing-pharma.com 2003). A few years later in 2007, GSK launched Centers of Excellence for External Drug Discovery (CEEDDs) to marry external innovation partners and their ideas with GSK's areas of expertise. More recently, GSK has further reorganized its innovation centers into Therapy Area Units (TAUs) consisting of even smaller Drug Performance Units or DPUs (BiotechLive.com 2011). Each unit is led by a CEO with the

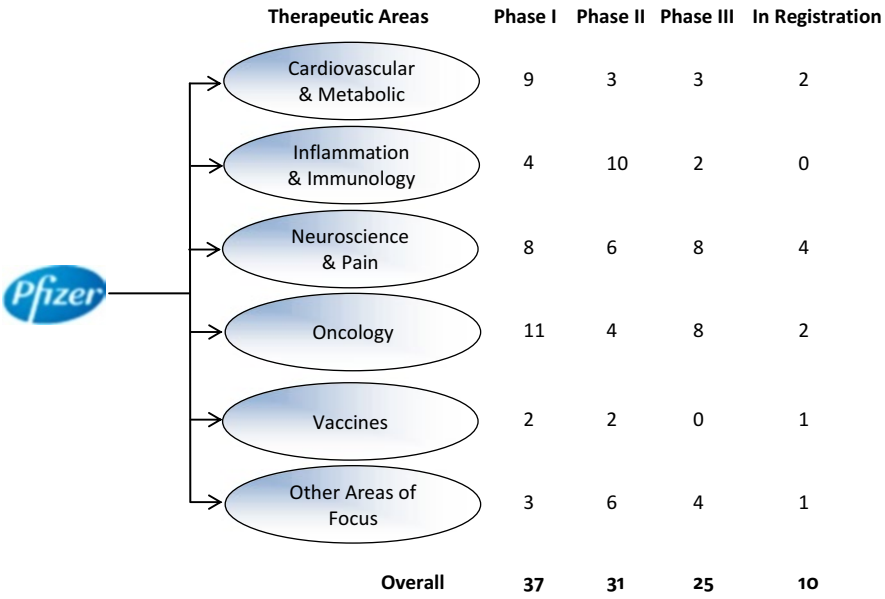

Fig. 3.3 Product development portfolio of Pfizer (2011)

authority to initiate and kill projects, with fewer management layers and increased focus on specific initiatives for scientists within a unit (Garnier 2008). Similar organizational transformations are evidenced in other firms such as Pfizer (Taylor 2009). From this example, it appears that pharmaceutical firms are still exploring optimal organizational structures to manage their R&D portfolios to combat the decline of 20 % in R&D productivity between 2001 and 2007 (IMAP 2011). Further, pharmaceutical firms are also dealing with how to minimize bureaucracy, align research objectives with incentives, and maintain balance between flexibility and control (IMAP 2011).

3.1.5 Managerial Issues Discussed in This Chapter

The remainder of this chapter covers the two major areas of portfolio management (portfolio evaluation and optimization) and discusses various execution issues in portfolio management.

To manage a new drug portfolio, the first step is to accurately evaluate a portfolio and its constituent projects. In Sects. 3.2.1 through 3.2.3, we review popular methods for evaluating the value and risk of individual projects and portfolios including decision trees, real options, and the Capital Asset Pricing Model (CAPM). In Sect. 3.2.4, we discuss managerial heuristics used in interpreting data such as portfolio measures.

In Sect. 3.3, we discuss three topics in portfolio optimization. In Sect. 3.3.1, we describe the effect of competition on overall R&D investment. In Sect. 3.3.2, we discuss portfolio composition in terms of the tradeoff between incremental and radical innovation. In Sect. 3.3.3, we discuss methods for optimal project selection and prioritization.

In addition to portfolio evaluation and optimization, we discuss four execution issues in Sects. 3.4. We separate execution from portfolio optimization based on a large literature that suggests that strategy should precede execution (Day 1990; Lehmann and Winer 2006). However, we recognize that portfolio optimization and execution can be intertwined in reality and in some cases even beneficially so, as organizations "improvise" (Moorman and Miner 1998). Thus, we suggest to the reader that clarity in portfolio optimization (which typically results from an explicit strategic planning phase) can help guide purposeful execution. Specifically, we discuss how organizational design impacts portfolio performance (Sect. 3.4.1), how to manage the frequency of change in the portfolio and organization (Sect. 3.4.2), acquisition and licensing as alternative vehicles to source new projects (Sect. 3.4.3), and incentive design to motivate decision makers to act in the firm's best interest (Sect. 3.4.4).

We conclude in Sect. 3.5 by positing open questions for future research.

3.2 Portfolio Evaluation

Managing a portfolio requires a clear definition of the metrics used for evaluation. Since the financial stakes are high in making large-scale R&D investment decisions, it is imperative to select the most diagnostic measures for evaluation. Typical metrics of interest include market value and risk of individual projects as well as entire portfolios (Davis 2002). The operationalization of value and risk are not trivial as there exist multiple ways to value innovation programs with high levels of uncertainty. Note that to produce an estimate of portfolio value, risk is often taken into account and vice versa, generating an interplay between the two metrics. In this section, we focus on methods of valuing individual projects, methods of valuing an entire portfolio, methods for measuring risk, and managerial heuristics used in interpreting data such as portfolio measures.

3.2.1 Valuation of Individual Projects

A classical approach to project valuation invokes DCF analysis. As outlined in any introductory finance textbook (e.g., Ross et al. 2003), given a set of cash flows based upon project parameter values such as cost of development over several years, projected drug sales and manufacturing costs, and the cost of capital, the NPV and IRR values can be computed and used to make decisions with a threshold rule. The

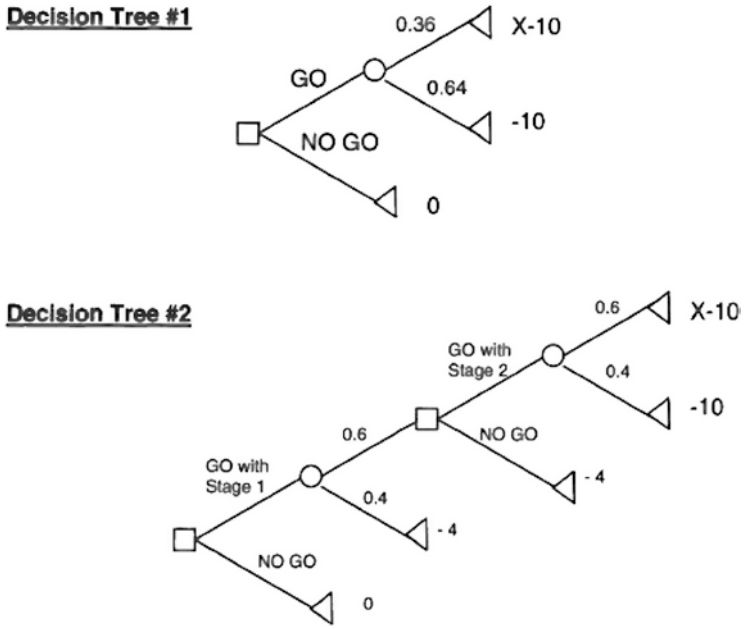

Fig. 3.4 Example decision trees (reproduced from Ding and Eliashberg 2002)

limitations of the relatively "rigid" approach of NPV are exposed in the complex and uncertain environment of drug development. There is considerable uncertainty in all costs and revenue projections, and decisions are in fact made on a stage-by-stage basis which provides considerably more managerial flexibility than NPV allows for.

An extension to NPV which takes into account the probability distributions of various parameters involves Monte Carlo analysis (Myerson 2004) to provide a distribution of possible NPVs that provides a better picture of worst, best, and expected case scenarios compared to standard DCF analysis. However, to model the phased decision-making process, methods such as real options pricing or decision trees need to be used.

While the terms "real options" and "decision trees" are sometimes used interchangeably in practice, they represent different approaches rooted in fundamentally distinct methodologies. Decision trees originate from the decision analysis literature and allow the specification of conditional probabilities of events depending on staged decisions. The payoffs are calculated from an *internal* perspective of the firm or decision maker. In Fig. 3.4, we reproduce two example decision trees in Ding and Eliashberg (2002).[4] The first tree shows a single-stage decision, while the second

[4] Another relevant example of a drug development decision tree is found in Loch and Bode-Greuel (2001).

tree shows how a phased approach can account for probabilities of success or failure along with the expected final payoff. The decision which maximizes expected value or expected utility can then be identified. This approach can be combined with Monte Carlo analysis to perform sensitivity analysis with respect to uncertain parameters.

Real options theory originates from the financial economics literature and defines value in terms of what the asset would be worth in the marketplace, not just based on its worth to the decision maker, which is a point of distinction from decision analysis (Smith 1999). Based on Black and Scholes' (1973) seminal paper on pricing call and put options, real options theory applies the principle to valuing managerial flexibility inherent in drug development projects based on the assumption that asset value over time can be modeled as a continuous-time stochastic process (Tan et al. 2010).

The key equation from Black and Scholes (1973) defines the value of an option (w) which can only be exercised at maturity date t^* for a given current asset price (x) and time (t) given exercise price c, and variance rate of the return on the asset (v^2) :

$$w(x,t) = x\Phi(d_1) - ce^{r(t-t^*)}\Phi(d_2)$$

where

$$d_1 = \frac{\ln\left(\frac{x}{c}\right) + \left(r + \frac{1}{2}v^2\right)(t^* - t)}{v\sqrt{t^* - t}} \text{ and } d_2 = \frac{\ln\left(\frac{x}{c}\right) + \left(r - \frac{1}{2}v^2\right)(t^* - t)}{v\sqrt{t^* - t}}$$

However, as Smith (1999) points out, the difficulty in solving such models when options can be exercised at any time focuses real options analyses on the evolution of a small number of stochastic factors. Smith (1999) contrasts the "dynamic complexity" of real options models with the "detail complexity" that decision trees can incorporate. In principle therefore, real options theory helps the pharmaceutical portfolio manager to factor in the potential upsides of a drug investment that may not necessarily be predictable in advance. A well-known example to illustrate this point is the development of Viagra® by Pfizer. Originally targeted at lowering blood pressure, a chance finding that it had a side effect of treating erectile dysfunction significantly boosted the drug's market potential. While not every drug may have such an upside, factoring in managerial flexibility to change course often allows for greater realism and firms have found options pricing to yield substantially higher valuations than a DCF approach (Faulkner 1996).

Loch and Bode-Greuel (2001) show that decision trees are equivalent to options pricing for risks that can be priced in the financial markets and can also capture risks that are not traded in financial markets. Thus, the downside of options pricing is the requirement for complete financial markets. However, the principle of "real options" whether modeled as a decision tree or options pricing problem brings more realism to planning for phases of development.

We now examine other approaches in the literature for project valuation. Girotra et al. (2007) measure the value of a project to the firm with the impact of its failure in Phase III. Their rationale was to use the natural experiment of a product development failure to determine the interaction effects from other projects in the portfolio. Using a combination of new drug portfolio data and stock market data, Girotra et al. (2007) show that the impact of a project's failure in Phase III is lessened when other projects targeting the same market are still being pursued by the firm. Further, the impact of a failure is also smaller if resources used in the failed project have synergies with other projects. This approach provides an *ex post* measure of a project's market value and can be a useful benchmarking exercise to compare internal valuation with that of the stock market.

Market research is one approach to developing an *ex ante* measure of project value. Conjoint analysis is a popular approach to estimate the market value of improving product attributes. Ofek and Srinivasan (2002) show that when determining the market value of attribute improvement, customers who exhibit a very high or very low probability of choosing the product should be weighted less. In addition, customers whose utility functions consist of a larger random component should be given less weight in determining market value because there is more uncertainty about their choices. We suggest that customers in this context can be interpreted broadly as stakeholders of pharmaceutical firms including physicians, health insurance firms, and patients.

We observe that the extant literature focuses either on an external measure of value (such as from the stock market, real options pricing) or internal measure of value (NPV, IRR, expected utility). An interesting research question may be to evaluate how correlated the internal and external measures are. Posed another way, does the firm or the market do a better job of valuing a new drug? Clearly, managers within a firm would have detailed insights about a project's prospects. However, due to federal regulations, data from clinical trials is publicly available information (Grewal et al. 2008) which allows the market to weigh in on the perceived value of the project. Of course, the challenging of separating a causal effect from noise in financial data is considerable and may pose a barrier that has to be overcome. Yet, since some of the key decisions for a pharmaceutical firm may involve strategic choices of therapeutic areas and preclinical resource allocations, further research can explore feasible valuation procedures that go beyond current state-of-the-art.

3.2.2 Valuation of Portfolios

While the valuation of individual projects can be useful, pharmaceutical firms also need to understand the total value potential of their portfolios. A common approach is to roll-up individual project valuations into an aggregate valuation.

Grewal et al. (2008) use an alternative approach, measuring the value of new drug portfolios using shareholder expectations derived from stock market-based indicators (Tobin's Q). They argue that the absence of historical performance for new drug portfolios makes it challenging to measure value, and propose four descriptors of portfolios that may be associated with shareholder expectations:

- Portfolio breadth: Number of different markets (therapeutic categories) targeted by a firm's new drug portfolio.
- Portfolio depth: Variation in the number of diseases targeted across therapeutic categories. This definition of depth is slightly different from a traditional notion in that it captures *variation* in the intensity of resource allocation rather than absolute number of diseases in a given category.
- Blockbuster strategy: Portfolio targeting a few diseases with high expected market potential.
- Stages of drug development: Earlier stages (preclinical trials, Phase I of clinical trials) and later stages (Phases II and III of clinical trials).

Grewal et al. (2008) show that shareholders have positive expectations of firms with higher *portfolio breadth* and *a blockbuster strategy*. For most firms, they find that the final stage of the drug development process is most critical for shareholders to form their expectations and portfolio depth is usually de-emphasized. However, for a minority of mostly small firms, the earlier stages of drug development process and portfolio depth are also valued by shareholders.

While the set of four descriptors is valuable to capture the taxonomy of portfolio strategies, the limitation of this research is that only 1 year of data was available from 308 firms. Capturing within-firm market value changes over time akin to Girotra et al. (2007) may add further insights. In general, the literature in the area of developing suitable descriptors to measure market value of portfolios is sparse, and future research can expand upon models and data from financial markets to construct more detailed descriptors.

3.2.3 Portfolio Risk

Thus far, we discussed the valuation of portfolios. However, managers are also concerned with the riskiness or spread of possible outcomes in their portfolios, and their preferences are linked to the overall strategies of the business. A small entrepreneurial biotechnology firm may place all bets on a small number of projects due to capital constraints and the desire to achieve high returns by the owner-entrepreneur. In contrast, a large pharmaceutical firm can be faced with agency issues due to separation of owners (shareholders) from managers who may be risk-averse. Thus, we may observe diversification of new drug portfolios as noted from the examples of GSK and Pfizer.

The classical measures of portfolio risk include *Beta* from the CAPM, which originates from the financial economics literature (Black 1972; Lintner 1965; Markowitz 1952; Sharpe 1964) and mean-variance.[5] These are widely used firm-level and portfolio-level measurements in the strategic management literature (Ruefli et al. 1999).

The key equation of CAPM (from Black 1972) states that under certain assumptions the expected return on an asset R_i for a given period will satisfy $E(R_i) = R_f + \beta_i[E(R_m) - R_f]$, where R_f is the return on a riskless asset for the same time period, R_m is the return on the market portfolio of assets, and β_i is the slope indicating the covariance of R_i with R_m. It essentially values an asset (e.g., a portfolio) against a set of chosen assets (e.g., a set of portfolios), and β_i is widely used as a measure of the risk of R_i.

However, the CAPM's fit to the product development setting is questioned since its assumptions are based on financial markets (Devinney et al. 1985; Ruefli et al. 1999; Wernerfelt 1985). Devinney and Stewart (1988) suggest that managers have more control over product development than financial assets, risk and return of new products may be less related than in financial assets, and that CAPM does not capture interactions among projects in a portfolio. In addition, financial economics assumes that firm-specific risk can be diversified away (Fama and Miller 1972) whereas for a pharmaceutical firm undertaking product development, the firm-specific risk component is not as easily diversifiable (acquisitions and licensing can help to some extent). Devinney and Stewart (1988) propose a generalized model that addresses these shortcomings.

Taggart and Blaxter (1992) introduce a methodology of assessing the risk associated with a firm's research portfolio by separating the technical risk and market risk components, and suggest this can be used for tracking a firm's risk profile over time. An alternative approach to yield *ex ante* measures of risk is to survey top executives (Singh 1986) or conduct market research on stakeholder risk perceptions as discussed earlier (Ofek and Srinivasan 2002).

We join Ruefli et al. (1999) in calling for further investigation of risk measures, especially tailored to the pharmaceutical drug development context.

3.2.4 Impact of Information Presentation on Decision Making

Assuming that portfolio valuation and risk are defined and measured, there remains the challenge of distilling the vast amount of information that exists about a portfolio such that managers can make decisions. This information can be summarized in multiple ways to support decision making (Ahn et al. 2010; Day 2007; Dvir et al. 2006). Decision making can be influenced both by heuristics managers use to

[5]The mean-variance approach to evaluate projects or portfolios is popular due to its ease of computation and interpretation (Ruefli et al. 1999).

interpret data (Hutchinson et al. 2010) and the format used to present information (Elting et al. 1999).

Hutchinson et al. (2010) suggest that managers use heuristics when making resource allocation decisions based on numerical or graphical data displays and that these heuristics create biases in some situations. Thus, it is of interest to better understand how portfolio metrics are communicated to and perceived by managers, and its impact on decision making due to "bounded rationality."

Three types of heuristics were identified by Hutchinson et al. (2010) in portfolio decision making: difference-based, exemplar-based, and trend-based. Difference-based heuristics examine local changes in allocations for each resource variable and compare those changes with related changes in the outcome variable. Trend-based heuristics involve "smoothing" the data to look for global trends. The exemplar-based heuristics look to imitate success via best practices benchmarking. The prevalence of benchmarking in the pharmaceutical industry suggests that managers should maintain awareness of a bias towards imitating the conditions leading to successful projects even in the absence of correlation between those conditions and success.

Elting et al. (1999) performed an experiment using 34 faculty members at the University of Texas MD Anderson Cancer Center as subjects, to determine the effect of different data display formats on physician investigators' decisions to stop clinical trials. The underlying data presented was chosen to have a statistically significant treatment effect so that the correct decision is to stop the trial on ethical grounds. The results indicated that showing the same information in the form of a table, pie chart, bar graph, or icon format did not result in the same decisions. In addition, the display formats preferred by the clinical investigators did not lead to the highest percentage of correct decisions. The takeaway for pharmaceutical managers is that when granular data such as results from clinical trials are subject to bias based on the format of presentation, higher level of summaries of R&D portfolios, whether presented as bubble charts, tables, or pie charts should also be closely examined to ensure the reduction of known biases.

We join Ziemkiewicz and Kosara (2010) in calling for a structural theory of visualization to understand how people derive meanings from visual structures. There is much research to be done in this area, especially as it relates to representation of new drug portfolio information, given the billions of dollars of investment at stake.

3.3 Portfolio Optimization

Portfolio optimization entails choosing (1) the overall level of investment, (2) the type of projects (incremental or radical innovation) to include in the portfolio, and (3) the strategy for optimal project selection and prioritization to fit the available R&D budget. Portfolio optimization is at the heart of portfolio management and a rich literature is devoted to addressing these questions, which we review in this section.

3.3.1 Overall R&D investment

A key decision for the pharmaceutical firm is to select the overall R&D spend year-after-year. This then determines the number and variety of programs and therapeutic areas can be funded. While the popular business press (e.g., Jaruzelski et al. 2011) tends to report R&D spend as a percentage of sales (top players spending about 11–21 % of annual sales on R&D), these decisions also tend to be driven by competition.

Using a dynamic game, Ofek and Sarvary (2003) show that when success enhances R&D competence, the leader firm increases R&D investment relative to rivals to sustain its position with higher probability. In contrast, when success enhances reputation (such as through brand value), the leader firm tends to expend less R&D effort relative to followers. The implication to pharmaceutical firms is obvious: increased R&D competence and market reputation from commercializing a molecule for an indication can allow for "follow-on" drugs based on similar technology. In some sense, the success of a blockbuster drug may impede the development of future blockbusters as a firm looks to capitalize on possible extensions. On the other hand, the expiration of blockbuster drugs' patents may reduce the ability of a firm to continue R&D investment and eventually lead to a merger or sale to another pharmaceutical firm. Hence, strategic investments in R&D portfolios can make or break a firm's future as an independent entity.

The intensity of competition also drives R&D investment. Recent work in the dynamic oligopoly literature (Goettler and Gordon 2011) has found that competition dampens the rate of innovation compared to a monopolist. In the context of the pharmaceutical industry, a firm which enjoys a monopoly position for a given drug and indication would be more inclined to reinvest more of the profit from being a monopolist (which enables higher prices to be set). Once "me-too" drugs are introduced, the incentive to innovate in that indication is lowered as the profitability is decreased due to competitors' entry. Hence, the optimal amount of investment in R&D may depend on level of competition rather than being a fixed percentage of sales, which is often a benchmark in the industry. Further research can examine the optimality of basing R&D on a percentage of sales basis rather than in response to competitive conditions.

3.3.2 Portfolio Composition

Selecting the appropriate balance between incremental and radical innovation and having the right mix of short, medium, and long-term developments requires a "big picture" view of the new drug portfolio and how it fits with corporate objectives.

A plethora of tools exist in the form of checklists, scoring models, and mapping tools (e.g., bubble charts) to guide managers and their teams to make decisions about portfolio strategy. Day (2007) discusses the "Is it Real? Can We Win? Is It

Worth Doing?" scoring model for constructing portfolios that balance risk and reward. In particular, Day (2007) suggests that firms across industries shy away from risky, disruptive innovations in favor of incremental ones, stemming from a risk averse attitude that can hamper long-term growth. We do not focus on the extensive variations of scoring models and strategic guideposts which are available for decision making such as the Diamond model (Ahn et al. 2010; Dvir et al. 2006; Shenhar and Dvir 2007), but examine the literature on the evidence in favor of certain strategic choices.

In the pharmaceutical context, radical innovation represents investment in developing NCEs/NMEs which involve higher risk as unproven APIs can be used. Incremental innovation tends to utilize known APIs/molecules to develop drugs, such that the hurdles for regulatory approval are lower. Another dimension that differentiates radical from incremental innovation is the complexity/level of knowledge about the mechanism of action and the corresponding a priori risk of failure. Cancer drugs may be inherently more difficult to develop than anti-infective drugs, for example. Hence, Wuyts et al. (2004) define radical innovations as those which incorporate a substantially different core technology and provide significantly greater customer benefits than previous drugs.

3.3.2.1 Does Radical Innovation Pay Off?

Lee (2003) studies the US pharmaceutical industry from 1920 to 1960 and identifies two types of firms (innovators and imitators) which react differently to the radical innovation in antibiotics in the 1940s. During that period, innovators hired more biologists and other scientists than imitators, and introduced eight times as many NCEs as did imitators between 1940 and 1960. As a result, Lee (2003) concludes that "the innovators dominated in developing new drugs and the gap between innovators and imitators steadily increased."

Wuyts et al. (2004) examine the consequences of upstream interfirm agreements on the performance of radical innovation, incremental innovation, and overall profitability. They point out that the number of R&D agreements is less informative of success than the diversity of programs and repeated partnering that fosters deeper collaboration and knowledge transfer. The importance of radical innovation to long-term profitability is highlighted based on data collected from 58 pharmaceutical firms from 1985 to 1998, covering 991 R&D agreements.

3.3.2.2 What Types of Firms Have Invested in Radical Innovation?

Sorescu et al. (2003) study the characteristics of firms which introduce radical innovations and the resulting rewards. Their data set is based on a census of innovations from 1991 to 2000 from the NDA Pipeline, a database of drugs administered by F-D-C Reports, of which 380 out of 3,891 new products introduced were breakthrough or "radical" innovations, representing only 7 % of total drugs. The sample is a cross-sectional

time-series data set of 255 radical innovations introduced by 66 firms, for which complete accounting and financial data were collected. Sorescu et al. (2003) find that (1) the majority of radical innovations come from a minority of firms, (2) the financial rewards across firms have a large variance, (3) firms with better marketing and technology support benefit more from radical innovations, and (4) firms that have a portfolio with greater depth and breath obtain higher rewards from radical innovations.

Yeoh (1994) argues that radical innovations are also characterized by their speed of global introduction, with one definition suggesting such drugs demonstrate multinational approval by at least six major industrialized countries within 4 years. Yeoh (1994) demonstrates using a dataset of "global" NCEs that such radical innovations are more likely when the development is self-originated, competitive intensity is low, and the firm has prior experience in the therapeutic category.

It seems that being an innovator and investing in radical innovation can pay off handsomely. However, considering risks and commitments associated with radical innovations, a natural question arises as to the extent a firm should focus on radical innovation versus "surer bets" that are incremental innovations.

3.3.2.3 Selection and Balance between Incremental and Radical Innovation

When should firms favor incremental versus radical innovation? Ali et al. (1993) examine the effects of firm characteristics on project selection. They set up a game-theoretic model in which duopolists face two business opportunities and two alternatives strategies, i.e., a radical innovation project and an incremental innovation project. Firm characteristics such as their differential efficiencies in completing projects, differences in the degree of substitutability between the two types of products, and first mover advantages are examined. They find that beyond the project development costs and reward flows, some firm characteristics (e.g., firms' comparative efficiencies in developing projects), project characteristics (e.g., technical uncertainties), and market characteristics (e.g., potential demand substitutability between different types of new products) will all affect the optimal choice between a radical innovation project and an incremental innovation project.

Chao and Kavadias (2008) use a theoretical framework based on strategic buckets to examine the balance between incremental and radical innovation. Strategic buckets divide the R&D budget into a set of smaller subsets each of which is aligned with a particular innovation strategy, to lower the bias of project valuation tools such as NPV or real options against radical innovation due to the long-term rewards and high likelihood of failure if the entire portfolio was considered as a whole. They point out the trend among firms to move towards incremental-innovation-dominated portfolios and suggest that the right balance depends on the amount of interaction between performance drivers such as technology and market parameters (complexity) and the degree of environmental instability. Specifically, the portfolio should emphasize radical innovation when there is high complexity but low instability (as radical innovation can break away from local performance optima), and incremental

innovation when there is neither high complexity nor stability, or when there is instability but not complexity (as instability may not provide enough time for radical innovation to realize results). In the scenario where both complexity and instability are present, the balance of the portfolio depends on the parameters and does not have a clear cut direction.

Another stream of research suggests that the choice of innovation strategy is affected by a firm's position in the market. Kauffman et al. (2000) model technology development as a search problem in the space of technological possibilities. Incremental innovation is modeled as searching over small distances relative to the starting point, and radical innovation is modeled as searching over large distances. Using simulation and analytical tools, they conclude that if a firm's position is poor or average at the initial position, it is optimal for the firm to search far away (i.e., to conduct radical innovation). Once the firm finds the technological improvement (succeeds in the radical innovation), it is optimal to limit its search to a local region on the technology landscape (i.e., to conduct incremental innovation).

The key equation governing the firm's optimal search strategy is given by:

$$(1-\beta)z_c(d) = -c(d) + \beta \int_{z_c(d)}^{\infty} \left(\theta - z_c(d)\right) dF_d(\theta)$$

where d is the search distance, $z_c(d)$ the reservation price, β the discount factor, $c(d)$ the search cost, and $F_d(\theta)$ the cumulative distribution of "technology efficiency" at distance d. The firm should search at the distance with the highest reservation price.

However, DiMasi (2000) presents empirical evidence which contests this theoretical result. The firms with the most number of NCEs in the period from 1963 to 1969 continued to dominate filings of NCEs from 1969 to the 1990s. Though the percentage of NCEs that were self-originated declined from 71.6 to 60.9 % from the 1960s to the 1990s, the data does not seem to support that innovators "sit on their laurels" after initial successes. However, as a counterpoint, the increasing growth in small biotechnology firms that take on radical innovation projects, and their subsequent licensing deals with big pharmaceutical firms suggests that there may be areas in which Kauffman et al. (2000)'s theory may apply.

To summarize the discussion on radical versus incremental innovation, we note that extant literature has suggested a variety of conditions and reasons to pursue either type of innovation. It appears that the decision depends on both firm characteristics and the external environment. One opportunity for further research is to consider how to construct a portfolio that balances the two approaches. Most of the previous work focused on an "either-or" choice between incremental and radical innovation, whereas per Day (2007), the real decision is how much of each type to include in the portfolio. Achieving the right balance requires alignment with the goals of the organization. However, we suggest that firms which focus too heavily on incremental innovation may want to consider the opportunity cost of not investing in areas which promise higher returns (albeit with higher risk).

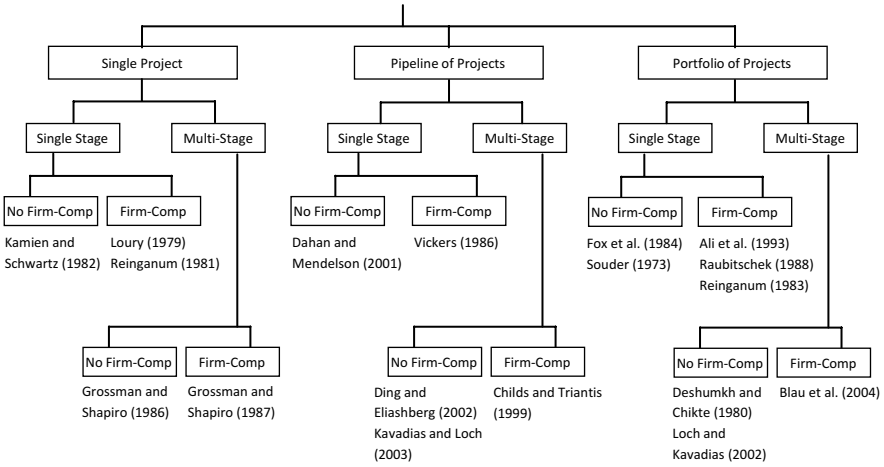

Fig. 3.5 A taxonomy of project selection problem, updated from Fig. 3.1 in Ali et al. (1993)

3.3.3 Optimal Project Selection and Prioritization

Once strategic choices are made regarding the areas and types of projects to undertake, the resulting possibilities of projects to resource still require prioritization as no one firm has unlimited resources to take on all potential projects. In this subsection, we review methods for optimal project selection and prioritization, and follow up with a discussion on interactions among projects.

Ali et al. (1993) provides a nice summary of the models dealing with project selection problems. We update their taxonomy to accommodate the recent studies relevant to the pharmaceutical industry (Fig. 3.5).

In order to accommodate a wider range of approaches, we altered the taxonomy as follows. In our taxonomy, "Single Stage" and "Multi-Stage" refer to the number of decision stages (which need not correspond to the number of stages of the drug development process). Moreover, the notation "No Firm-Comp" means no firm-level competition is modeled; it does not necessarily mean the model assumes no firm-level competition. Additionally, "Firm-Comp" means firm-level competition is modeled.

3.3.3.1 Prioritization Using Optimization Methods

The Pearson index (Pearson 1972) and Gittins index (Gittins 1979) are two widely used indices for prioritizing projects in a portfolio. An excellent summary of the differences between these indices is provided in Talias (2007), who models an R&D project as a Markov decision process.

The Pearson index is a profitability index of a project. It is defined as:

$$\text{Pearson Index} = \frac{E[\text{Net Value}]}{E[\text{Cost}]} = \frac{R\prod_{i=1}^{n} p_i - \sum_{i=1}^{n}\left(c_i \prod_{k=0}^{i-1} p_k\right)}{\sum_{i=1}^{n}\left(c_i \prod_{k=0}^{i-1} p_k\right)}$$

where R is the final reward, $c_i\ (i=1,\ldots,n)$ is the cost in stage i, and $p_i\ (i=1,\ldots,n)$ is the conditional probability of success given success at the previous stages $p_0 = 1$. It is the optimal decision rule according to Neyman–Pearson lemma (Neyman and Pearson 1933) and can be used to decide whether a project should be implemented or not by ranking all potential projects.

The Gittins index is used in a sequential selection setting (also known as a multiarmed bandit problem) in which resources must be dynamically allocated among several independent alternative projects, each divisible into stages. The Gittins index solves the problem by associating each project with a priority index and picking the project with the largest current index using the following form:

$$\text{Gittins Index} = v_i(x_i) = \sup_{n>1} \frac{E\left\{\sum_{t=1}^{n-1} \alpha^t R_i\left[x_i(t)\right] \mid x_i(1) = x_i\right\}}{E\left\{\sum_{t=1}^{n-1} \alpha^t \mid x_i(1) = x_i\right\}}$$

where $n > 1$ is the number of stages, $0 < \alpha < 1$ is a fixed discount factor, $x_i(t)$ is the state of project i in stage t, and $R_i\left[x_i(t)\right]$ is the contemporaneous reward given the state of project i in stage t. Therefore the numerator represents the expected discounted reward for project i up to n stages; the denominator represents the expected discounted time up to n stages. Hence, the Gittins index is "the maximum expected discounted reward per unit of expected discounted time" (Talias 2007). It is an example of a Dynamic Allocation Index that is updated at each decision node to reprioritize projects.

Talias (2007) suggests that the Pearson index is appropriate in a static context where selected projects will be implemented, and the rest will never be considered again. However, in a dynamic scenario, the Gittins index is more appropriate as it maximizes the expected reward accumulated sequentially.

Ad hoc linear and nonlinear programs can also be formulated using some of the above approaches as starting points, while adding constraints specific to a particular firm (Dickinson et al. 2001). These can bring more realism to the problem definition beyond a mathematical definition of optimality. Loch and Kavadias (2002) develop a dynamic programming model of portfolio choice in which marginal analysis is used to demonstrate the structure of optimal policies. The unit of analysis is not a single project but resource allocation of a limited budget across strategic programs. They provide a closed form characterization of the optimal policy in the presence of a number of project and market characteristics and provide a theoretical basis to validate managerial "rules-of-thumb" on how the optimal allocation policy would change with these characteristics.

Table 3.2 A summary of dynamic project selection studies related to the pharmaceutical industry

Study	Pipeline vs. Portfolio	Number of stage	Cost/ resource interaction	Outcome/ technical interaction	Benefit/impact interaction	Methodology
Dahan and Mendelson (2001)	Pipeline	Single	No	No	No	Analytical
Ding and Eliashberg (2002)	Pipeline	Multiple	No	No	No	Analytical
Kavadias and Loch (2003)	Pipeline	Multiple	Yes	No	No	Analytical
Childs and Triantis (1999)	Pipeline	Multiple	Yes	Yes	Yes	Simulation
Loch and Kavadias (2002)	Portfolio	Multiple	Yes	No	Yes	Analytical
Blau et al. (2004)	Portfolio	Multiple	Yes	Yes	Yes	Simulation

As an extension of the Gittins index, Kavadias and Loch (2003) set up a model in which there are multiple projects but only one scarce resource (could be scientists, lab time, budget, etc). Only one of the project can use this scarce source at a time. If the projects are independent of one another and equally affected by delays, this reduces to a multiarmed bandit problem solved by the Gittins index. However, if projects are affected differently by delays, as is likely the case in a diverse portfolio, a new policy is needed. The dynamic prioritization policy of Kavadias and Loch (2003), called the "Expected Delay Loss Index," is to work on the project "with the highest expected delay loss as if the other project was completely finished first," and prove it to be optimal if (1) the delay cost increases with the delay regardless of the performance state, (2) costs are not discounted (or, discounting is dominated by delay costs), (3) projects are not abandoned based on their performance state during processing at the scarce resource, and (4) there are no stochastic delays.

3.3.3.2 Prioritization Using Decision Trees

Another stream of literature on solving project selection and sequencing problems uses decision trees. Approaches using decision trees consist of analytical methods (e.g., Dahan and Mendelson 2001; Ding and Eliashberg 2002) and simulation methods (e.g., Blau et al. 2004; Childs and Triantis 1999). Analytical methods provide closed form solutions which suggest clearer causal relationships, but simulation methods are able to accommodate complex scenarios which give the model a more realistic flavor. In Table 3.2, we categorize the key papers mentioned above.

We define a pipeline[6] as a series of new drug developments targeting one business opportunity (a single indication). The key question revolves around the number of projects/products a firm should keep in the pipeline.

Dahan and Mendelson (2001) examine a setting in which there is only one stage of product development and multiple potential projects can be tested in parallel. They investigate the trade-off between the benefits and costs by assuming that the profits follow extreme-value probability distributions. The key result is that optimal number of projects for a pipeline is the ratio of the scale parameter of profit uncertainty to the cost per project. In other words, greater profit uncertainty or lower cost per project drive a fatter pipeline.

Ding and Eliashberg (2002) take a further step and study the optimal number of projects to be funded at each stage in a multiple stage development setting. They find the optimal structure of the pipeline (i.e., the pipeline with optimal number of projects at each stage) is determined by the cost of developing a project, its success probability, and its expected reward. Comparing their normative results with empirical practice data, they find that firms tend to have fewer projects in their pipelines than the optimal structure. Hence, pharmaceutical firms may be better off increasing the investment for a given pipeline. However, even if the optimal number of projects in the pipeline is determined, a sequencing of funding these projects may be needed if resources are scarce (which is usually the case).

Childs and Triantis (1999) conduct a simulation scenario analysis which accommodates multiple characteristics of R&D projects, including learning-by-doing, collateral learning between different projects in the program, interaction between project cash flows, periodic reevaluations of the program, different intensities of investment, capital rationing constraints, and competition. Their model considers complex interactions of multiple factors and is therefore much more realistic. However, they do not obtain analytical optimal policies. Childs and Triantis (1999) demonstrate that it may be profitable for a firm to fund multiple projects even if only one can be launched, and during the development procedure, it is possible that the firm may alter its prioritization policy significantly at different stages. The findings from the simulation model appear to fit the reality of pharmaceutical innovation fairly well.

Blau et al. (2004) propose a simulation-based approach to selecting sequences of projects in a portfolio, which maximizes the expected economic returns for a given level of risk and budget. They do not obtain closed form optimal solutions, but demonstrate an improvement of 28 % in expected return using the simulation approach as compared to a traditional bubble chart approach. The approach takes into account interdependencies among projects which is otherwise difficult to quantify in closed form.

[6]Note that the term "pipeline" is sometimes used interchangeably with the term "portfolio" in the business press. Our definitions for each of these terms are distinct and not synonymous with one another.

3.3.3.3 Interactions Among Projects

Extant literature has recognized the importance of considering project interdependencies in portfolio selection decisions (Aaker and Tyebjee 1978; Baker and Freeland 1975; Blau et al. 2004; Childs and Triantis 1999; Czajkowski and Jones 1986; Dickison et al. 2001; Santhanam and Kyparisis 1996; Weber et al. 1990; Weingartner 1966).

Gear and Cowie (1980) specifically distinguish between two types of interdependencies in R&D: *internal* and *external* interaction. Internal interaction exists when the resource requirements and benefits of a project are impacted (in magnitude and/or timing) by the selection or rejection decisions of other projects. Fox et al. (1984) further classify the internal interactions into three categories: (1) cost or resource utilization interaction; (2) outcome, probability, or technical interaction; and (3) benefit, payoff, or effect interaction. External interaction or "shocks" arises over time from overall environmental changes in social and economic conditions whose effects cut across multiple projects.

For example, if a firm could pursue two projects which require common skill sets, it could leverage the same pool of personnel, thus achieving cross-fertilization of ideas and avoiding duplication of skill sets in the organization. However, the internal interaction plays a role as changing the scope of one project affects the timing and impact of the other due to common resources. An example of external interaction would be scientific knowledge addressing potential solutions to new diseases that could either depreciate the efforts of multiple projects using older technology, or provide a new market opportunity for existing projects.

The literature on optimal project selection and prioritization we have examined thus far have focused on internal interactions, while environmental changes leading to external interactions are less commonly modeled since these can quickly lead to a proliferating number of factors and large decision trees. One solution is to use simulations to model these interactions (e.g., Blau et al. 2004; Childs and Triantis 1999). However, a closed form optimal solution may still be preferable to investigate the effect of outcome/technical interactions on project selections and sequencing and is an open topic for researchers to pursue.

3.4 Portfolio Execution Issues

While accurate portfolio evaluation and effective portfolio optimization strategies are necessary conditions for developing a successful new drug portfolio, execution is where the rubber meets the road for pharmaceutical firms. Portfolio execution translates strategies into action. In this section, we discuss four execution issues: (1) the impact of organizational design on portfolio performance; (2) how to manage the frequency of change in the portfolio and organization; (3) acquisition and licensing choices (the make or buy decision); and (4) incentive design to motivate decision makers to take actions in the firm's best interest.

3.4.1 Organizational Design

While some technologies will be acquired from other firms, a large percentage of R&D spend continues to be invested in internal projects. The key question is whether to staff a centralized or decentralized R&D organization to execute a portfolio. In Sect. 3.1, we reviewed GSK and Pfizer's approach to organizational design, which is in the direction of decentralized "Centers of Excellence" (CoE). The benefit is the focus within each CoE that is realized by reduced levels of management hierarchy. However, this directly impacts the synergies that can be leveraged across programs. For example, it is possible that two different therapeutic areas may both benefit from the same underlying molecule, and decentralization may not easily enable cooperation across units.

Argyres and Silverman (2004) examine the relationship between internal organizational structure and innovation outcomes. They find that centralized R&D facilitates more distant or "capabilities-broadening" search, generating innovations with a broader impact and drawing from previous research in a wider set of technological domains. In contrast, decentralized R&D tends to encourage proximate or "capabilities-deepening" search. There is a rough analogy between this work and that of Kauffman et al. (2000), which suggests that centralized R&D organizations are better equipped for radical innovations (since they can more easily look across domains) and decentralized R&D organizations are more suited for incremental innovations. Based on their findings, the trend of firms focusing on smaller decentralized units may result in further investment into incremental drug portfolios, which could impact long-term growth.

Further research is needed to analyze the impact of different organizational structures on new drug portfolios. We suggest that facilitating some cross-fertilization of ideas across decentralized units through mechanisms such as annual technology fairs (where people come together from different units) or a corporate-level team that maps out the synergies between units may be an intermediate step. Marketers may also have a role to play in connecting market opportunities to technologies which may cut across R&D units.

3.4.2 Frequency of Change

How often should firms change course in their portfolio strategy and execution? In today's turbulent economic conditions, personnel reshuffling from top to middle management is the norm and can give rise to frequent modifications to projects within a portfolio, and the organizational design itself (consolidation, centralization, decentralization, etc). Amburgey et al. (1993) use dynamic models of organizational failure and change estimated using a population of 1,011 Finnish newspaper firms to determine that organizational change increases the hazard of organizational failure and that there is an increased likelihood of additional changes of the same

type. While this study was based on small firms with relatively simple organizational structures compared to large pharmaceutical firms, it corresponds with the reality that firms prefer to make changes whose effects they understand. This research points out that change may or may not be beneficial to organizations and depends on the circumstances. This suggests that firms should carefully consider the history of changes made in the R&D organization and in the portfolio, to assess whether further change is likely to help or hinder overall performance.

Further research from the finance literature (Kuhn and Luenberger 2010) suggests that the right timing of portfolio revisions and adjustments is essential for long-term growth in a dynamic investment situation. This builds on work in portfolio theory such as Markowitz (1952). The key insight from Kuhn and Luenberger (2010) is that a balance needs to be struck between very infrequent portfolio rebalancing (not reacting enough to changes in the economic environment) and overly frequent rebalancing (comes at a cost). This insight is applicable to R&D portfolios in the sense that changes that are too frequent can drain organizational resources in simply managing the modifications as opposed to accelerating progress to deliver on objectives. Further research can explore how to balance the twin needs of flexibility and stability in a new drug portfolio.

3.4.3 Acquisition and Licensing

There are varying opinions in literature about whether a firm should fill its portfolio via acquiring projects from other firms. Some researchers argue that acquisitions tend to hurt innovation because they may distract managers from innovation (Hitt et al. 1990), compete for funds with existing innovation projects (Hitt et al. 1991), and trigger the exodus of key employees (Ernst and Vitt 2000).

However, other researchers argue that for some firms, acquisitions could be a tonic for innovation. For example, Prabhu et al. (2005) suggest that firms with better internal knowledge have higher ability to utilize external knowledge from acquisitions. Sorescu et al. (2007) use the term "product capital" to refer to the product development and product support assets that a firm has, and argue that firms with high product capital are better able to select the right acquisition target and deploy the acquired knowledge to gain competitive advantages.

The trend, however, points to a continuation of large acquisitions, mega-mergers, and drug licensing deals (DiMasi 2000; PharmaProjects 2010; IMAP 2011). What empirical evidence supports this trend? Higgins and Rodriguez (2006) examine the performance of 160 pharmaceutical acquisitions from 1994 to 2001, and find that on average, acquirers realize significant positive returns. They find that firms experiencing the greatest deterioration in R&D productivity are most likely to undertake the acquisition of a research-intensive firm to replenish their portfolio. They also find surprisingly, that 71 % of acquiring firms either maintain or improve their product portfolios post-acquisition, leading to positive returns. They suggest pharmaceutical firms realize gains from acquisitions because of their ability to obtain

significant information about the drug portfolio of the target firm, and appropriately value their worth thereby avoiding the "winner's curse."

3.4.4 Incentive Design

Incentives affect how organizational strategies are carried out by the people tasked with execution: managers and scientists. Most pharmaceutical firms have a hierarchical structure with a Chief Technology Officer reporting to the CEO, and a further hierarchy within the R&D organization. Given the multilevel organization, misaligned incentives can result between strategists designing R&D portfolios, and the executors, or even for the strategists themselves.

Manso (2011) examines the problem of how to motivate riskier innovation projects using a principal–agent setting and finds that substantial tolerance (or even reward) for early failure and reward for long-term success is needed for agents (such as managers or scientists) to explore riskier options. If short-term success is rewarded, then agents are more inclined to choose safer options (i.e., those which can lead to incremental innovations). In publicly held firms, a real tension exists between the short-term financial results expected by investors and the need for long-term investment to provide future growth opportunities for the firm. Manso's work suggests that incremental innovations could arise endogenously due to incentives. Thus, firms need to ensure that those responsible for strategic choices and executing on them are rewarded appropriately for their decision making, especially in the high risk world of new drug portfolios.

Chao et al. (2009) examine the incentive problem for managers allocating resources between incremental and radical innovation projects, as a function of funding authority. When funding is variable (i.e., manager can use revenue from existing product sales to fund NPD efforts), the manager is induced to focus on incremental rather than radical innovation. However, variable funding results in overall higher effort towards both types of innovation as compared to fixed funding. These authors also point out a substitution effect between explicit incentives in the form of compensation and implicit incentives (i.e., career concerns). Thus, pharmaceutical firms should carefully consider the implications of how R&D programs are funded.

There is a growing body of work relating to incentives for portfolio managers. Szydlowski (2012) focuses on a situation where a firm chooses how to allocate funding for a portfolio of projects, and a manager is responsible for multitasking across these projects. This is a commonly arising scenario in R&D departments where a person may be responsible for multiple projects. Szydlowski (2012) suggests that performance-related bonuses at the project level lead to more optimal managerial behavior than issuing firm-level equity in the form of shares. Care is therefore needed in designing incentives so that managers will undertake the right amount of effort in the right projects at the right time.

Providing the appropriate incentives to the task at hand is also a challenge faced by firms. Will a one-size-fits-all incentive system drive the right behaviors, versus tailoring the incentives according to the nature of the project? Chao et al. (2011) use principal–agent theory to determine that incentives depend on the interaction of project complexity and desired type of innovation. An organization focused on incremental innovation should set higher incentives for more complex projects. However, an organization focused on radical innovation should set lower incentives for more complex projects. This finding reconciles two differing schools of thought: the first suggests that complex problems are difficult to solve and incentives should be provided to enable managers to invest adequate effort; the second suggests that incentives in fact result in lower performance for complex tasks. Chao et al. (2011) explain this dichotomy as arising due to the choice of incremental or radical innovation (what they refer to as "search distance"). Empirical validation of these hypotheses will provide useful insights to pharmaceutical firms in designing incentives in light of projects of varying complexity and varying innovation goals.

Another critical incentive design issue is to motivate managers to kill the right projects at the right time. Simester and Zhang (2010) argue that it is difficult to reward decisions to kill projects simultaneously with rewards for success. Rewarding success may mean that an agent persists with a project even if its prospects have dimmed since its inception. Rewarding failure, on the other hand, undermines motivation for persisting to find solutions to challenging projects, as it could be "argued" that the project should be discontinued. Therefore, while a firm with a large project portfolio may prefer to kill projects with low prospects, the fact that different managers are responsible for different parts of the portfolio may jeopardize the efficient updating of the portfolio over time.

Overall, there is further ground to explore the problem of incentives and the various behaviors that result in the context of pharmaceutical portfolio management, building upon the recent research in this area. We suggest that careful alignment is required between how managers and scientists are compensated and the actions the firm would want them to undertake, to preempt "moral hazard" issues.

3.5 Concluding Remarks and Open Questions

The literature on portfolio management is inherently interdisciplinary, with work from decision theory, game theory, principal–agent mechanism design, empirical data analysis, finance, simulation analysis, and statistical theory informing this crucial topic. Extant literature has made significant contributions to the theory of portfolio valuation and optimization, as well as characterizing the empirical findings from actual practices at pharmaceutical firms. Yet, significant questions remain open for further exploration which we now outline.

Research on portfolio valuation has focused on either market-based measures (using stock market reactions to discrete events) or internal measures of value (NPV, expected utility, IRR, etc). While there is a belief that both external and internal

value measures should be highly correlated, it is still open as to the extent to which both measures are related to ex-post value. In other words, which measures have greater predictive power? Does the firm or the market do a better job of valuing a new drug? Do firms know better because they have internal know-how that gives them better insights over the prospects of various projects in their portfolio? Or is it possible that the market mechanism can efficiently price the value of various projects due to the "aggregate wisdom" of investors?

In addition, accounting for synergies between projects and pipelines in a portfolio is still an open challenge. Research such as Girotra et al. (2007) and Blau et al. (2004) attempts to model the interaction effect of multiple projects. Yet, a systematic study of how organizational capabilities, know-how, and market needs come together can enhance the understanding of valuing portfolios. Modeling external shocks that can affect multiple projects in a portfolio alongside internal interdependencies will enhance understanding of prioritizing projects in a portfolio. Using Grewal et al. (2008)'s descriptors, does the diversity from higher portfolio breadth truly counteract the positive synergy from a lower portfolio breadth with greater resources allocated to fewer areas? Are firms diversifying portfolios as a result of competitive pressures akin to a "Prisoner's Dilemma" or because this is the most value-adding strategy?

We can further our understanding of portfolio diversity by considering all sources of diversity, not just in terms of therapeutic areas. For instance, partner diversity (work with few or many other firms in collaborative efforts) and product-market diversity (potential presence in multiple geographic and product segments) can also be further investigated to determine whether portfolio risk and value are optimally traded off with such choices.

Drawing upon Grewal et al. (2008), further investigations on the key descriptors of a portfolio and the key metrics that firms should use to measure portfolios' worth needs to be undertaken.

Further implications of data visualization and presentation also need to be explored. Measurement of a portfolio's state can involve hundreds of metrics ranging from extremely granular measures at the project-level to projections in multiple dimensions at the aggregate level. The literature on managerial biases suggests that the problem of managerial decision making based on such complex data is tied to how data is presented and interpreted. Do scoring models and bubble charts, so often favored by managers, enable optimal portfolio decision making? Empirical research can investigate the biases that impact portfolio management decisions as managerial judgment continues to be a key ingredient alongside analytical methods.

For portfolio optimization, a rich literature has contrasted the merits of incremental versus radical innovations. However, the choice for firms is usually not "either-or" but how much of each type to include in the portfolio. Hence, research on optimal mixtures of incremental and radical innovations would push the frontier closer to the actual decision problem for pharmaceutical firms. While tools and frameworks exist for managing portfolio risk and return (Day 2007), an assessment of how these frameworks translate into innovation outcomes would enhance understanding of what works and what does not.

A related question is whether a pharmaceutical firm should invest more efforts into fundamental science or be opportunistic with regard to external partnerships and licensing while focusing efforts on the *execution* of portfolios as well as marketing new drugs. Recent trends suggest that big pharmaceutical firms are better suited to the operational nous required for large-scale clinical trials and marketing drugs whereas small biotechnology firms explore niche areas with a strong science-based focus. This requires further research in terms of the balance between in-house research and external partnerships, and how this depends on the firm's strategy. Acquisitions, which seem to be increasingly popular, combine new drug portfolios of the acquiring and acquired organizations and it is unclear how best to "optimize" value from two sets of portfolios which may have significant overlap.

Various papers have looked at how to prioritize projects both as a dynamic and static problem. One stream of work uses decision trees, whereas another stream examines strategic choices under competition. There would be value in bringing the streams together to simultaneously consider dynamic project prioritization given competition. In other words, pharmaceutical firms are often pursuing similar therapeutic areas and indications in parallel, and viewing the prioritization decision as a purely internal exercise may not bring enough external emphasis in the sense of the battle between portfolios of firms. Theoretical work could examine this issue as it may be difficult to empirically examine how competition affects portfolios of multiple firms.

Pharmaceutical firms are frequently changing their R&D organizational structure, ranging from centralized to decentralized units. Each camp has its advocates, yet there is insufficient empirical evidence to conclude which approach is better, or at least which types of firms would prosper under each structure. The relationship between organizational structure and incremental/radical innovation appears to be strong and requires attention so that firms can understand the optimality of the choices they make. Additionally, understanding the relationship between the frequency of change and its impact on performance is crucial as pharmaceutical firms have to manage a careful balancing act between flexibility and stability. The trend in portfolio management seems to favor more flexible and accountable drug development units, and more research is needed to evaluate this approach and how it impacts portfolio optimization.

Attention is also needed on understanding how incentives affect managers and scientists in terms of their motivation to take actions aligned with firm interests. The firm is often seen as a single entity deciding and executing strategies, but the reality of multilevel hierarchical organizations executing and adapting new drug portfolios cannot be ignored. Recent theoretical work suggests that killing projects can be challenging, and that motivating riskier radical innovation may be more challenging than expected. This may be one reason why smaller firms, which perhaps have less agency issues, are able to take larger risks than large firms. The question for investigation is whether this is in fact the optimal arrangement for larger firms.

The new center for advancing translational sciences (NCATS) created by the NIH appears to be a public-private partnership effort to promote better practices in quickly delivering new drugs to patients by overcoming current bottlenecks (NIH 2012). Given the recency of the announcement (Collins 2011), there is no existing

literature on how NCATS can facilitate experimentation in innovative approaches to develop new models of drug development and delivery. For instance, interactions across disease categories will be a critical issue as therapeutics of the future may not be limited by historical designations. The areas targeted by NCATS include therapeutic target validation, chemistry, virtual drug design, preclinical toxicology, biomarkers, efficacy testing, phase zero clinical trials, rescuing, repurposing, clinical trial design, and post-marketing research (Collins 2011). With over $720 million in annual research support, NCATS presents a new opportunity for researchers to collaborate across disciplines to address varied challenges.

As can be seen, there exist a number of open questions for future research on pharmaceutical portfolio management, both on the theoretical and empirical fronts. We hope this review of current work on the topic will spur researchers across multiple disciplines to bring state-of-the-art methodologies to address these key issues.

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Chapter 4
Grassroots Innovation: A Promising Innovation Paradigm for Pharmaceutical Companies

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Abstract Pharmaceutical firms face a period of unparalleled turmoil. Major societal, technological, and regulatory challenges require firms to quickly respond to a rapidly changing environment. In particular, the issue of how to improve R&D productivity is considered *the* key challenge faced by the pharmaceutical industry nowadays. The core thesis of this chapter is that grassroots innovation programs—structured processes aimed at stimulating employees in all corners of the organization to contribute to innovation efforts—may be an essential complement to pharmaceutical firms' more traditional and top-down stage gate processes. However, academic research to guide pharmaceutical firms in the implementation of grassroots innovation is scarce. This chapter discusses an in-depth case study of a grassroots innovation process (*Innospire*) at Merck KGaA, Darmstadt, Germany. The process design and implementation was based on theoretical derivation, to facilitate the transfer of knowledge to other firms and contexts. Hence, we also discuss our

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conceptual framework, grounded in self-determination theory, which managers at other pharmaceutical (or any other innovation-intensive) firms can use to *design* their own grassroots innovation processes. We also discuss a multitude of possible future research directions in this area, with high dual impact to both academia and business.

4.1 Introduction

Pharmaceutical firms face a period of unparalleled turmoil. Major societal, technological, and regulatory challenges require firms to quickly respond to a rapidly changing environment. Healthcare practitioners and payers demand that firms bring new, better, and cheaper therapies to market while providing extensive clinical data to prove their superiority and safety. All these trends put considerable pressure on life sciences firms' innovation productivity and performance. Open the annual report from any major life sciences firm and sustainable *innovation* figures prominently as a key imperative for value creation and business growth. Academics also agree with practitioners and consider innovation and therapy creation a key research area for life sciences firms (Stremersch 2008; Stremersch and Van Dyck 2009). Unfortunately, despite this recognition, in the last decades, the suboptimal productivity of pharmaceutical firms' R&D engines is a widely recognized challenge to the industry's fate.

The cost per new molecular entity (NME) approved by the regulatory agencies to enter the market has been increasing for decades with R&D investments of the pharmaceutical industry rising at an average compounded rate of 12 % per year and the output in NMEs stagnant (Munos 2009). Even though this trend seems to have reversed in recent years—for example, approvals of NMEs by the FDA hit a 15-year high in 2012 (Osborne 2013)—the issue on how to improve R&D productivity is considered *the* key challenge faced by the pharmaceutical industry nowadays (Paul et al. 2010; Betz 2005). Garnier (2008), former CEO of GlaxoSmithKline (GSK), states that the historically low R&D productivity has been caused by the increasing size and complexity of the pharmaceutical R&D organization. According to Garnier (2008), "if not creatively managed, complexity can cause passionate engagement and courageous risk-taking to give way to risk aversion, promises with no obligation to deliver, and bureaucratic inertia" (p. 72).

Pharmaceutical firms are obviously not alone in showing bureaucratic inertia, which may stifle innovation and creativity. In a widely cited study of sustainability of innovation in large and mature firms, Dougherty and Hardy (1996) conclude that most organizations indeed exhibit a top-down approach to innovation, emphasizing control over flexibility and creativity. Such approach, however, frequently fails to engage and energize innovative employees and creates strong barriers to successful innovation (Dougherty and Hardy 1996).

Innovation theorists have for long suggested alternative sources of innovation, such as employees, consumers, and other partners (e.g., academia, suppliers, manufacturers; see von Hippel 1988). More recently, innovation and strategy scholars have converged around the notion that top-down vision, planning, and goal setting need to be complemented by other sources of new ideas, such as *grassroots*

innovation, i.e., new business ideas that arise from employees in several corners of the organization (Anand et al. 2007; Huy and Mintzberg 2003). Grassroots innovation is increasingly seen as the most natural and sustainable source of change (Huy and Mintzberg 2003).

The core thesis of this chapter is that for pharmaceutical firms, grassroots innovation programs may be an essential complement to their more traditional and top-down stage gate processes. Therefore, we propose pharmaceutical companies to adopt a proactive approach to grassroots innovation. This proposal mirrors calls by other scholars. Anand et al. (2007), for example, defend that organizations need to actively setup a process capable of offering the organizational support, political sponsorship, and access to resources needed to nurture grassroots innovation. In *The Future of Management*, Hamel and Breen (2007) advise companies to (1) dramatically accelerate their pace of strategic renewal, (2) make innovation everyone's everyday job, and (3) create a highly engaging and inspiring work environment capable of motivating employees to give their best to achieve the company's strategic goals.

Despite the increasing number of scholars defending grassroots innovation principles, there is a lack of clear practice guidelines for innovation managers on how to embrace such principles. Such lack of guidelines may be hampering firms' adoption of grassroots innovation (Grant 2008). To fill this void, this chapter (1) provides a conceptual framework that pharmaceutical managers can use to *design* their own grassroots innovation processes and (2) presents an in-depth case study (*Innospire* at Merck KGaA, Darmstadt, Germany,[1] a global pharmaceutical and chemical company) providing the practical steps needed to successfully[2] *implement* our proposed framework.

The conceptual framework, the in-depth case study, and the anecdotal evidence from other companies lead us to the following main conclusion: in line with predictions from self-determination theory (Ryan and Deci 2000), *successful grassroots programs need to promote employees' intrinsic motivation for innovation by satisfying three innate human needs—autonomy, competence, and relatedness*.

4.2 A Conceptual Framework for Grassroots Innovation

4.2.1 Grassroots Innovation Roots

The concept of grassroots innovation dates back to the 1940s and stems from an unlikely source: the Tennessee Valley Authority (TVA). TVA is a federally owned

[1] In the remainder of this chapter, for parsimony, we always refer to Merck KGaA, Darmstadt, Germany as Merck KGaA.

[2] We consider implementation of a grassroots innovation process to be successful when the business objectives that led an organization to invest in such a process are achieved. Even such objectives are firm-specific, they typical fall in one of the three major categories: (1) development of new business (increased revenues), (2) identification and development of human talent, and (3) stimulation of an entrepreneurial culture in the organization.

corporation established by the United States Congress in 1933. TVA was created to help the Tennessee Valley, a region which was particularly badly hit by the Great Depression, solve a range of problems which required innovative solutions, such as the delivery of low-cost electricity to citizens and companies and better management of natural resources.[3] On June 25, 1942, the British newspaper *The Times* published an article praising TVA's management style, which involved an approach aimed at "reconciling overall planning with values of democracy" (Selznick 1949, p. 3). To better understand TVA's response to the need for systematic generation of out-of-the-box innovations, a research project was conducted in 1942–1943 to study their "democratic" or "grassroots" method (Selznick 1949). Selznick (1949) synthesized the ideas behind this and subsequent studies, while defining three essential conditions behind a grassroots approach in the context of implementation of new programs of the public enterprise:

- *Managerial autonomy*: the local agency has freedom and power to make significant decisions regarding its innovative programs and adapt general values to local conditions.
- *Active participation by the people in the ranks*: management and government stimulate people working at state and local agencies to actively and consciously participate in the development and successful execution of the agency's programs.
- *Self-coordination*: the decentralized administrative agency becomes the key unit of administration and responsible for coordinating the resources needed, with the goal of achieving the "job to be done," thus also assuming the key role in coordinating the work of different layers of the organization (e.g., state and local programs) with the higher-level goals and vision of the federal government.

The definition has then been adapted by different authors who typically equate grassroots innovation with informal innovation processes. For example, Knight (1967) introduces the concept of bootlegging, which refers to new ideas which are developed and implemented by highly motivated employees, typically "under cover from the disapproving power in the organization until it is introduced" (p. 493). Knight (1967) also described less contrarian forms of grassroots innovation, in which groups of innovative employees join in a cohort group or coalition in order to gain sufficient political muscle to bring their innovative ideas to life. Yet, he still classified them as informal mechanisms. By the same token, Huy and Mintzberg (2003) refer to grassroots innovation as *organic change*, which they define as innovation which "tends to arise from the ranks without being formally managed" (p. 80).

Over the years, several companies have adopted grassroots innovation principles. An early adopter was 3M Corp., which has for long allowed its scientists to spend up to 15 % of their time in projects of their own interest. In the early 1980s the company was described as nurturing a culture characterized by a "loose

[3] http://www.tva.com/abouttva/history.htm.

network of laboratories and cubbyholes populated by feverish inventors and dauntless entrepreneurs who let their imagination fly in all directions" (Peters and Waterman 2004, p. 14). More recently, other firms have taken the same cultural approach to grassroots innovation. Google is known for its democratic "brink of chaos" management system, IBM for its Emerging Business Opportunities program (launched in 2000), and Whirlpool for its company-wide innovation philosophy as described in Hamel and Breen (2007). All these rely on informal mechanisms to promote grassroots innovation.

Another well-known deployment of grassroots innovation principles is the entrepreneurial bootcamp program of French telecom equipment manufacturer Alcatel-Lucent. In 2006, Alcatel-Lucent Belgium started organizing an annual Entrepreneurial Boot Camp with the goal of inspiring all employees to propose new ideas and identify new business opportunities for the company (Camacho et al. 2012). By 2012, this practice has been globally rolled out within Alcatel-Lucent from US over Europe to China and is an important component of the innovation funnel of the company and its R&D organization Bell Labs.

Grassroots innovation initiatives have also been implemented in the pharmaceutical industry. Germany-headquartered Bayer AG launched its *Triple-i* initiative in 2006. Standing for "inspiration, ideas, innovation," *Triple-i* is a grassroots innovation initiative through which Bayer seeks to strengthen the innovation culture throughout the organization and develop new lines of business consistent with the company's mission statement.[4] Employees can use *Triple-i*'s portal to submit their ideas and rate or expand on their colleagues' ideas.[5] In order to filter such ideas, innovation experts—based at Bayer's headquarters—filter the most promising ideas in terms of customer benefits, novelty, feasibility, and fit with the company's mission and portfolio.[6] The screening questions are kept simple and the whole process is quite informal and entrepreneurial. Between 2006 and 2011, more than 11,000 ideas have been submitted, 150 of which have been approved, from which five have translated into new products.[7]

[4]Goals that Werner Wenning, Chairman of the Board of Management of Bayer AG in 2006, was confident were already being achieved by *Triple-i's* first edition, see Bayer Annual Report 2006, p. 7. Available in http://www.bayer.com/en/gb-2006-en.pdfx, last accessed on March 3rd, 2013.

[5]Bayer, *Sustainable Development Report 2010*, p. 31. Available in http://www.sustainability2010.bayer.com/en/online-supplement-to-the-sustainable-development-report-2010.pdfx, last accessed on March 3rd, 2013.

[6]Waghorn, T. 2010. "How One Company Gets Its Employees Innovating." *in Forbes.com*, March, 15th. Available in http://www.forbes.com/2010/03/15/bayer-employee-innovation-leadership-managing-engagement.html, last accessed on March 3rd, 2013.

[7]Bayer News Channel (2011), "Record Participation in Triple-i," April 20th. Available in http://www.bnc.bayer.com/bayer/bnci.nsf/id/F3EF9641170DB993C12578770026A87C, last accessed on March 3rd, 2013.

Another example of a grassroots innovation initiative in the pharmaceutical industry is GSK's Spark network (Birkinshaw and Robbins 2010). Spark started as an informal network of globally dispersed marketing and R&D employees from GSK's Consumer Healthcare division. The goal was to "spark" new ideas for GSK's consumer brands. In 2008, Spark organized its first get-together: an Innovation Jam held in Kew Gardens, London. Then, in 2009, Spark championed an informal idea contest whereby network members and other employees were invited to submit new business ideas and trained on how to persuasively present them. The ideas were then voted by other employees and a winning idea was selected by delegates at GSK Senior Leaders meeting 2009 from those that made it to a Top 50 list. The winning idea was supported for future commercialization (Birkinshaw and Robbins 2010).

Some scholars claim that GSK Spark and other informal grassroots innovation initiatives (e.g., UBS's Idea Exchange, Best Buy's resilience program) have achieved modest success (Birkinshaw et al. 2011). Despite being able to find entrepreneurial talent and benefit from employee engagement, informal grassroots initiatives may sometimes miss key benefits associated with top-down innovation, such as direct alignment with the company's goals and a high level of internal sponsorship of the resulting projects (Birkinshaw et al. 2011). Hence, to be sustainable, grassroots innovation processes need to combine bottom-up passion and engagement with a structured *process* capable of guaranteeing internal sponsorship and fit with the overall strategy of the company. Such structured process needs to provide formal training and development opportunities, help employees focus on ideas that fit well with the company's mission, and ensure that the firm is able to acquire the necessary buy-in and resources.

In this chapter, we describe more in full, the experiences of Merck KGaA, a global pharmaceutical and chemical company headquartered in Darmstadt, Germany, with such a structured process for grassroots innovation. Merck KGaA's award-winning *Innospire* process, the in-depth case study we discuss later in this chapter, is one of the first examples we are aware of a more formalized grassroots innovation process in a company operating in life sciences. At *Innospire*, the full process is managed and supervised by a dedicated team, which monitors and supports participating teams since the start of the process until incubation and handoff to strategic business units. Moreover, employees are required to form self-assembled teams and to constantly work to improve their ideas and business plans, for instance, by participating in innovation bootcamps. Such formal process guarantees that participating teams have access to internal sponsors and to a series of resources set aside to help converting their ideas in new businesses for the company. Thanks to its formalization of grassroots principles, the process has shown to be sustainable in the long term.

Based on the conceptual roots of grassroots innovation and the study of cases, we define *grassroots innovation processes* as a set of mechanisms, processes, and resources which a company puts in place to (1) promote the emergence of self-coordinated and self-assembled teams (2) composed by selected employees in the ranks (typically from different organizational levels and functions) with (3)

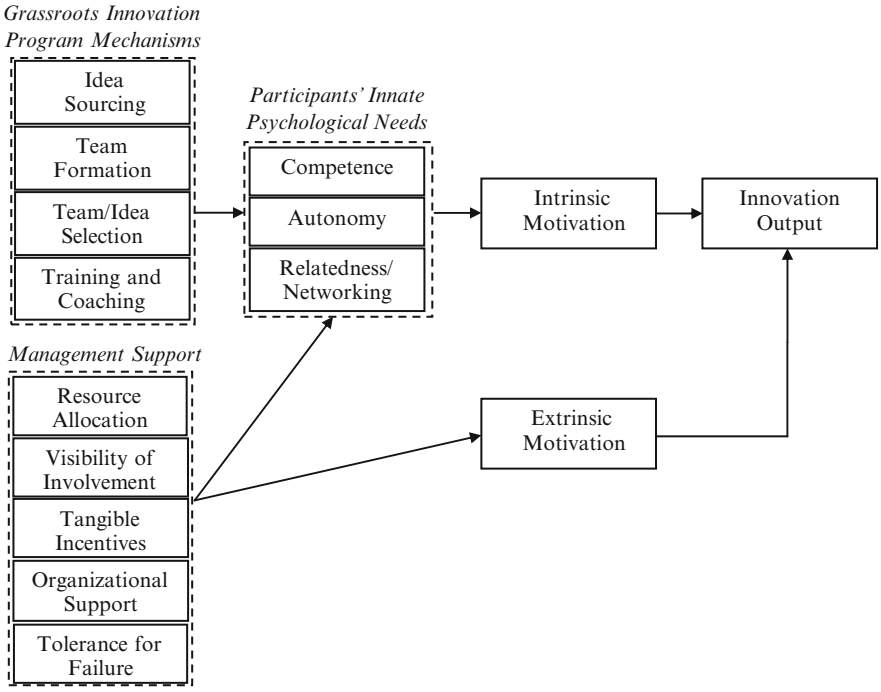

Fig. 4.1 Grassroots innovation: drivers of innovation success

sufficient managerial autonomy to propose new business ideas and, (4) who are given, conditional on predetermined strategic fit and market opportunity criteria, sufficient resources to take those ideas to market.

4.2.2 Designing Grassroots Innovation Processes: A Conceptual Framework

Our conceptual framework (see Fig. 4.1) builds upon self-determination theory (Ryan and Deci 2000) to relate the mechanisms behind grassroots innovation programs (e.g., participant selection, formation of innovation teams, the possibility for employees to receive training and coaching) to basic human needs of competence, autonomy, and relatedness and to the key drivers behind probability of success, namely, intrinsic motivation.

In addition to adequate design of the grassroots innovation program's mechanisms, management support is crucial to the success of grassroots innovation programs. We focus on key management support drivers of successful corporate entrepreneurship efforts synthesized by Hornsby et al. (2002): (1) *resource allocation*, (2) *visibility of involvement*, (3) *tangible incentives* (or rewards), (4) a structure

that fosters *organizational support*, and (5) *tolerance for failure*. We now discuss how SDT can help managers, in innovation-intensive firms[8] (such as pharmaceutical and life sciences), design better grassroots innovation programs.

4.3 Theoretical Foundation for Grassroots Innovation: Self-Determination Theory

SDT provides a comprehensive explanation of the microlevel drivers of human motivation which has been repeatedly validated in a variety of contexts (Deci and Ryan 1985, 2000; Ryan and Deci 2000), including employee motivation (Gagné and Deci 2005), which is a key driver of sustainable innovation (Amabile 1997).

4.3.1 Intrinsic Versus Extrinsic Motivation

With its origins in the concept of autonomy (Deci 1975), SDT distinguishes between intrinsic versus extrinsic motivation of behavior (Ryan and Deci 2000). Intrinsic motivation is "the inherent tendency to seek out novelty and challenges, to extend and exercise one's capacities, to explore, and to learn" (Ryan and Deci 2000, p. 70). Intrinsically motivated employees participating in grassroots innovation would thus be moved by autonomous reasons, i.e., by their authentic interest in the act of innovating and creating new business. In contrast, extrinsic motivation occurs when people are motivated by the possibility that their actions will allow them to achieve a desired consequence or avoid an undesirable one, i.e., their action is instrumental to its consequences (Gagné and Deci 2005).

Several authors have demonstrated, over the years, that intrinsic motivation, being more "authentic" than extrinsic motivation, leads to better outcomes such as enhanced performance, persistence in desirable behaviors, creativity, energy and even well-being and self-esteem (Ryan and Deci 2000). Amabile (1996) argues that intrinsic motivation boosts employee creativity. Lakhani and Wolf (2005) surveyed programmers who had voluntarily contributed code to open source software projects and found that, for almost half of them, intellectual stimulation and self-improvement were among the most important reasons cited for such time investment. Von Hippel (2005) suggests that "employees of a firm may wish to experience this

[8] By innovation-intensive firms we mean firms in sectors characterized by frequent product, service, process, or business model innovation and firms with high innovation-related expenditures and/or high R&D intensity. Hence, we believe that our framework is applicable and valuable R&D-intensive firms, such as pharmaceuticals, but also to firms in sectors—namely services—that may have lower levels of formal R&D but depend on frequent process, service, or business model innovation.

type of intrinsic reward in their works as well, but managers and commercial constraints may give them less of an opportunity to do so" (p. 61).

In contrast, some self-determination theorists argue that tangible incentives, such as monetary or other rewards contingent on task performance, may *undermine* intrinsic motivation (Collins and Amabile 1999; Condry 1977; Deci et al. 1999). Yet, not all authors agree with this claim. Baer et al. (2003), for instance, found more complex relationships whereby the effects of extrinsic rewards depend on job complexity and employees' creative problem-solving style. In psychology, Eisenberg and Cameron (1996) argue that the detrimental effects of extrinsic reward occur in restricted and easily avoidable conditions.

Hence, prior literature suggests that trying to enforce an entrepreneurial mindset *solely* through tangible incentives is unlikely to yield benefits in terms of innovation performance. This does not mean that allowing entrepreneurs to participate in the commercial success of their idea is counterproductive. In fact, prior research has shown that senior management can promote innovation by rewarding—through tangible incentives such as bonuses and opportunities for career progression—creative performance (Abbey and Dickson 1983; Jung et al. 2003). However, these tangible incentives will most likely be more impactful for employees who are already intrinsically motivated for innovation or whose motivation can be triggered with adequate organizational mechanisms.

4.3.2 Innate Psychological Needs: Competence, Autonomy, and Relatedness

In order to better understand and explain variation in intrinsic motivation, Deci and Ryan (1985) introduced cognitive evaluation theory (CET), which suggests that intrinsic motivation can be enhanced by supporting three innate psychological needs: *competence*, *autonomy*, and *relatedness* (Ryan and Deci 2000).

In the context of grassroots innovation programs, *competence* refers to participants' perceived capability, or self-efficacy, to transform their original ideas into a viable and implementable idea for a new business. Successful innovation in technology-intensive firms requires access to knowledge diversity and to channels capable of enabling the transfer of complex knowledge (Wuyts et al. 2004). At a microlevel, the need for innovation *teams* to have adequate levels of knowledge depth and diversity is also well-established (e.g., Griffin and Hauser 1996; Nakata and Im 2010; Pinto and Pinto 1990). This entails, for example, being able to actively contribute to the success of a new venture team, write a business plan, and pitch a business idea to senior management. As such, feelings of competence should be higher for people or teams with access to the relevant knowledge sources, which can be spurred by mechanisms such as team formation, training, and coaching. For example, allowing participants to form their own teams (self-assembled team formation) and providing participants with skills facilitation training and professional coaching should facilitate the team's knowledge depth and diversity.

Table 4.1 Beneficial program design features in grassroots innovation programs

Grassroots innovation program mechanisms	Suggested program design features	Benefit according to SDT
Idea sourcing	An inspiring call for ideas	Selecting employees who are *intrinsically motivated* for innovation
Team formation	Allowing participants to voluntarily join in self-assembled teams	Promoting participant and team *autonomy*. Facilitating *relatedness* and efficient *networking*
Team/idea selection	Setting meetings outside normal working hours. Carefully selecting the ideas which proceed to the next stages of the program	Guaranteeing that the teams which continue in the program to further develop their ideas are the most promising ones (select those with high *competence*). Promoting *intrinsic motivation* through "hard-won" victory
Training and coaching	Collaborating with external organizations for training and coaching of participating employees	Complementing internal knowledge and improving employees' perceived *competence* to bring new ideas to market

While competence is a necessary condition for intrinsic motivation, it is not sufficient. According to SDT, participants also need to perceive their innovation efforts to be driven by their own volition, i.e., they need to have a sense of *autonomy* (Deci and Ryan 2000; Fisher 1978). The idea call, participant/idea selection, and reliance on self-assembled teams play an important role here. Firms can use these mechanisms to attract intrinsically motivated employees and increase their perceived autonomy.

Finally, if the members of a grassroots innovation team enjoy higher levels of *relatedness*, intrinsic motivation will also be reinforced. Relatedness means that employees get along with their colleagues (e.g., other team members) and find it easy to establish mutually beneficial ties with like-minded colleagues. Certain program mechanisms, such as networking events and reliance on self-assembled team formation, help promote relatedness. Recent research proposes that a firm's ability to promote relatedness and new networks actually plays a more important role in promoting corporate entrepreneurship than participants' individual networks (Kelley et al. 2009).

In sum, successful grassroots innovation programs need to be able to promote employees' perceived autonomy (e.g., employee participation should be supported by their supervisors, but completely voluntary instead of delegated by management into a project), competence (e.g., through delivery of necessary training and coaching for employees to transform their ideas into business plans), and relatedness/networking (e.g., by promoting interaction with colleagues from different divisions, hierarchical levels, regions, etc.). In Table 4.1, above, we give examples of desirable design features, organized according to the mechanisms behind grassroots innovation programs (see also Fig. 4.1).

4.3.3 Senior Management Support

Despite the benefits of intrinsic motivation, employees often need to be extrinsically motivated by incentives such as approval and support by senior management or other tangible rewards (Gagné and Deci 2005). There is a well-established literature on the importance of senior management's role in encouraging an entrepreneurial mindset among employees (Gupta et al. 1986; Hornsby et al. 2002; Roberts and Fusfeld 1981; Quinn 1979). In the case of grassroots innovation programs, management support actions capable of motivating employees include prospects of career progression unlocked by participation in such programs, the visibility gained in the organization, the chance to access unique knowledge and new career development paths, or simply being able to work on something one is passionate about. We organize these management support actions along the five dimensions identified by Hornsby et al. (2002).

The first dimension, *resource allocation*, refers to the level of resources—such as budget, personnel, and time—that senior management invests to promote grassroots innovation. Literature in psychology and organizational behavior shows that availability of resources is associated with higher employee motivation (Schaufeli and Bakker 2004), higher employee engagement (Demerouti et al. 2001; Kahn 1992), and willingness-to-experiment and take risks (Burgelman and Sayles 1986). In grassroots innovation programs, availability of resources should promote employees' perceived autonomy (no need to constantly go through formal approval processes) and intrinsic motivation for innovation. For instance, it streamlines advancement of projects (e.g., through access to dedicated budget lines) and it signals the support of senior management to grassroots innovation.

Second, *visibility of involvement* refers to the willingness of managers to support and facilitate grassroots innovation and employees' entrepreneurial activities (Damanpour 1991; Kuratko et al. 1993). Besides allocation of sufficient resources (as discussed above), managers can increase the visibility of their involvement in grassroots innovation by championing employee innovation, by institutionalizing grassroots innovation within the firm and guarantee the involvement of senior managers in the program to signal its importance (see Hornsby et al. 2002). Innovative employees will easily relate with managers who champion grassroots innovation. Most employees will also feel that, with so visible senior management support, it will be easier to connect with other like-minded employees and establish mutually beneficial relationships with them.

The third dimension, *tangible incentives*, refers to performance-based rewards (monetary or non-monetary) aimed at spurring employees' motivation and entrepreneurial activity. Both common wisdom and prior literature (Barringer and Milkovich 1998; Hornsby et al. 2002; Sykes 1992) suggest that appropriately setting reward systems tends to spur entrepreneurial activity among employees. Yet, according to SDT the use of extrinsic reward mechanisms will only boost entrepreneurial activity if such nonintrinsic motivators are

adequately internalized by employees. A key tangible incentive which is seen as personally relevant by most employees—and thus of crucial importance for the mid- and long-term sustainability of grassroots innovation processes—is the career rewards to employees who participated and contributed to the grassroots innovation initiative. Prior literature shows that career benefits and compensation strongly influence employees' actions and decisions (Gibbons and Murphy 1992). Hence, companies should ensure that innovators and intrapreneurs get high status and recognition in the organization and that participation unlocks new career paths. In addition, companies can also offer bonuses or other financial rewards. These actions are very important for the sustainability of a grassroots innovation program as other employees will carefully monitor whether the innovators who participate in previous editions are rewarded, tolerated, or punished and whether initial top management communication is backed-up by real actions later down the road.

The fourth dimension, *organizational support*, refers to the deployment, by senior management, of a supportive administrative and organizational structure capable of supporting the grassroots innovation program (Burgelman and Sayles 1986; Hornsby et al. 2002; Zahra 1993). The boundaries of such organizational structure should typically go beyond the firm and offer channels for teams to acquire knowledge from external organizations. Cohen and Levinthal (1990) suggest that the knowledge generated by external partners may be used to complement and leverage a firm's internal knowledge and resources, contributing to higher levels of organizational innovation. More recently, Gumusluoglu and Ilsev (2009) found that external support played a key role in boosting a firm's capacity to develop and bring to market new or improved products or services. Specifically, a higher level of external support significantly increased the capacity of *transformational leaders* (i.e., those who are able to motivate their followers to transform nonintrinsic incentives into intrinsic motivation; Jung 2001) to boost innovation output (Gumusluoglu and Ilsev 2009). In terms of SDT, both an internal support organization and access to external knowledge can boost participants' sense of autonomy and competence, leading to higher intrinsic motivation and, consequently, innovation output.

The fifth and final dimension of management support is *tolerance for failure*, i.e., managers' willingness to show a tolerance for failure and to take risks in grassroots innovation (Hornsby et al. 2002). Tolerance for failure promotes employees' intrinsic motivation and willingness to undertake entrepreneurial (and risk-taking) activities (Hornsby et al. 2002). If senior managers are intolerant to failures, employees will feel less capable and willing to autonomously experiment with new ideas and learn from smart errors, hurting intrinsic motivation for innovation (Kriegesmann et al. 2005). Hence, companies should acknowledge that failure is often part of developing a successful innovation, in order to signal tolerance for failure and to promote experimentation and smart risk-taking. In Table 4.2, we summarize examples of management support actions, in each of these five dimensions, along with their predicted benefits according to SDT.

Table 4.2 Beneficial management support actions in grassroots innovation programs

Management support dimension	Suggested management support actions	Benefit according to SDT
Resource allocation	Establish a dedicated team to supervise and manage the project. The team should ensure participating teams have access to adequate budget and organizational resources for advancement and nurturing of projects Allow employees sufficient time to work on innovation projects they feel passionate about	Boost employee *autonomy* and *intrinsic motivation*
Visibility of involvement	Frequent and visible involvement of senior management in the promotion of grassroots innovation	Boost *relatedness* and *intrinsic motivation* for grassroots innovation
Tangible incentives	Provision of appropriate rewards and recognition for innovators. For example, offer participating employees incentives such as career progression or financial rewards	Boost *extrinsic motivation* for grassroots innovation
Organizational structure	Offer participating employees training in business case preparation and the chance to access new knowledge and career development paths	Boost *extrinsic motivation* for grassroots innovation. Improve employees' perceived *competence* to bring new ideas to market
Tolerance for failure	Acknowledge that failure often is part of developing a successful innovation. Avoid being too critical of breakthrough ideas too soon. Do not push or blame people when they make "smart" errors. Risk-taking	Boost *intrinsic motivation* for grassroots innovation. Improve employees' perceived *competence* to *autonomously* bring new ideas to market

4.4 The Innospire Initiative at Merck KGaA: An In-Depth Case Study

4.4.1 The Birth of Innospire at Merck KGaA

In late 2008, Merck KGaA,[9] headquartered in Darmstadt, Germany, initiated a new innovation initiative to collect and advance innovative ideas to generate new business at all levels inside the company. Merck KGaA is a global pharmaceutical and chemical company with total revenues of €10.3 billion in 2011, a history that began in 1668, and a future shaped by more than 40,000 employees in 67 countries.[10]

[9] www.merckgroup.com.

[10] In 2009 when innospire started Merck had total revenues of € 7.7 billion and approximately 33,000 employees in 61 countries.

The companies' activities come under the umbrella of Merck KGaA, in which the Merck family holds an approximately 70 % interest and free shareholders own the remaining approximately 30 %. In 1917, the US subsidiary Merck & Co[11] was expropriated and has been an independent company ever since.

Innospire, a word composition from innovation and inspiration, was designed with four main goals in mind. The first goal was to mobilize the full innovation potential of a large global organization, from all employees, across organizational boundaries. The second goal was to promote relatedness and networking across both the chemicals and pharmaceutical divisions of Merck KGaA in order to boost cross-fertilization. The third goal was to generate an environment for entrepreneurial individuals to form highly motivated teams and move forward with their new business idea. The fourth goal was to foster an innovative and entrepreneurial spirit within the organization and to signal that innovation is important, also and especially in budgetary challenging times.

The first author started the initiative to design and implement the *Innospire* program at Merck KGaA. After convincing management of the benefits of such a grassroots innovation process, the first and third authors jointly rolled it out in collaboration with the fourth author who served as a process consultant on *Innospire* and designed the bootcamp program, developed the training plan, and served as principal facilitator of the bootcamp program, delivering both skills training sessions and acting as a professional external coach for the six finalist teams. The first and third authors also acted as coaches to the teams, allowing the collection and analysis of observations and data to be collaborative.

The first idea call for *Innospire* was launched in 2009, about 9 months after starting the preparation. The branding and communication of *Innospire* was carefully planned to appeal to intrinsically motivated employees and spread through extensive distribution via Merck KGaA's internal systems. In its first edition, more than 462 ideas from 550 idea champions—some ideas were joint submissions with multiple idea owners[12]—were submitted from all corners of the organization, from all divisions, and from 32 countries all over the world, affording ample opportunities to measure the acceptance and impact of *Innospire* through interviews with managers and employees.

From the 462 submitted ideas, the most promising 17 ideas were then selected by a global cross-divisional selection committee of scientific, technical, patent, and business experts. Merck KGaA organized an innovation marketplace at which idea owners presented their ideas and composed project teams of volunteers that had all skills required for the process. From these 17 ideas and their respective teams, again a selection of 6 finalist teams was made which were offered a program to assist them in advancing their idea to a professional business plan, which we called the *Innospire* bootcamp.

[11] www.merck.com.

[12] And there were also some participants who submitted more than one idea.

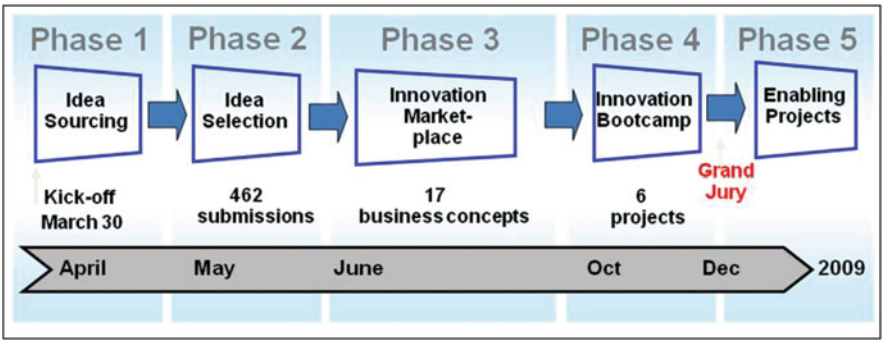

Fig. 4.2 The five phases of Merck KGaA's *Innospire* process (initial year, 2009)

These six finalist teams all presented a business plan in front of a "grand jury," which was a combination of the executive management boards for the pharmaceuticals and chemicals divisions. From the six finalist teams, two won support of the grand jury and received direct *Innospire* seed funding, while three others obtained executive committee buy-in for their new business ideas to be supported directly by the respective divisions.

The idea pool generated was so rich that in the following year the available set was again mined and the top 15 ideas among those not already picked for the 2009 process were further advanced to business concepts in the frame of a first bootcamp meeting. We then used a "wisdom of the crowds" approach and gave all Merck KGaA employees a chance to discuss pros and cons, in an online corporate discussion forum, and vote in the corporate Intranet for the most promising projects according to their view (thumbs-up/thumbs-down voting). This approach is also in line with the tenets of SDT, as it should promote feelings of autonomy, competence, and even relatedness among employees involved in grassroots innovation. Almost 2,000 Merck KGaA employees participated, demonstrating that the initiative was able to achieve a considerable mobilization of employees for innovation. The five projects collecting the most support from other employees were allowed entry into the second bootcamp and advanced to full business plans. From the five finalist teams, one won support of the grand jury and received direct *Innospire* seed funding, while three others were implemented directly in their respective divisions.

4.4.2 Design Features of the Innospire Process

This section presents design features of the program in terms of the grassroots innovation program mechanisms (idea sourcing, team formation, team/idea selection, training, and coaching) and the management support (resource allocation, visibility of involvement, tangible incentives, facilitation of external support, and tolerance for failure) described in our conceptual framework (see Fig. 4.1). Figure 4.2

summarizes the five phases of the *Innospire* process: (1) idea sourcing, (2) idea selection, (3) innovation marketplace (to promote self-assembled innovation teams), (4) innovation bootcamp (to offer skills training and professional coaching) and, after a grand jury event selecting the projects to be incubated, (5) enabling projects phase, where a few ideas are selected for incubation, which is the natural step after the conclusion of the grassroots innovation process per se (which comprises the first four phases).

(a) Idea sourcing

We communicated the new process to the organization and solicited ideas in diverse ways. Very important for the process was the full support from top management. The heads of the Chemicals and the Pharmaceutical business sectors started the idea submission process with an e-mail sent to all employees encouraging them to participate and think outside-the-box. To support the idea collection phase further, we built an Intranet site giving all background information required plus video statements of the two board members. Several site managers organized local idea brainstorming sessions to enhance idea submission from a certain site or country even further. At the main sites of Merck KGaA, we put up posters with eye-catchers at main entrances and at highly frequented local places informing about the idea submission phase.

We made it clear from the start that this was not a pure idea contest but that the idea owner would step into a process that would last at least for a year in which he would, together with his team, turn the idea into a viable business plan. In line with the predictions of SDT, we expected this decision to help us craft an entrepreneurial mindset among idea champions and reduce the focus on extrinsic motivators for participation. In addition, besides the *Innospire* mechanisms per se, top management gave a clear signal that Merck KGaA is serious about leveraging these ideas into business providing support for implementation beyond a mere idea contest. With this decision, we expected to improve participants' feelings of relatedness and security with respect to their participation in grassroots innovation and also accelerate transformation of extrinsic motivators (e.g., career progression) into more internal sources of motivation and regulation.

We did not provide any restrictions on the minimum size of the business or the time to market. This was done in order not to discourage or kill-off immature ideas from the start, but rather to create an environment where everything can be proposed and optimized further throughout the process. One clear direction provided was that ideas that exploited cross-divisional synergies between our chemical business and our pharmaceutical business were especially welcome. Seven of the 13 ideas we eventually would retain were of such nature.

Another important expectation to manage already in the idea generation stage is that the time the teams invest in the process is "on top" of their current duties. In this early stage it would be politically not feasible to remove active objectives and get people additional dedicated time assigned by their line managers. Yet, another important reason for this decision was, again, to allow a

self-selection mechanism guaranteeing that participants had higher-than-average propensity of being intrinsically motivated toward grassroots innovation. In the end, this is part of the selection process, making sure that only teams form that are really dedicated and fully believe in the benefit of their idea.

(b) First idea selection

Many ideas submitted were "early stage" ideas. In the selection process, it is important not to be too critical of certain ideas too soon, otherwise one may signal intolerance for failure and reduce the sense of security and relatedness of participants with more radical or less developed ideas, ultimately failing to see the value of such ideas. The overall goal was to retain approximately six ideas per year of which the teams would undergo an intensive bootcamp program.

The path to boil the submitted ideas down to the six finalists was composed of a mixture of "valuation" and "survival of the fittest." Only the ideas that manage to recruit a dedicated enthusiastic team survive. In other words, to survive, an idea owner needs to be able to assemble an intrinsically motivated team that believes in the project idea to an extent that it is willing to invest own time after end of business or at the weekend.

As a first step, an interdivisional committee, of 17 people with diverse backgrounds, ranging from R&D, manufacturing, marketing, legal, IP, business development to HR and workers council representatives evaluated the submitted ideas on the following questions: (1) is the idea suitable for further optimization to a full business plan?, (2) is the market attractive in terms of its potential revenue?, (3) is the industry the idea is in attractive, in terms of its competitive situation?, (4) is the idea interdisciplinary (across pharmaceuticals and chemicals)?, (5) does the idea fit Merck KGaA?, (6) is it a breakthrough or incremental idea?, and (7) what is the risk profile of the idea (in terms of proof of concept feasibility)?

This was not an easy task and 2 full day meetings with the entire committee, plus extensive preparation, pre-evaluation, and consultation with further experts outside the evaluation committee were required to do the job. Portfolio aspects played a role too, to make sure that in the final set a good mixture was represented concerning: Pharmaceuticals versus chemicals, representation of various sites, quick wins versus blue sky ideas, etc. The final decision was taken by majority of vote.

(c) Innovation marketplace: promoting self-assembled team formation

To foster team formation, innovation marketplaces were organized at three major sites: Darmstadt (HQ of Merck KGaA), Geneva (HQ of Merck Serono), and Boston (HQ of Merck Millipore in 2010). At these events, idea owners presented their ideas to a broader audience within the company, discussed the idea with interested colleagues, and tried to recruit additional team members. All project ideas had a poster on which the core of the idea was represented, supplemented by a PowerPoint presentation or video of the idea champion shown on a screen. We announced this market place to all employees and invited people desiring to be "innospired" to attend the event. Top management was present at all events to signal support.

In addition to the local marketplace events, the teams presented their ideas on a virtual Intranet marketplace with a videotaped oral presentation and a presentation file. All Merck KGaA employees had the chance to get more information about the concepts and expertise still missing to complement the teams. To fill the vacant functions employees had the opportunity to contact the idea champion directly. Some ideas could not be presented in full detail on the Intranet platform due to confidentiality and know-how protection.

Subsequently, team champions were actively coached on team formation and offered in-roads to the organization to find the right competences. Typically team leaders were scientists and the skills they searched for in the organization to complete their team consisted of experienced business developers, marketers, and finance executives. In pharmaceuticals, specialized skills were often considered crucial for teams' therapy innovation efforts. Prior literature has shown that the market success of new therapies requires a deep understanding of specialized topics such as pricing (Verniers et al. 2011), reimbursement and regulatory regimes in different countries (Stremersch and Lemmens 2009), and experience with the increasingly complex clinical studies required for market approval (Gassmann and Reepmeyer 2005). Thus, several teams at *Innospire* attempted to add such specialized skills to their team.

In the first year, the six strongest ideas and teams that would enter the innovation bootcamp were selected by the interdivisional evaluation committee on the basis of the following criteria: (1) idea progression since the previous stage, (2) leadership potential of the idea champion, (3) completeness of skills in the team, (4) business potential of the idea, (5) fit of the idea with Merck KGaA, (6) probability of success in (further) developing the underlying technology, and (7) portfolio balance.

In the second year, as stated above, a "wisdom of the crowds" approach was used to select the projects allowed access to the bootcamp. Experiences with this approach were mixed. We found that two main disadvantages of the popular voting approach were: (1) people voted disproportionately for projects that had an emotional appeal (e.g., a cool new technology or "save the planet" type of ideas); (2) people voted disproportionately for people they knew and liked. The big advantage was that the approach allowed for a strong engagement to be generated and thousands of employees were exposed to the ideas and voted and many even contributed with proposals for further improvement. The visibility of the entire *Innospire* process was greatly enhanced by the public voting exercise.

(d) Innovation bootcamp: skills training and professional coaching

The six finalist teams gathered in an intensive program in which about five members of each team received a basic management training, optimized towards writing a business plan, found time to advance their ideas together with coaches, and also underwent a series of challenge meetings and dry-run presentations in order to make sure that the business plans to be presented to the grand jury were of the highest quality. The bootcamp consisted of 7 days, divided in two blocks

of four and three days. The first block of four days covered innovation strategy (e.g., platform versus product innovation), marketing strategy (mission, vision, goals, objectives, market definition, SWOT, and market strategy), and market forecasting (e.g., market size forecasting and temporal pattern). Participants presented their initial business concept on the first day and then an initial business plan on the last day of this four-day block. About half of the time was devoted to coaching the teams on business case issues. This first four-day block was mainly intended to "test the business case." The fourth author was the main facilitator of the bootcamp and we inserted internal speakers to discuss with participants' technological hurdles in development and manufacturing, financial management of the firm, and pricing.

Besides the further development of the business cases, the fun factor for the bootcamp participants was also addressed by special team building events which were very important for the interaction between teams and for energizing the individual team power and *Innospire* spirit after long sessions of tough team work and challenging presentations.

The second block of three days, which commenced about four weeks after the first block, was mostly intended to "further develop and present the business case." Beyond work on timing of entry (is the time right? roadmapping) and NPV (net present value) calculation, all time was devoted to coaching and presentation training. At the end of the three days, we organized a "dry-run" attended by two senior business development executives who had never seen the business plans before, to provide a fresh view.

The innovation bootcamp component served as a key supporting factor to the success of *Innospire*. It was a unique opportunity to complement participants' perceived competence and increase their relatedness (through teamwork and coaching). Furthermore, the collaboration with the fourth author as external facilitator and dedication of a sufficient number of days to the innovation bootcamp sessions was perceived by participants as a signal of high managerial support for grassroots innovation (through resources, visibility of involvement, the tangible incentive of the training itself, and the access to external knowledge and support) and thus as a key incentive for their participation. It is of utmost importance, however, to make sure that scientific and technological questions, probability of technical success, strengths and weaknesses of the suggested approach, critical issues, go-no go milestones, and a thoroughly thought through project plan receive sufficient attention in the project teams coaching towards preparation of a final business plan. We have further strengthened these very important points by adding scientific advisory boards for thorough scientific and technological assessment of the proposed ideas. In addition, the teams received the internal support of the patent and legal departments.

(e) Final idea selection: grand jury event

The final step was a two-day grand jury event. We convened 1 day before the grand jury meeting for a last "dry-run" of the presentation. After additional preparation the following day, the teams presented to the combined management boards of the chemicals and pharmaceutical business sectors.

(f) Enabling projects and incubation
After the grand jury event, proper project incubation and governance of the winning projects are crucial for success. In order to enable project incubation, Merck KGaA provided a budget within a ring-fenced innovation incubator with the goal of allowing the advancement of projects in the frame of an innovation greenhouse.

The governance of the *Innospire* incubator projects was done by a special Innovation Steering Committee with members from both the chemicals and pharmaceutical business sector. This governance and the dedicated *Innospire* budget set project teams into a "greenhouse" environment for a certain timeframe. This helped the projects to move forward independently of organizational constraints or restrictions from current operative business unit strategies. Project champions were asked to report on a quarterly basis and the Innovation Steering Committee is responsible for approving budget for the following years. The Innovation Steering Committee is also regularly informed on the progress of the *Innospire* projects pursued within the divisions.

A key mechanism needed to successfully enable and incubate promising projects is to adequately prepare and implement the transfer of projects from the innovation incubator/greenhouse to the internal customer, the strategic business unit interested in developing and launching a successfully researched innovation or product to the market. This process required extensive communication to ensure a smooth handover. In that regard an involvement of business unit representatives early on, including invitations to the Innovation Steering Committee and project team meetings, was deemed essential.

Consecutive editions of the *Innospire* process taught us that to make the process sustainable, the incubation step is crucial. In this step, it is important to maintain a stringent follow-up of the best ideas and handoff the ideas to the strategic business units at (and only at) the right time. Sufficient attention during incubation and existence of a specific budget allocated to help mature the idea (conditional on successful performance in certain key performance indicators) are essential. It is also crucial that management supports the projects up to market launch and that all innovators and team members get their deserved reward and recognition. We have also organized acceleration workshops for the incubated teams to support them in trying to accelerate their time to market. In a way, the real process really just starts after the grand jury approval.

4.4.3 Results of the Innospire Process

The *Innospire* program transformed the innovation landscape at Merck KGaA. The main benefits obtained were (1) employees' perceptions about the competence-enhancing aspect of *Innospire*, (2) their greater sense of autonomy, (3) unique opportunities for networking and improved relatedness and, consequently, (4) new promising innovations in Merck KGaA's pipeline. We discuss each in turn.

(a) Competence-enhancing effects of innospire
The feedback of the participants was outstanding. Several participants stated that they would have not been able to bring their idea forward if it was not through the *Innospire* process. A considerable number of participants found *Innospire* a life-changing event. Many of them were scientists who had barely been exposed to business. This process was an initiation in business logic for many of them, boosting their skills and perceived capacity to autonomously transform ideas into full-fledged projects for new businesses. We repeatedly solicited feedback on the process. In one such session, one participant commented that "*Innospire* is a great opportunity to bring ideas into business while learning in a professional way," hinting at the competence-enhancing benefits of the program he enthusiastically concluded that it was "definitely the best education you can get at Merck." Similarly another participant expressed her gratitude to the "great opportunity to broaden my expertise and knowledge." As one participant pointed out, "*innospire* has helped me to develop my personality."

(b) Increased autonomy
Besides its competence-enhancing benefits, another key benefit of *Innospire* was to spread the idea that innovation is a responsibility of every employee. We observed a high level of dedication and motivation of project teams. A culture was shaped that allowed the entrepreneurial teams to consider a project as their "baby," being provided resources by the company to move it forward. This turned out to be highly motivating for project teams and helped to rapidly change perceptions of some of being treated as a dispensable turning wheel at the merit of line management. In the words of a participant, "*Innospire* makes the *whole* company more aware of how dependent we are on new products." Indeed, many participants indicated they were very pleased with the enhanced sense of autonomy they gained and the trust they felt was being put on their capacity to innovate. These feelings also helped increasing employee loyalty to the organization. For example, one participant said "*Innospire* adds a lot to the fun I have in my job and makes Merck a more attractive employer."

(c) Increased relatedness and networking
Besides this competence- and autonomy-enhancing aspects, the *Innospire* process stimulated networking and relatedness among employees in several ways. The opportunity to come together and discuss with colleagues from other divisions was highly appreciated and contributed substantially to idea advancement. Summarizing his experience at *Innospire*, one participant said that "it gives the opportunity to discuss with people that you would not meet normally, and this allows you to come up with breakthrough ideas." The process especially succeeded in bringing forward ideas at the crosssection of both business divisions, suggesting that the relatedness of people from different corners of the organization was significantly improved. Teams working on such projects were mixed teams, with representatives from the chemicals and pharmaceuticals business sectors. In one case, the technology base lied within the division Merck Serono (prescription pharmaceuticals) and the application lied in the Merck

Millipore division. In another case, the technology base lied within the Performance Materials division, while the application lied in the Consumer Health division. Recognizing this key advantage, another participant said that "*Innospire* gives us a chance to make cross-divisional ideas real… such ideas would have no home in the business units and would not have a chance otherwise." In hindsight, we can conclude that networking was certainly a key pillar of success of the *Innospire* process.

(d) Improved innovation output at Merck KGaA

Besides the very important benefits for employees, the organization also benefitted from the innovative ideas that were discovered, polished, and improved through the *Innospire* process. Recognizing such improvement in innovation output due to the program, one of the participants said that *Innospire* helped "opening new horizons for the company to move forward in innovation."

Senior management was also very enthusiastic with the results of *Innospire* and, therefore, a second idea call was initiated in 2011 with the number of submitted ideas for new products up 20 % versus the first call in 2009 (we do recognize that number of ideas is a bad metric for innovation but disclose it here for full information). Nineteen ideas out of the 2011 campaign were advanced to the innovation marketplace stage, six were advanced through the bootcamp and out of these four were approved by management and received funding.

The next *Innospire* idea call is scheduled for autumn 2013. In total, so far, the *Innospire* initiative has resulted in approximately 800 ideas submitted via two idea collection campaigns in 2009 and 2011. Fifty-one of these were advanced to business concepts and presented to a broader audience at the physical and online innovation marketplaces. The 17 most promising business concepts were advanced to full business plans and presented to Top Management for approval. A total of 13 projects have received funding and went operational. Four of these projects were funded from a centrally dedicated *Innospire* incubator budget and nine received direct funding from the business units. Topics were very broad reflecting the strategic fields of Merck KGaA, including areas located at the interface between the divisions: improved monoclonal antibodies for drug discovery, new approaches for personalized medicine, imaging technologies, a new medical device, new drug discovery tools, improved formulation technologies, probiotics, cosmetics, energy, water, gas separation, and next generation display materials.

In terms of pharmaceutical innovation, the *Innospire* program was a success, too. It resulted in six promising projects for Merck KGaA's pipeline:

- A new innovative preclinical assay system to assess compounds early on in discovery for side effects profile.
- Two highly innovative new technologies for formulation of poorly soluble compounds.

- A new highly innovative protein engineering technology for improved biological drugs.
- An innovative medical device in the OTC field.
- A new probiotic product in the OTC field.

Typical annual project budgets were approximately 1 M€ per project in the central *Innospire* incubator. Average projected running time from project inception to expected product launch is about four years. Total project attrition rate according to data collected so far is 33 %. Termination in most cases occurred during or right after the first year.

Up to now, more than 20 patents have been submitted based on work done within the *Innospire* projects. A first product launch took place in 2012 with two more product launches scheduled for 2013, all derived from projects initiated in 2010 and more down the road based on the 2011 idea call. The total business volume that the new business ideas represent is currently estimated to be several 100 millions of Euros in total.

(e) What happened to non-selected ideas?
While "survival of the fittest" was a key driver in the success of the *Innospire* process, Merck KGaA proactively managed the possible disappointment of employees whose ideas did not succeed in advancing through the process. To avoid such disappointment to contaminate the success of the project, three strategies were followed. The first was to encourage employees whose ideas did not pass a certain milestone to join their colleagues and help them improve their ideas.

The second was to conduct further analyses of the non-chosen ideas to select additional ideas that could be followed-up directly by the business units. Dozens of ideas were taken up by Merck KGaA's business units either directly after idea submission or after the innovation marketplace without going through the bootcamp process. In addition, in 2010, Merck KGaA decided to re-evaluate the ideas submitted in 2009 and, again, many additional promising projects were initiated. In retrospect, we conclude that an idea pool is never really completely harvested and while one needs to apply stringent criteria to be able to focus on the breakthrough ideas with higher business potential, it is crucial to manage disappointment of employees with non-chosen ideas and avoid losing good ideas due to too stringent filtering.

The third strategy involved giving visibility to idea owners and signaling care, by offering them the possibility to have their idea forwarded directly to the evaluation team of their own business unit, guaranteeing the process was transparent and fair. This proved very important for the reputation of the process and recruitment of idea owners in subsequent editions.

(f) External recognition of the innospire process
In the meantime Merck KGaA's *Innospire* program has received considerable external attention and recognition. For example in April 2012, Merck KGaA

received the prestigious *2012 BioIT World Best Practice Award*,[13] in the category of knowledge management, for the capacity of *Innospire* to "mobilize the innovation potential of all Merck KGaA employees for generation of new innovative products." An *Innospire*-derived product for formulation of poorly soluble compounds has been honored with the CPhI (Convention on Pharmaceutical Ingredients) 2012 Innovation Award.[14] These results demonstrate that a formalized process aimed at promoting grassroots innovation can contribute to mobilizing the full innovation potential of employees, boost the passion, competence, autonomy, and relatedness and improve pharmaceutical firms' innovation pipelines. In addition, the concepts of self-assembling teams, the wisdom of the crowds approach, and the survival of the fittest philosophy add new innovative approaches for managing discovery portfolios (Betz 2011).

4.5 Discussion

4.5.1 Summary of Key Findings

In this chapter, we offer a conceptual and theoretical framework to help pharmaceutical firms structure their grassroots innovation programs. Our framework is grounded on self-determination theory (Ryan and Deci 2000) and posits that (1) the integral mechanisms in grassroots innovation programs (idea sourcing, team formation, team/idea selection, and training and coaching of participating employees) and (2) key identified dimensions of management support (resource allocation, visibility of involvement, tangible incentives, and facilitation of a supportive organizational structure and tolerance for failure) need to be geared towards boosting employees' intrinsic motivation for grassroots innovation. Our key findings are as follows.

Employees' entrepreneurial spirit, business skills and competences, and sense of autonomy were clearly boosted by the *Innospire* process. The capacity of the *Innospire* program to promote networking and connect employees at different hierarchical levels and from different divisions and regions (i.e., increasing their relatedness) proved a crucial aspect of the process and a strong motivator for future participants. These findings are in line with self-determination theory, which defends that intrinsic motivation is promoted when employees' intrinsic needs for competence, autonomy, and relatedness drive intrinsic motivation.

[13]Established in 2003 by Bio-IT magazine, the World's Best Practices Awards recognize "organizations for their outstanding innovations and excellence in the use of technologies and novel business strategies that will advance biomedical and translational research, drug development, and/or clinical trials," see http://www.bio-itworld.com/2012/04/25/bio-it-world-announces-winners-2012-best-practices-awards.html.

[14]http://www.cphi.com/pharma-awards.

Certain design choices in a grassroots innovation program help satisfying these innate human needs. First, it is important to promote a self-selection mechanism that attracts the most intrinsically motivated employees to the program. Second, it is important to facilitate the formation of self-assembled teams. Third, idea champions have to successfully recruit team members to be able to proceed in the program, which works as a "survival of the fittest" mechanism capable of filtering out ideas whose owners are unable to garner sufficient support from intrinsically motivated colleagues. Fourth, it is crucial to offer professional training and coaching in order to boost participants' business skills and competences and increase their possibilities for networking. Fifth, senior management needs to show significant support to the process, in terms of devoted resources, visibility of involvement, facilitation of external support, and tolerance for smart failures. We believe that to achieve sustainable success, grassroots innovation programs need to be *structured* as a *formal process* that simultaneously addresses the three fundamental human needs of autonomy, competence, and relatedness/networking. In *Innospire*, self-assembling teams proved crucial to boost participants' autonomy and relatedness/networking. Innovation bootcamps were pivotal in the development of participants' market and business-planning competences and capacity. Last but not least, the corporate culture needs to be ready for a grassroots innovation program such as *Innospire*. This was the case at innovation-oriented Merck KGaA.

4.5.2 Future Research on Grassroots Innovation

The literature on grassroots innovation processes is still nascent and, therefore, there are several promising research directions in this topic.

First, future research could focus on conducting large-scale empirical work to generalize the ideas proposed in this chapter. Research focusing on multiple firms, multiple countries, and even industries is particularly welcome. Such research efforts would benefit from extensive primary data collection—for instance, self-reported data (on intrinsic versus extrinsic motivation and on competence, autonomy, and relatedness/networking perceptions)—across a sufficiently large sample to allow empirical generalizations of the current chapter's findings.

For instance, cross-firm or cross-industry research could focus on the interaction of culture and process. Obviously, the extent to which a company has a culture of innovation is an important moderator on the success and design of a structured process such as the one described in this chapter. For instance, from our experience at Merck KGaA, we found that it is crucial for such a program to be tailored to the company's culture, to ensure a smooth buy-in throughout the organization, including acceptance of the program by middle management.

Besides corporate culture, large-scale empirical work could focus on cross-national differences in the implementation and consequences of grassroots innovation. Prior research suggests that national culture can strongly affect innovation outcomes (Tellis et al. 2009) and employee and managerial behaviors in an

organization (Hofstede 2001). For instance, *power distance*—the extent to which less powerful members of an organization accept or even expect that power is unequally distributed (Hofstede 2001)—is typically much higher in Asian countries than in Western European nations or in the United States. It may be that grassroots innovation processes need to be implemented differently in more hierarchical societies, when compared with less hierarchical societies. The fourth author has observed such differences in roll-outs of grassroots innovation in continents as diverse as Asia (China), North America (USA, Canada, and Mexico) and the Middle East. But if cross-national research could uncover such diverse mechanisms in a more formalized and quantitative manner, this would be a valuable addition to the literature.

Second, our SDT-based framework focuses mostly on employee motivation as the key success driver in grassroots innovation. Future research could study other factors that may influence the success of grassroots innovation programs. In particular, it would be important to study the antecedents and consequences of employee disappointment triggered by not being selected to proceed to the next step in the process. We have discussed Merck KGaA's strategies to manage possible disappointment among employees whose ideas did not advance beyond a certain milestone in the *Innospire* process. Future research could identify alternative mechanisms to deal with such disappointment and test which are the most effective ones. Interesting research directions include framing effects in feedback communication and how to ensure that evaluations are perceived as fair by all participants. Experimental studies or multiple case study analyses could help highlight these issues.

Third, one of the central tenets of SDT is that competence-enhancing mechanisms are pivotal to boost employees' intrinsic motivation and the success of grassroots innovation. At *Innospire*, innovation bootcamps played a key role in boosting employees' capacity to transform their ideas into full-fledged business plans. Yet, recent research shows that coaching and training in the early stages of idea generation is also very effective in enhancing creativity and ideation (Burroughs et al. 2011). It would be interesting for future research to test the extent to which a training program during the ideation phase can help improve the quality of the ideas submitted. Also, would a program focused on promoting competence alone (e.g., customized training programs on innovation and entrepreneurial thinking) be beneficial for companies which may find they are not ready for a full-fledged grassroots innovation process?

Fourth, despite the growing popularity of innovation tournaments and games (see, e.g., Terwiesch and Ulrich 2009), future research should also investigate some drawbacks of *gaming* mechanisms in innovation. For example, in crowd-voting mechanisms, after a few employees make their evaluations of other ideas public, several others may tend to disregard their private information and simply *follow the herd* (Bikhchandani et al. 1992). Yet, more scientific scrutiny is needed to understand the prevalence and magnitude of these effects and help firms improve their voting and selection mechanisms.

Fifth, we have studied one formalized approach to grassroots innovation. However, many of the examples discussed in this chapter depend on informal drivers of grassroots innovation, such as a company's overall bottom-up culture

(e.g., Google, 3M) or the introduction of less formal processes (e.g., GSK's Spark Network). Given their prevalence and mixed results (Bikhchandani et al. 1992), future research should document the drivers of success in *informal* grassroots innovation processes.

Sixth, firms are also increasingly interested in implementing *open innovation* models, such as Procter & Gamble's famous *Connect and Develop* approach (Huston and Sakkab 2006) or Cisco's I-Prize (Jouret 2009). Such models look for new ideas outside the boundaries of the firm, i.e., next to suppliers, academia (scholars or even students), government, research institutions, clients, and even competitors. Future research could study how firms can implement structured processes such as the one discussed in this chapter with the goal of finding ideas outside the company's boundaries; Merck KGaA has recently started an open innovation portal of its Merck Serono division (www.merckserono.com/open_innovation).

Seventh, in order to boost internal validity, the causal mechanisms depicted in our conceptual framework should be explored in a controlled setting. That is, it would be very interesting to devise laboratory (or field) experiments where the actual causal mechanisms of interest can be tested. Such proof of causal mechanisms may prove to be very challenging, but highly rewarding.

4.5.3 Future Research on Grassroots Innovation in the Pharmaceutical Industry

There are also several interesting avenues for future research on specific applications of grassroots innovation in the pharmaceutical industry. First, it is important to study to what extent grassroots innovation is better attuned to promote radical breakthroughs or more incremental innovations.

Second, it would be interesting to quantify whether the benefits of grassroots innovation are more important for certain therapeutic categories that may demand closer contact with customers. For example, do pharmaceutical firms need to be closer to the consumer when engaging in innovation in targeted therapies or diagnostics? If yes, it would be interesting if future studies could test whether grassroots innovation processes can be particularly effective in more customer-oriented innovations.

Third, pharmaceutical industry's blockbuster innovation model is prone with risk and uncertainty. Could the wisdom of crowds' philosophy behind grassroots innovation reduce some of this risk and make innovation outputs more predicable? How should pharmaceutical firms combine bottom-up and top-down innovation philosophies in a new model combining closeness to the customer, employee motivation and entrepreneurial spirit, and strong strategic fit and leadership?

Overall, research focused on grassroots innovation in large corporations is scarce. This chapter provides an early in-depth study based on theoretical derivation and an in-depth case study of one process at one firm. Clearly, there is room for a multitude of future contributions in this area, with high dual impact to both academia and business.

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Chapter 5
New Challenges in Alliance Portfolio Management

Stefan Wuyts

Abstract In order to expand the pool of opportunity and access external R&D, many pharmaceutical firms have accumulated portfolios of alliances with other industry participants over the past decade. Academic research has amply demonstrated that such alliance portfolios can contribute to firm innovativeness and profitability. Yet, alliance portfolios don't always pay off and much remains to be done to arrive at a theory of effective alliance portfolio management. This chapter pursues a number of contributions to this area. First, the author offers an overview of the key dimensions of portfolio management: scale, partners, governance, technology diversity, cost, and dynamics. Second, the author singles out the technological diversity of the alliance portfolio and elaborates on its definition and measurement. Third, the author addresses three challenges that relate to managing technologically diverse alliance portfolios in the pharmaceutical industry. The first challenge is theoretical in nature: the author contrasts two competing theoretical perspectives that raise different expectations with regard to optimal portfolio diversity, and he motivates why the real options perspective may prove to outperform the learning theory perspective. The second challenge stems from the observation that not all firms benefit equally from similar levels of alliance portfolio diversity: the author argues that such differences across firms can be explained by differences in the commitment of managerial resources to implementing a portfolio strategy and by differences in internal routines and capabilities. The third challenge relates to the changing nature of collaboration: the evolution of biotechnology as a scientific field, the emergence of nanotechnology, the increasing potential of personalized medicine, and particular institutional changes such as healthcare reforms have reshaped the pharmaceutical landscape and require novel approaches to alliance portfolio management.

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5.1 Introduction

Pharmaceutical firms rely increasingly on external R&D as they organize and restructure to optimize their pipelines. Eli Lilly, for example, is transforming itself from a fully integrated pharmaceutical company to a fully integrated pharmaceutical network to "expand the pool of opportunity" (Lechleiter 2010). There are many ways in which pharmaceutical firms can expand the pool of opportunity.

First, the licensing exchange market offers opportunities as pharmaceutical firms can purchase, or license-in, externally developed technology. For years, licensing agreements have been a primary source of opportunity for many pharmaceutical firms to build and sustain their drug pipelines (Simonet 2002).

Another route to internalize externally developed knowledge is by acquiring the entire dedicated technology company. Especially pharmaceutical firms that face reduced internal productivity tend to acquire other firms to replenish their research pipelines (Higgins and Rodriguez 2006). Zhao (2009) finds that while reduced innovativeness motivates a firm to engage in acquisitions, acquisitions in turn do more than only compensate for the decrease in innovativeness and also effectively increase the firm's innovation efforts.

A third route to benefit from external knowledge is by allying with other industry partners and jointly developing new technologies. In this chapter, I focus on such alliances and I will argue that alliances offer the benefit of strategic flexibility, as opposed to purchasing licenses or acquiring companies. Eli Lilly, for example, has formed a Corporate Business Development group for forming alliances to innovate more efficiently and more effectively (Eli Lilly 2011).

As companies are increasingly engaging in alliance activities to expand the pool of opportunity, a new phenomenon has emerged: the alliance portfolio, which refers to a firm's collection of alliances. The effects of alliance portfolios on firm innovativeness and profitability have been studied in strategy and organization behavior (e.g., Hoffmann 2007; Ozcan and Eisenhardt 2009; Sarkar et al. 2009; Wassmer 2010) as well as marketing (Cui 2013; Cui and O'Connor 2012; Wuyts and Dutta 2008; Wuyts et al. 2004a). This domain of research is important, for at least two reasons.

First, from an academic perspective, the study of alliance portfolios in the pharmaceutical industry can be approached from different perspectives, all of which have their merit: a resource perspective, as alliances are vehicles to access external resources that may complement internal resources; a relational perspective, as alliance portfolios offer unique governance problems; a risk perspective, as alliance portfolios, if properly designed, serve a risk reduction function; and a cost perspective, as the cumulative investment costs associated with expansive alliance portfolios can be very substantial.

Second, from a managerial perspective, pharmaceutical companies differ in terms of their understanding of the phenomenon and their ability to shift focus from an alliance approach to a portfolio approach. Even if they do realize that a portfolio is more than the sum of its parts, not all firms are equally equipped to reap the benefits from their alliance portfolios.

In this chapter, I will first derive key dimensions of alliance portfolio management on the basis of previous research. Subsequently, I will single out the technological diversity of the alliance portfolio as my focus of attention. Diversity exposes the firm to nonredundant knowledge, which in turn contributes to firm innovativeness and performance. Its importance in a science-based field such as the pharmaceutical industry is illustrated by GlaxoSmithKline's (GSK's) business development strategy: "Our Worldwide Business Development group is a global team of scientific, transaction, and alliance management experts building *diverse* collaborations relating to compounds (early stage discovery programs through to marketed products) and technologies" (GlaxoSmithKline 2011—italics added).

Interestingly, the literature has not been conclusive regarding the effects of portfolio diversity. First, I argue that this can be partly explained by the use of problematic proxy measures for technology diversity; hence, I will contrast technology diversity with other facets of diversity. Second, the lack of generalizable insights can be caused by (1) imperfect behavioral assumptions of established theories, (2) a lack of attention to firm differences, and (3) the changing nature of collaboration in the pharmaceutical industry. After contrasting technology diversity with other facets of diversity, I elaborate on these three challenges.

The first challenge consists of contrasting competing perspectives on why firms benefit from portfolio diversity. I focus on two alternative perspectives: the learning perspective and the real options perspective. The learning perspective holds that firms seek to assimilate knowledge from their individual alliance partners. The real options perspective holds that firms consider their alliances as real options on new products under uncertainty and form diverse alliances to spread their bets and delay choice until uncertainty is resolved. This comparison of theories is more than a thought exercise as learning theory and real options theory lead to different implications as to the composition of an *optimal* alliance portfolio.

A second challenge is to acknowledge firm differences. While not all firms benefit equally from portfolio diversity, firm differences are not commonly accounted for in interfirm network studies. I argue that differences among firms in their commitment of managerial resources to portfolio management and in their internal R&D strategies help explain why some firms benefit more than other firms from portfolio diversity.

A third challenge is more contextual: technological developments such as the rise of nanotechnology and institutional developments such as healthcare reforms change the very nature of collaboration and alliance portfolios in the pharmaceutical industry. From a discussion of these three questions, I will derive next steps for academic research as well as recommendations for managers in the pharmaceutical industry.

5.2 Key Dimensions of Portfolio Management

The literature has identified four principal dimensions of portfolio management that relate to scale, partners, governance, and technology. The literature has been remarkably silent on two other relevant dimensions, namely the costs and dynamics

associated with alliance portfolio management (see Wassmer's 2010 review article for a notable exception).

The first portfolio descriptor relates to the scale of the alliance portfolio, mostly operationalized as *portfolio size* (Goerzen 2007; Hoffmann 2007; Wuyts et al. 2004a). Portfolio size is a simple count of the number of alliances that make up the portfolio and gives a first impression of access to external knowledge.

The second core descriptor relates to the partners that are selected for the respective alliances. Apart from some obvious partner descriptors, such as the need for high-quality partners (Rothaermel 2001), the most prominent variable that describes the mix of partners in an alliance portfolio is repeated partnering (Goerzen 2007; Jiang et al. 2010; Wuyts et al. 2004a). The key insight is that collaborating repeatedly with the same partners helps in transferring knowledge but constrains accessing novel knowledge. Wuyts et al. (2005) provided empirical support for an inverted-U effect of repeated partnering on the value of learning.

The third key dimension relates to the governance of the alliances that make up the alliance portfolio. Prior research shows that firms in knowledge-intensive industries should balance strong and weak ties because weak ties help firms stay ahead of developments in novel knowledge domains (Uzzi 1997; Rowley et al. 2000).

A fourth key descriptor is the portfolio's *technological diversity* (Wuyts et al. 2004a), sometimes referred to as efficiency (Hoffmann 2007). Other scholars have identified other forms of diversity such as industry diversity (or dispersion, see Hoffmann 2007), product market diversity (Ansoff 1958), and governance diversity (Jiang et al. 2010).

The fifth dimension of portfolio management, costs, has received less attention. Portfolio management, however, requires not only opportunity management but also cost management. Allying with new alliance partners increases partner qualification, coordination, and governance costs; diversifying across technological fields increases investment costs, such as training and educating employees, investing in equipment and machinery, and initial investments in the alliance partner.

Finally, also the sixth dimension has received very little attention: alliance portfolio management is intrinsically dynamic. On the one hand, firms should stay on the lookout for new opportunities in rapidly developing fields and be prepared to adapt to changes in the technological environment. On the other hand, even a snapshot of an alliance portfolio will reveal a dynamic aspect: alliances are signed at different stages of the new drug development process. Early literature on technology portfolio management in marketing already suggested that firms should strive for a balanced allocation of resources along the stages of technology development (Capon and Glazer 1987, p. 10). Following a similar logic, one can infer that an alliance portfolio should balance early and late stage alliance projects to sustain a balanced drug pipeline. This inference, however, lacks empirical substantiation and requires further study.

Assembling the pieces, alliance portfolio management should incorporate the dimensions of scale, partners, governance, technology, costs, and dynamics (see Fig. 5.1). Clearly, these dimensions are not orthogonal. A portfolio that covers a large diversity of technologies tends to be very costly, which is illustrated by Wuyts

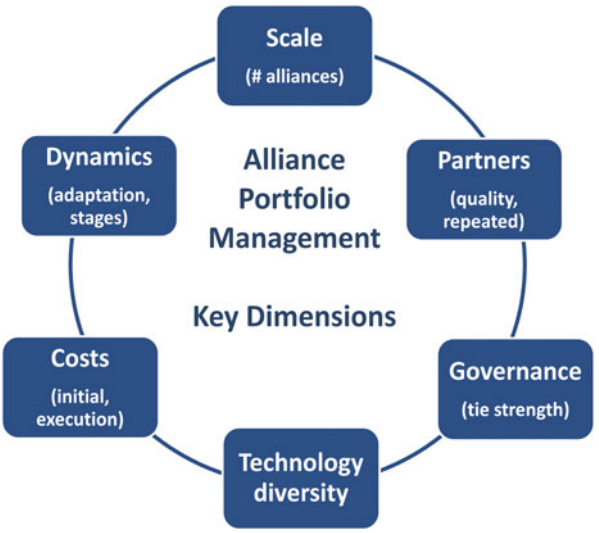

Fig. 5.1 Key dimensions of alliance portfolio management

et al.'s (2004a) finding that the profitability of technological diversity can be decomposed into a positive effect via radical product innovation *and* a direct negative direct effect that is likely caused by high investment costs. Also, technological diversity can drive dynamic adaptation as technological diversity increases the firm's ability to identify and select new external opportunities, a finding often ascribed to the firm's increased *absorptive capacity* (Cohen and Levinthal 1990). When discussing Challenge 2 below, I will elaborate on new advances in the absorptive capacity literature (e.g., King and Lakhani 2011; Lewin et al. 2011) that are helpful in this regard.

Having laid out different dimensions of alliance portfolio management, I now narrow down the focus in this chapter to the key role of diversity in portfolio strategy. Below, I will first discuss several facets of diversity and motivate my focus on technology diversity. Then, I will discuss three new challenges that we face today as we try to grasp the true effects of technology diversity in the pharmaceutical industry.

5.3 The Diverse Facets of Diversity

Diversity is a concept that has received much attention in the strategy literature. The multifaceted nature of diversity, however, has been insufficiently acknowledged. Different studies have examined different forms of diversity, including technology diversity, partner diversity, industry diversity, and product market diversity. Arriving at generalizations about diversity is difficult if these differences in conceptualizations and operationalizations are not accounted for. In particular, I focus on how technological diversity differs from the two most common alternative diversity constructs, namely (1) partner diversity and (2) industry or market diversity.

5.3.1 Technology Diversity

An examination of trade and academic literature, as well as prior conversations with industry professionals, has indicated that the main motivation for pharmaceutical firms to build alliance portfolios is to stay ahead of the technological developments. Despite the large body of research on diversification and the economic importance of technology-intensive industries, there is relatively little systematic evidence with regard to technology diversity. Technologically diversified firms spread their technology development efforts across a diverse range of technology domains (e.g., Miller 2006). A few prior studies underscore its key role in corporate economics (e.g., Granstrand 1998) and suggest that technology diversity enables the firm to take options on technological opportunities (Pavitt et al. 1989) and contributes to firm performance (Suzuki and Kodama 2004). Unfortunately, researchers have been very liberal in their measurement of technological diversity, using proxy measures as diverse as partner diversity and industry diversity, making it difficult to arrive at empirical generalizations.

5.3.2 Partner Diversity

Partner diversity refers to forging agreements with different partners rather than with the same partners over time.[1] Partner diversity is thus the counterpart of repeated partnering (Wuyts et al. 2004a). In the network literature, partner diversity has often been interpreted as a proxy for access to non-redundant knowledge bases (Reagans and Zuckerman 2008). This quite impressive leap from construct to measure is often justified on the basis of the strength-of-weak-ties argument which holds that weak ties are more likely to give access to non-redundant knowledge bases. This argument emerged as a post hoc interpretation of unexpected research findings in a study on simple bits of information, namely job leads (Granovetter 1973).

When knowledge is more complex, however, weak ties have the disadvantage that they are not effective as vehicles for knowledge transfer (Hansen 1999). It is an important insight that what makes weak ties interesting in situations, such as those analyzed by Granovetter, is not their inherent weakness itself but essentially the non-redundancy that they are associated with. Consequently, non-redundancy turned into a core concept in later network literature, such as in structural holes theory (Burt 1992) and bridging theory (DiMaggio 1992; McEvily and Zaheer 1999).

Using partner diversity as a measure of non-redundancy of knowledge bases is problematic. First, one partner may work in diverse technology domains simultaneously and keep up or even shape the scientific developments in those domains over time, making it a useful source of non-redundant knowledge for the allying firm.

[1] Note that some authors have defined partner diversity differently, such as the diversity of structurally equivalent partner types (e.g., Baum et al. 2000); also these operationalizations fail to capture actual redundancy and suffer from similar problems as discussed in this paragraph.

Second, switching partners regularly does not necessarily expose the allying firm with non-redundant knowledge bases as all partners may be active in the same technology domain and have similar technological expertise. Third, partner diversity captures also relational elements that influence collaboration. Collaborating regularly with the same partners can lead to better knowledge transfer and the development of trust (Wuyts et al. 2004a). In sum, not only is partner diversity likely a flawed proxy for non-redundancy, its effects on firm innovativeness and performance mask possibly contrasting sub-effects if relational factors are not explicitly accounted for.

5.3.3 Industry and Product Market Diversity

The most commonly studied type of diversification is industry diversification (e.g., Montgomery 1985), calculated on the basis of industries entered into by the firm (mostly defined in terms of 4-digit SIC codes). Some studies on industry diversification have argued that it confers competitive advantages (e.g., Caves 1981), but according to other studies it reduces the firm's competitive position in each individual industry because of a lack of resource commitment (e.g., Montgomery 1985).

The decision to enter new product markets is, however, more at the core of day-to-day managerial decision making than the decision to enter new industries. Interestingly, it has been argued that the benefits of diversification are most apparent when diversifying *within* a given industry (Soni et al. 1993; Stern and Henderson 2004; Varadarajan 1986). Ansoff (1958) conceptualized product market diversity as the product market makeup of the firm, where a market is defined in terms of "the job which the product is intended to perform" (p. 393).

For instance, drugs that reduce blood pressure, such as ACE-inhibitors, differ along different submarkets. While some patients are in need of an ACE-inhibitor only, an ACE-inhibitor with a diuretic is targeted at patients with kidney problems, implying different product markets based on different patient needs. While related, product market diversity differs from technology diversity. Product market diversity relates to the variety of downstream patient groups that the pharmaceutical company targets, whereas technology diversity relates to the upstream technology domains that the pharmaceutical firm draws from to serve its target markets.

In the excerpt below, I briefly summarize a research project that was focused on pharmaceutical firms' *internal* product market diversification and technology diversification. A key take-away is that while product market diversity and technology diversity are related, they are empirically distinct constructs that exert separate effects on firm profitability. More precisely, their effects are positive and log-linear, indicating decreasing returns to diversification. The log-linear nature of the effects may be explained by the focus in this study on internal rather than external diversification: internal resource constraints may cause resource allocation problems when diversifying internal R&D too intensively. Since externalizing R&D provides firms with access to external resources, an effective response to internal resource constraints, the positive log-linear effects of internal technology diversity may not generalize to alliance portfolio diversity.

Illustration: Technology Diversity Versus Product Market Diversity

To substantiate that different forms of diversity are empirically distinguishable, I briefly reflect on a pharmaceutical study into the performance consequences of product market diversity and technology diversity (Wuyts et al. 2010). The study is limited to diversity *within* firm boundaries and corroborates that technology diversity differs empirically from closely related forms of diversity.

Product market diversity is likely a profitable strategy. A pharmaceutical firm with a strong reputation in a given therapeutic class, access to distribution channels, and accumulated knowledge on testing and approval procedures may carry over these benefits to any new product market it enters giving it an edge over less experienced competitors. Also technology diversity is likely a profitable strategy as it is associated with experimentation and recombination, better match with customer requirements, and more valuable innovations, all of which increase performance (Argyres 1996; Clark and Fujimoto 1991; Kodama 1992). Because of internal resource commitments, firms likely experience decreasing returns to further internal diversification: we expect log-linear effects of diversity on profitability.

To test whether both types of diversity exert separate effects on performance, we analyzed 29 pharmaceutical firms over 2 decades (1982–2001). The firms produced around 80 % of the drugs listed in the Food and Drug Administration (FDA) database and close to 75 % of the patents owned by all pharmaceutical firms. We operationalize "product markets" as therapeutic classes. For each sample firm, we collect information on its approved new drugs (NDAs) from the U.S. FDA. Following Ellison et al. (1997), we use the Uniform System of Classification (USC) of Intercontinental Medical Statistics (IMS) which categorizes drugs into therapeutic classes on the basis of 5-digit codes. The degree of therapeutic substitutability is much greater within than across these therapeutic classes. For example, the anti-infective drugs Keflex and Ceclor (Eli Lilly), Duricef and Ultracef (Bristol Myers Squib), and Velosef and Anspor (SmithKline Beecham) share the same USC code (15310) and are close therapeutic substitutes (Ellison et al. 1997). On the basis of therapeutic classes, we construct an entropy measure of product market diversity (Palepu 1985). Our measure of technology diversity is based on patent classes, which capture the notion of distinct "technological areas" (Lerner 1994; Moser and Nicholas 2004). Much of the pharmaceutical industry's intellectual property is captured in patents. Patent information and classifications are obtained from the US Patent and Trademark Office (USPTO) and Community of Science (COS) databases for the sample firms. Each patent is assigned a 9-digit US classification code by USPTO, which corresponds to a position within the hierarchical technology classification system. This system has been used in a number of papers to study issues related to innovation and technology (e.g., Lerner 1994; Moser and Nicholas 2004; Paruchuri 2010). Analogous to

(continued)

(continued)
the measure of product market diversity, we apply an entropy measure for technology diversity. Profitability is measured as Return on Assets on the basis of COMPUSTAT databases.

We find that product market diversity and technology diversity are related, as their correlation is 0.49. Regression analysis showed, however, that they are distinct as both exert a separate positive significant log-linear effect on profitability. The effects remain unchanged when we include control variables (advertising, R&D, and capital intensity) or when we estimate more complex system models where both types of diversity are endogenized.

5.4 Technological Diversity of Alliance Portfolios in the Pharmaceutical Industry: Three Challenges

Having addressed the multifaceted nature of diversity and singled out technology diversity, I now turn to three challenges that need to be addressed to advance our knowledge on technology diversity in alliance portfolios in the pharmaceutical industry.

5.4.1 Challenge 1: Competing Theoretical Perspectives

In order to understand the consequences of a diverse alliance portfolio, insight into firm motivations is essential, especially in case different theoretical perspectives lead to different normative recommendations. As much of the prior alliance literature has relied on learning theory, several authors source from learning theory to study alliance portfolios. The learning perspective suggests that an alliance should be arranged such that knowledge transfer and integration are optimized. That perspective has important consequences. If each alliance should allow for knowledge transfer, all ties should be strong given the scientific nature of knowledge.

Building portfolios of strong ties, however, severely constrains the level of diversity one firm can manage: close ties require time and resource commitments, and mobilizing and coordinating knowledge transfer is difficult (Koka and Prescott 2008). In addition, on top of time and resource constraints, assimilating knowledge from very diverse partner firms creates problems of overload and complexity (Ahuja and Lampert 2001). Further, learning theory has highlighted the importance of knowledge integration and recombination, which again constrains the level of diversity any firm should pursue: assimilating and integrating highly diverse knowledge from technology domains, more diverse than a single firm can manage, can pose insurmountable difficulties (Fleming and Sorenson 2001). If learning theory applies and these hindrances add up, a diverse alliance portfolio creates unwieldy management structures (Goerzen and Beamish 2005). Following this line of logic, Phelps

(2010) recently argued that diversity is beneficial at moderate levels (i.e., an *inverted-U-shaped* effect). Interestingly, though, he did not find empirical support for that argument; on the contrary, Phelps found evidence for a positive linear effect. Since this finding rejects the arguments derived from learning theory, we may want to look for alternative explanatory theories.

Interestingly, the assumptions of knowledge assimilation in each alliance and integration across alliances also seem to contradict what we observe in practice, i.e., large pharmaceutical firms' actual strategies. Pharmaceutical firms increasingly incorporate options in their deal structures (Ernst & Young 2010): they make initial investments in risky alliances with the *option* to further invest in the future, when uncertainty is reduced and the most promising alliances can be identified. Option logic in alliance portfolio management thus refers to the possibility to postpone choice.

Option-based collaborations are the primary vehicle for GSK to develop new medicines, as indicated by the following quote from their Worldwide Business Development brochure: "We seek organizations that have a robust discovery engine and the capability of developing compounds to clinical proof of concept, at which point GSK *would have the option* for further development and commercialization" (italics added). This approach is quite different from SmithKline Beecham's approach in the 1990s when it determined project portfolio composition and resource allocation in one and the same phase (Sharpe and Keelin 1998). A real options approach implies that (part of) resource allocation decisions are postponed to a later phase.

Similar to GSK, Eli Lilly makes equity investments in promising emerging companies that have the *potential* to contribute to firm value in the long run (Lechleiter 2010). As a final example, Novartis allies with biotechnology firms in diverse technology domains to increase the *likelihood* that some of these alliances will successfully produce superior drugs (Novartis Venture Fund activity reports). In sum, pharmaceutical firms do not seem to consider each alliance as a source of knowledge that should be assimilated and integrated, contrary to what learning theory assumes; rather, they increasingly adopt a real options perspective with regard to their alliance portfolio to more effectively deal with risk.[2]

Formally, an investment in a real option (a particular domain of knowledge) conveys the right, but not the obligation, for a firm to make further investments or defer such investments in the future (McGrath and Nerkar 2003). Real options reasoning can be applied in any context characterized by uncertainty regarding the link between investments and outcomes, time dependence of future events on current decisions, and a possibility to exercise options (Chatterjee et al. 1999; Kogut and Kulatilaka 1994).

Central to real options reasoning is that the value of an options portfolio increases with its diversity. If real options reasoning is adopted by most firms, we should

[2] Interestingly, a further analysis of the data described in the excerpt showed that internally diversified firms faced lower turbulence in terms of profitability and stock prices, which may be indicative of reduced vulnerability to risk as a consequence of diversification.

expect a positive linear or even convex effect of portfolio diversity on profitability. Arguably, not all firms choose to strategically bet on different horses; it is well accepted that specialization can also be beneficial as firms gain in-depth knowledge that may give them a competitive edge (Fleming 2001; Katila and Ahuja 2002). Given the observations in managerial practice, in particular in evolving science-based industries such as pharmaceuticals, the effect of portfolio diversity on profitability may well be U-shaped, where the most profitable firms are those that gain a competitive edge by specializing in only a few technology domains and those that spread their bets by taking real options in diverse technology domains. Firms that fail to specialize or diversify are stuck in the middle.

In conclusion, alternative theoretical perspectives lead to vastly different expectations. The very scant empirical evidence does not appear to support the learning theory perspective; moreover, observations of managerial practice suggest that pharmaceutical firms have increasingly adopted a real options perspective, which is based on different behavioral assumptions. More empirical research is required to contrast alternative perspectives, and in particular to examine the explanatory power of real options theory, in order to derive informed managerial recommendations. In his recent review paper on alliance portfolios, Wassmer (2010) calls for more research on the profitability consequences of alliance portfolio composition. I suggest we start with improving our understanding of technological diversity.

Importantly, there may also be an additional reason why previous research studies have not delivered clear-cut generalizations: firms differ. Some firms are better equipped than other to benefit from a diverse alliance portfolio, but we know very little about firm heterogeneity. What distinguishes those firms that not only compose diverse alliance portfolios but also manage to reap the benefits? This question brings us to Challenge 2.

5.4.2 Challenge 2: Firm Heterogeneity

Not all firms benefit equally from alliance portfolio diversity. Yet, the portfolio literature has not paid much attention to firm differences. A possible explanation is that the portfolio literature draws on network theory, where characteristics of the actors are seldom accounted for (a limitation of the literature that is often referred to as "over-socialization"). The lack of attention to firm characteristics contrasts sharply with the key role of firm differences in the innovation and strategy literature. An important challenge that needs to be addressed to advance our understanding of alliance portfolios is to explicitly account for firm heterogeneity. Below, I argue that differences across firms in terms of (1) managerial resources committed to portfolio management and (2) the presence of internal routines to deal with extramural knowledge help explain why some firms benefit more from a diverse alliance portfolio than other firms.

First, when firms take a portfolio perspective, they need to commit appropriate managerial resources. The commitment of managerial resources is likely to

improve the articulation and implementation of a portfolio strategy as well the evaluation of its performance. Bamford and Ernst (2002) underscored the importance of top level involvement in alliance portfolio management: "Unless a corporate executive accepts responsibility for overseeing all or most of a company's alliances, no one will take the time to identify broader performance patterns or to assess the company's alliance strategy" (p. 31). Eli Lilly recognizes that alliance portfolios risk becoming a drain on valuable resources if not sustained by top management: "we at Lilly must maintain a focus on the core capabilities and senior management skills necessary to manage a diverse and growing portfolio" (Lechleiter 2010, p. 23).

Recent studies in the marketing field have pointed to the key role of top management in explaining differences in innovativeness across firms. Yadav et al. (2007) find that the future focus of banks' CEOs hastens their adoption of online banking, while Rao et al. (2008) report that, in the biotechnology context, the composition of a firm's board of directors (i.e., the presence of technical directors) increases abnormal stock returns to new product announcements. Finally, Wuyts and Dutta (2008) find that biotechnology firms' position in the network of interlocked directory boards influences their success with obtaining new licensing deals. Thus, there is ample evidence that top management plays a role in explaining differences in innovativeness and performance, opening up a research opportunity for portfolio studies.

Second, the company should also have the appropriate internal routines to deal with the exposure to diverse technological knowledge that results from portfolio diversity. One of the flagships of successful drug co-development, Merck Research Laboratories, attributes its successful external knowledge sourcing strategy to its internal innovative strategy (Pisano 2002). Even though academic scholars have acknowledged for quite some time that internal strategic choices and capabilities affect a firm's ability to screen external opportunities (Arora and Gambardella 1994; Veugelers and Cassiman 1999), very little progress has been made both from a theory and from an empirical point of view.

Interestingly, however, very recent advances in the absorptive capacity literature offer a theoretical angle that may help revive the research that links internal firm characteristics with external knowledge sourcing. According to the traditional notion of absorptive capacity (Cohen and Levinthal 1990), direct associations between a firm's internal knowledge and external knowledge aid in the assimilation, transfer, and use of new knowledge. A more recent insight that is gaining acceptance in the absorptive capacity literature, however, is that firms' ability to value and absorb external knowledge is a function of higher-order internal routines (i.e., behavioral regularities that result from cumulative experiences). These routines constitute the building blocks of firm capabilities that are essential in benefiting from external linkages. Lewin et al. (2011) consider the internal higher-level routines for managing variation and selection as critical for the development of absorptive capacity. King and Lakhani (2011) focus on internal invention as a way to learn about alternative problem-solving modes that can subsequently be practiced when confronted with external ideas.

Admittedly, the discussions of higher-order routines and capabilities are rather abstract; moreover, they are inherently intangible and notoriously difficult to measure: these are serious hindrances for empirical testing (Lewin et al. 2011). How can the recent insights from the absorptive capacity literature be used to derive actionable managerial recommendations? Future research on alliance portfolios and firm capabilities should highlight what concrete firm actions or strategies help generate the routines and capabilities that facilitate external knowledge sourcing. As mentioned earlier, routines result from accumulated experiences. What are the firm actions that produce these experiences? If we can identify firm actions that help build the routines for valuing extramural knowledge, we can derive concrete recommendations that help managers benefit from an alliance portfolio.

The most logical starting point, in my view, is to examine the strategies that firms employ to generate knowledge *internally*. These strategies generate experiences that help value extramural knowledge. In order to identify what strategies may be most effective to this end, we need to understand the challenges of dealing with a diverse alliance portfolio. For example, Ahuja and Lampert (2001) identify three organizational pathologies in the realm of breakthrough innovations: "a tendency to favor the familiar over the unfamiliar; a tendency to prefer the mature over the nascent; and a tendency to search for solutions that are near to existing solutions rather than search for completely de novo solutions" (p. 522). The diversity of alliance portfolios and the associated need for a broad outlook on the technological field form a fourth challenge. Firms that organize their internal knowledge creation strategy to meet these four challenges may build the necessary routines to benefit from a diverse alliance portfolio (see Wuyts and Dutta 2012 for a further elaboration of these ideas and first evidence from the biopharmaceutical industry).

5.4.3 Challenge 3: The Changing Nature of Collaboration

A third challenge for alliance portfolio research and practice is particular to the pharmaceutical industry: technological and institutional developments will likely change the nature of collaboration. The evolution of biotechnology, the emergence of nanotechnology, the notion of personalized medicine, and industrial and institutional changes are among the factors that change the nature of collaboration.

Evolution of biotechnology. When biotechnology emerged as a commercially viable path to developing new drugs in the mid 1980s, pharmaceutical firms sought to keep track of the emerging technological field by allying with biotechnology firms. Even though still today there is a functional divide between biotechnology firms and pharmaceutical firms in the industry, the distinction is not as clear-cut as several pharmaceutical firms developed strong biotechnology capabilities by the end of the 1990s (Vassolo et al. 2004). This change in the functional divide of the industry has implications for the nature of collaboration.

The development of a science-based industry naturally follows a pattern similar to the development of science itself. The latter is discussed in the philosophy of

science and in particular in the literature on paradigms. A new paradigm fundamentally alters the approach used for search and problem-solving; thus, biotechnology can be categorized as a genuine new paradigm. It is intrinsic to scientific development that after the emergence of a new paradigm, a period of paradigm refinement and articulation is required as paradigms are open-ended, leaving many things unexplained (Kuhn 1962). Translated to the rise of biotechnology in the pharmaceutical industry, arguably the late 1980s and the 1990s correspond to the emergence of the paradigm in this industry. If the year 2000 denotes approximately the moment where biotechnology has become ingrained in the capabilities of pharmaceutical firms, the last decade is characterized by paradigm development and refinement.

Put differently, biotechnology has gradually moved from an emerging technological field to an established (developing) field. This development is important for both the study and management of firms in the biopharmaceutical industry, as an emerging technological field is characterized by exceptional uncertainty and complexity (Macher 2006) and the nature of scientific inquiry (e.g., persistence in a particular area of research and sensitivity to social dynamics of the research community) differs in early versus late stages of an emerging field (Rappa and Debackere 1995). In sum, even though there are no signs that the technological developments in biotechnology will abate in the near future, the way biotechnology firms as well as pharmaceutical firms select and collaborate with their partners is likely different from the 1980s and 1990s, i.e., from the period that has been subject to empirical scrutiny.

Emergence of nanotechnology. While many pharmaceutical firms continue to invest in biotechnology, other scientific fields are emerging. First, since the 2001 US National Nanotechnology Initiative, nanotechnology is becoming more and more important. Also in the pharmaceutical industry, nanoparticles have different areas of application, such as in biomarkers and diagnostics for early disease detection and drug delivery and efficacy improvements (Netzsch Fine Particle Technology, 2008).[3] Pharmaceutical companies consider nanotechnology a promising platform to improve drug design and streamline drug development (Hobson 2009). The consequences of nanotechnology for pharmaceutical firms may not be clear-cut, yet it is worthwhile to follow up on this emerging scientific field in the study of alliance portfolios.

Personalized medicine. Another potentially interesting development relates to the increasing potential of personalized medicine. Most of the prior literature on innovativeness in the pharmaceutical industry, including the studies on alliance portfolios, focused on the generation of radical innovations or blockbuster drugs. Some have argued, however, that if the promise of personalized medicine is to materialize, new business models are required that are not focused on the quest for one winner but rather on the creation of a broad palette of more effective and profitable,

[3] NETZSCH Fine Particle Technology, LLC, downloaded from http://www.pharmamanufacturing.com/whitepapers/.

targeted treatments (Aspinall and Hamermesh 2007). Such a development may have consequences for optimal portfolio management. Technological uncertainty coupled with resource restrictions will likely continue to motivate pharmaceutical firms to take options on alternative technologies. However, once select options are exercised, their exploitation may differ if the desired outcome is no longer a one-fits-all drug but a series of variants on a particular treatment.

Industry and institutional change. Pharmaceutical firms are confronted not only with scientific developments but also with a changing industry environment. Recent developments in IT and telecommunications have stimulated pharmaceutical firms to forge alliances with players in other industries (Ernst & Young 2010). To obtain a full picture of a firm's alliance portfolio, researchers as well as managers will have to look beyond the biopharmaceutical industry. Possibly, new portfolio constellations will consist of multiple sub-portfolios (e.g., sub-portfolios in biotechnology, nanotechnology, and ICT), bringing additional complexity to resource allocation decisions. The risk for unwieldy management structures (Goerzen and Beamish 2005) as well as the need for top management guidance and strong internal routines and capabilities may become even more pronounced.

Finally, the alliance literature has been remarkably silent on the role of the institutional environment. Yet, future research on alliance portfolios may need to account for the dramatic changes that the institutional environment is experiencing, at least in the United States. To give one example, healthcare reforms have changed the nature of individual partnerships where contractual milestones that were previously related to clinical-trial outcomes only, now often also relate to commercial targets (Ernst & Young 2010).

5.5 Conclusion

I conclude with a recapitalization of insights and a discussion of implications for managers and academicians with an interest in the pharmaceutical industry.

5.5.1 Recap

The study of alliance portfolios in the pharmaceutical industry remains a topic of high importance. This chapter focused on the key role of technological diversity in alliance portfolios. As a cautionary note, I pointed to the diverse facets of diversity and the need to carefully select the type of diversity to be studied and to select an appropriate measure. This message may not come across as thought-provoking. Yet, the gap between construct and measures in the previous literature is worrisome because some of the measures used to capture technological diversity also captured other theoretically relevant constructs (e.g., tie strength and partner diversity). Such confounds complicate the derivation of generalizations. An excerpt from a research

study on intrafirm diversification showed that even two closely linked aspects of diversity—technological diversity and diversity of therapeutic classes—are empirically distinguishable and exert differential effects on performance.

Subsequently, I outlined three major challenges that are food for thought for practitioners and provide research opportunities for academics. A first challenge relates to competing theoretical perspectives. The traditional learning perspective may not be the optimal perspective to understand portfolios in a fast-moving field such as the pharmaceutical industry. The scant empirical evidence does not appear to be supportive of the assertions that firms try to assimilate knowledge from each alliance and integrate knowledge across alliances. Managerial practice suggests we need to use a different perspective: option contracts are increasingly popular in the biopharmaceutical industry. Real options reasoning is bound to gain ground in this literature. More empirical research on the profitability consequences of portfolio diversity is necessary to explain performance differences across firms.

A second challenge relates to the need to account for contingencies, as not all firms benefit equally from similar portfolio compositions. It is insufficient to control for unobserved heterogeneity in an econometric way; on the contrary, the added value of future research will be more likely situated in making heterogeneity observable. New developments in the absorptive capacity literature may prove helpful, if concrete factors are derived from these abstract discussions. The explicit study of dimensions of internal knowledge creation, for example, may help explain why some firms benefit more from diverse alliance activity than other.

Third, the nature of collaboration in the pharmaceutical industry is changing. Biotechnology has moved from an emerging paradigm to an accepted source for opportunity search and problem-solving (i.e., for new drugs); new technological developments such as in the area of nanotechnology need to be followed up and eventually be incorporated in the study of alliance portfolios; developments in other industries have broadened the set of potential partners for pharmaceutical firms to include actors in IT, telecommunications, and the like; and the institutional changes in the healthcare sector lead to a reconsideration of milestones and targets in individual alliances.

5.5.2 Implications for Managerial Practice

I illustrated that some large firms already actively pursue an alliance portfolio strategy in the pharmaceutical industry. For those firms that don't, the need to *shift from managing alliances to managing the portfolio of alliances* is a first key take-away. Portfolio studies have shown repeatedly that alliance portfolios do impact firm performance above and beyond the impact of the individual alliances. The entire discussion on technological diversity, for example, is pointless if firms shape their strategies at the alliance rather than the alliance portfolio level.

A second key take-away for managers is that *technological diversity occupies a central place in portfolio management*. Diversity is worth pursuing in a

science-based field such as pharmaceuticals, especially if the alliances are drafted as option contracts. When the pharmaceutical firm considers and structures alliances as real options on new drugs, it can restrict its resource commitments to initial investments and postpone the decision to invest more, to later point in time when it is clearer if the alliance lives up to the promise. Ample evidence in the finance and management literatures shows that diversifying an option portfolio reduces risk and enhances performance outcomes (e.g., Aggarwal and Samwick 2003; Gavetti and Levinthal 2000). A real options perspective is therefore more than just another theory; it is a motivator for firms to diversify their alliance portfolio and deal with technological uncertainty in a more cost-efficient way and with higher likelihood of positive payoffs. In particular, McGrath and Nerkar (2003) provide a very clear insight into the fundamentals of real options reasoning.

A third key take-away is that *not all firms appear to benefit equally from a diverse alliance portfolio*: *senior management commitment and internal knowledge creation processes explain why some firms benefit more than other*. On the one hand, testimonials from pharmaceutical industry experts and recent papers in the marketing literature show that top-down commitment enables companies to take and benefit from strategic actions. While following logically from prior related studies, empirical evidence of the importance of senior management involvement in alliance portfolio management is scant as this branch of the literature is still in its infancy. On the other hand, I argued that the firm's internal knowledge creation processes determine how well it can benefit from diverse alliance activity. The first evidence (Wuyts and Dutta 2012) indicates that external knowledge sourcing is a complement rather than a substitute for internal knowledge development.

A fourth key take-away is that *alliance portfolio management is dynamic* (one of the dimensions of portfolio management, see Fig. 5.1). In an environment that is continuously changing along multiple dimensions, ranging from scientific breakthroughs to the legislative environment, what constitutes an optimal portfolio today may be source of constraint rather than opportunity tomorrow. As a practical consequence, alliance portfolio management should not be reduced to a task force that shapes the alliance portfolio strategy once and for all; rather, the assertions regarding the future developments of the field and the received wisdom of the environment that may guide portfolio decisions at one point should be regularly challenged.

Concretely, to tackle some of the current developments, individual alliance deals may need to be forged increasingly as option contracts. Further, the decision which alliance options to exercise will likely rely increasingly on commercial goals next to technological goals. In addition, a more complex, multilevel approach to portfolio management is likely to emerge—with an umbrella portfolio consisting of several sub-portfolios that cover main areas such as biotechnology, nanotechnology, and ICT. Finally, the primary goal of portfolio management, identifying one-fits-all blockbuster drugs, may need to gradually change to the identification of a broad palette of targeted treatments, in response to the promise of personalized medicine.

5.5.3 *Implications for Academia*

In previous research, the pharmaceutical industry has proven to be a fertile ground for research on external R&D, alliances, and technology licensing. The pharmaceutical industry is a prototypical example of a science-based industry with both high economic and societal values. Pragmatic concerns such as data availability undoubtedly helped trigger research in this industry. Also marketing scholars have become increasingly interested in the pharmaceutical industry, which is a manifestation of a widening interest domain that extends well beyond the "traditional" consumer packaged goods industries. It is a positive development that for more than a decade, marketing scholars have turned to the study of innovation in technology- and science-based industries. This necessary expansion has also opened up the marketing field to the study of new phenomena. This chapter covered one such phenomenon, external knowledge sourcing. More than one and a half decades ago, Powell et al. (1996) observed a change of the locus of innovation in the biopharmaceutical industry from the individual firm to network constellations. While in the marketing field, alliance research was initially restricted to individual alliances, more recent studies on interorganizational linkages in technology-intensive industries have looked beyond the dyad (e.g., Wuyts et al. 2004a, b; Yli-Renko and Janakiraman 2008).

The new challenges in managerial practice may guide academic scholars in formulating research questions and seeking for empirical generalizations in portfolio management. To tie back to the key role of portfolio diversity, it is noteworthy that alliance diversity can be both a cause and a consequence of new opportunities. While some studies looked into the emergence of alliance portfolios as a result of business strategy (Hoffmann 2007), other studies looked into their consequences for business strategy (e.g., Wuyts et al. 2004a). The latter was also my perspective in this chapter; rather than distinguishing cause from effect, however, we may want to acknowledge and examine the dynamic iterative process between portfolio composition and business strategy to further advance this field. This is only one possible route to advance. New research avenues emerge also more directly from the topics covered in this chapter, leading to new questions that hopefully future research will investigate. I conclude with four such research questions:

- What is the optimal alliance portfolio composition, in light of the six dimensions of alliance portfolio management identified in Fig. 5.1? Addressing this question requires a more integrative approach than prior research has offered.
- Do firm characteristics such as top management involvement and internal knowledge creation processes help explain variation across firms in how much they benefit from alliance portfolio diversity? Addressing this question requires a contingency perspective, which is uncommon in the alliance and network literatures but fundamental to the strategy literature at large.
- Which other factors—such as alliance contractual specifications and portfolio governance approaches—help explain variation across firms in how much they benefit from alliance portfolio diversity?

– How should pharmaceutical firms shape their alliance portfolio management approach to be receptive to a changing environment; in the case of the pharmaceutical industry, to address scientific developments beyond biopharmaceuticals such as nanotechnology, the promise of personalized medicine, and healthcare reforms? This approach requires a stronger institutional embedding of alliance portfolio studies than we have witnessed thus far.

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Chapter 6
Evaluating the Impact of Treatment Effectiveness and Side Effects in Prescribing Choices

Tat Chan, Chakravarthi Narasimhan, and Ying Xie

Abstract Drugs can be effective in curing an illness or relieving a symptom but can have harmful side effects. The value of a drug, among others, depends on the trade-off between treatment effectiveness and side effects. There has been a long history that treatment effectiveness and safety are used as two of the most important attributes to determine the value of a drug. This chapter provides an overview of research on evaluating effectiveness and side effects of prescription drugs. We first briefly review the standard industry practice of using clinical trials data to measure the effectiveness and side effects of a drug. We then discuss how researchers may utilize clinical trials to gauge participants' preferences. After that, we provide a literature review on studying treatment effectiveness and side effects using post-marketing prescription choice data. Lastly, we close the chapter with suggestions on future research questions, for both practitioners and academic researchers.

6.1 Introduction

Drugs can be effective in curing an illness or relieving a symptom but can have harmful side effects. The value of a drug, among others, depends on the trade-off between treatment effectiveness and side effects. There has been a long history that treatment effectiveness and safety are used as two of the most important attributes to determine the value of a drug. In fact, in the United States, since 1938 every new drug has been the subject of an approved NDA (new drug application) before commercialization,

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and the primary goal of the NDA is to provide enough information to allow the FDA (food and drug administration) to assess whether the new drug is safe and effective in its proposed uses and whether the treatment effectiveness of the drug sufficiently outweigh the risks associated with side effects.

A standard way to compare effectiveness and severity of side effects across drugs is through clinical trials. For example, in 2000, Bristol-Myers Squibb carried out a clinical trial to compare the effectiveness of its cholesterol lowering drug Pravachol against Pfizer's Lipitor. After four and half years the median cholesterol level was 95 mg per deciliter among those who took Pravachol compared to 62 mg per deciliter in the Lipitor group. Another measurement showed that 26.3 % of patients in the Pravachol group either died, suffered a heart attack, or other complications, compared to 22.4 % of those in the Lipitor group (see Cannon et al. 2004). Based on these findings, the researchers concluded that Lipitor provides greater protection against death or major cardiovascular events than Pravachol does. In another example of clinical trial, Bresalier et al. (2005) found from their study that patients who used Merck & Co.'s blockbuster painkiller Vioxx had a significantly higher risk of heart attacks and strokes compared with patients in the placebo group (1.50 vs. 0.78 thrombotic events per 100 patient-year). Safety concerns were so high that in September 2004 Vioxx was pulled out by the manufacturer from the market.

However, comparison along a single dimension does not reveal the full picture. Although less effective in lowering cholesterol, Pravachol may have fewer or less severe side effects than other drugs in the same therapeutic class. According to the same study by Cannon et al. (2004), only 1.1 % of patients in the Pravachol group had a higher level of enzymes that could lead to liver problems, compared with 3.3 % in the Lipitor group. Similarly, with the more severe side effect of a higher cardiovascular risk, Vioxx was more effective in treating rheumatoid arthritis—Bombardier et al. (2000) reported in their study that patients in the Vioxx group had significantly lower number of gastrointestinal and other complicated events than patients in the group who used another existing treatment. At a 3-day hearing held by the Food & Drug Administration in late February, 2005, even though the 32 outside experts agreed that Vioxx did pose serious risks, they also recommended that Vioxx was useful enough that it should not be banned (Carey and Capell 2005).

The goal of a clinical trial is to objectively measure effectiveness and side effects of a drug. However, as illustrated in the two examples above, a more effective drug may be associated with more severe side effects, and a safer drug may be less effective. It is important for researchers to understand the importance of treatment effectiveness and side effects from the physician and patient perspective. That is, how do patients and physicians *subjectively evaluate* these treatment outcomes?[1] Without understanding such evaluations it is impossible for policy makers to determine the value of a medical treatment. The reason is obvious. For example, would most patients rather take a more effective drug in relieving pain but with higher

[1] We define "evaluations" as how physicians and patients are willing to trade-off between treatment effectiveness and side effects across drugs.

cardiovascular risk such as Vioxx instead of a less effective but safer drug? If the answer is yes, it may benefit the society that Vioxx remains in the market as long as patients are well informed of the risk. Only after understanding the willingness of trade-off between effectiveness and side effects among patients and physicians can policy makers fully study the welfare impact of regulations on entry or termination of drugs in the market. From the managerial perspective, to effectively market their products, pharmaceutical companies have to convey through marketing communications the benefits of their drugs that most physicians and patients consider as important and that they have advantages over competitors.

Using clinical trial data alone, it is difficult for researchers to make inference of the physician and patient evaluations. This is because participants of clinical trials are randomly assigned to treatment groups, rather than actively choosing which treatment to receive. More recently, we have seen an increasing trend in clinical trial studies that researchers supplement the objective treatment outcome data with participants' evaluation of treatment outcomes or their compliance behavior to infer the importance of treatment effectiveness vs. side effects (e.g., Chan and Hamilton 2006; King et al. 2007; Lamiraud and Geoffard 2007; Bordeleau et al. 2010). In addition to clinical trials, pharmaceutical companies and consulting firms have routinely collected physician and patient prescription choice data at both aggregate and individual level after a drug's launch. This type of data records which treatment a physician chooses for a particular patient when faced with alternative treatments in the real market environment. In standard economic models consumer preferences for multiple product attributes are inferred from observed product choices. Similarly, physician and patient preferences for treatment effectiveness and side effects may also be inferred from observed prescriptions. One of the challenges of using this approach is the limitation of prescription data. To understand the trade-off between treatment effectiveness and side effects, we argue that prescription choice data alone is insufficient; instead, researchers have to use additional data sources, such as observed treatment length in Crawford and Shum (2005) and self-reported switching reasons in Chan et al. (2013). Furthermore, unlike some other product categories such as consumer package goods where consumers have more knowledge of the product quality and their own preferences, physicians and patients usually have large uncertainty when evaluating treatment effectiveness and side effects especially for those drugs new in the market. Physicians typically rely on a variety of information sources to learn about these attributes, in addition to the public domain information such as clinical trial reports. To correctly infer the physician and patient preferences, it is important for researchers to take account of how these uncertainties may impact prescription choices. It is also important for pharmaceutical companies to understand how various types of marketing channels may help to reduce the physician and patient uncertainty of the important drug attributes that eventually will influence prescription decisions.

This chapter provides an overview of research on evaluating effectiveness and side effects of prescription drugs. We first briefly review the standard industry practice of using clinical trials data to measure the effectiveness and side effects of a drug. We then discuss how researchers may utilize clinical trials to gauge

participants' preferences. After that, we provide a literature review on studying treatment effectiveness and side effects using post-marketing prescription choice data. Lastly, we close the chapter with suggestions on future research questions, for both practitioners and academic researchers.

6.2 Measuring Treatment Effectiveness and Side Effects Using Clinical Trials Data

In this section, we describe the industry-wide practice of measuring treatment effectiveness and safety of drugs through clinical trials. In particular, we provide a brief overview of studies in both the pre-marketing and post-marketing period, followed with a discussion on the statistical analysis typically performed on clinical trial data. We also discuss its limitations and conclude that it is important to investigate the impact of treatment effectiveness and side effects using the post-marketing prescription choice data.

6.2.1 Pre-marketing and Post-marketing Clinical Trials

Clinical trials conducted before the approval of NDA are normally called pre-marketing clinical trials, which can be further divided into three different phases. Phase I clinical trials are the first stage of testing a new drug treatment in human subjects. The goals are to determine whether the new treatment is safe to be used by patients, what is the best way to give the treatment (for example, through a pill or an injection), and what is the right dose of a drug treatment—that is, the amount that causes few side effects. This initial phase of testing, which may take several months to complete, usually includes a small group (often 20–100) of healthy volunteers,[2] who are generally paid for participating in the study. Participants will continue to receive the drug treatment until several half-lives of the drug have passed. They will then take many physical exams and tests (for example, blood tests) so that doctors can find out how the treatment affects them, including how it is absorbed, metabolized, and excreted. About 70 % of tested treatments[3] successfully complete Phase I studies.

Once a new drug treatment has been confirmed to be safe in Phase I trials, Phase II trials are performed on larger groups (often 100 or more participants) to test whether and how well the treatment helps patients, as well as to continue Phase I safety assessment to test if there are any less common side effects that may appear

[2]There are circumstances when some drug candidates skip Phase I and directly enter Phase II testing. Also, in cases of terminal cancer or HIV when patients lack other treatment options, control conditions (placebo) may not be used because it is considered ethically unjustifiable to deny treatments to patients with life-threatening conditions.

[3]We use "treatment" and "drug" interchangeably in this chapter.

when a larger group of volunteers and patients receive the treatment. This second phase of testing can last from several months to 2 years. Some Phase II trials are designed as case series, demonstrating a drug's safety and efficacy in participants. Other Phase II trials are designed as randomized clinical trials, where half of participants are randomly selected to receive the tested treatment while the other half of participants receive a placebo or a standard treatment. This design can provide the most compelling evidence on how the treatment under study affects human health. Often these randomized clinical trials are "double-blinded" in the sense that neither participants nor researchers know who received what treatments. This "blinding" has the advantage of preventing biases, which may be caused by researchers being tempted to give specific treatments to specific participants or by participants who may choose to quit the treatment process had they known they were getting the placebo. About one-third of study treatments pass both Phase I and Phase II trials.

Like most Phase II trials, Phase III trials are also randomized clinical trials, although these trials typically include far more participating patients (ranging from several hundred to several thousand) and can last several years. This large-scaled testing provides the pharmaceutical company and regulatory agencies with a more definitive assessment of how effective the tested drug is, in comparison with the so-called gold standard treatment, i.e., the standard or the best known treatment in the marketplace. In these trials, half of the participants in the study are chosen at random to receive the tested drug treatment and the others receive the "gold standard" treatment. Other reasons for performing Phase III trials include attempts by the pharmaceutical company to expand the label,[4] that is, to show the drug works for additional types of patients or diseases beyond the original use for which the drug was approved for marketing, to obtain additional safety data, or to support marketing claims for the drug. While not required in all NDA cases, it is typically expected that the pharmaceutical company proves the safety and effectiveness of the drug through at least two successful Phase III trials, in order to obtain approval from the regulatory agencies, such as the FDA in the United States and the EMA (European Medicines Agency) in the European Union.

After a new drug obtains approval from the regulatory agencies, pharmaceutical companies may also conduct Phase IV clinical trials, also known as post-marketing surveillance trials. Pharmaceutical companies have several objectives at this stage: (1) to provide a safety surveillance, which is designed to detect any rare or long-term side effects of the treatment over a much larger patient population and a much longer timer period than was possible during the Phase I, II, and III trials, after a drug receives permission to be sold; (2) to compare the drug with other drugs already in the market; (3) to monitor the long-term effect of the drug on a patient's quality of life; and (4) to determine the relative cost-effectiveness of the drug treatment. Harmful side effects discovered by Phase IV studies may result in the drug being taken off from the market or restricted to certain use. The aforementioned Vioxx case is one such example.

[4] Studies for this purpose are sometimes categorized as "Phase IIIB" studies.

6.2.2 Analysis of Clinical Trials Data

In a typical clinical trial, researchers collect data on participants' health for a defined time period. These data include multiple measurements such as vital signs, concentration of the studied drug in blood, and other indicators of participants' health improvement. Researchers then perform statistical tests to compare the mean or median of these measurements across drugs, based on which researchers make inferences about a drug's effectiveness and safety in comparison to a placebo or other treatments. Although less common, researchers may sometimes also calculate the variance of these measurements across participants. The VIGOR (Vioxx Gastrointestinal Outcomes Research) trial is an example that helps illustrate the standard approach of data analysis in the medical literature.

The VIGOR trial was designed to assess the effectiveness of Vioxx, a selective inhibitor of cyclooxygenase-2, relative to that of naproxen, a nonselective NSAID (nonsteroidal anti-inflammatory drugs), in treating rheumatoid arthritis (Bombardier et al. 2000). Treatment effectiveness was measured by the incidence of clinical upper gastrointestinal events (i.e., gastroduodenal perforation or obstruction, upper gastrointestinal bleeding, and symptomatic gastroduodenal ulcers). Researchers employed a randomized controlled double-blind study. More than 8,000 patients were randomly assigned to receive either 50 mg of Vioxx daily or 500 mg of naproxen twice daily. The incidence of clinical upper gastrointestinal events was recorded over a number of periods until the end of the study. For data analysis, the researchers used Cox proportional-hazards model to estimate the occurrence of the incidence. Results showed that the risk of confirmed upper gastrointestinal events for patients in the Vioxx group relative to those in the naproxen group was 0.5 (95 % confidence interval, 0.3–0.6; $P<0.0001$), and the risk of complicated upper gastrointestinal events was 0.4 (95 % confidence interval, 0.2–0.7, $P=0.005$). The rate of discontinuation of treatment owing to a lack of efficacy was not significantly different across the two groups (6.5 % for the Vioxx group and 6.3 % for the naproxen group). Based on these findings, the researchers concluded that Vioxx is associated with a significantly lower incidence of clinical gastrointestinal events, therefore more effective in treating rheumatoid arthritis than naproxen.

In this study, the researchers also assessed the safety of these two drugs by comparing the proportion of various adverse events in each treatment groups. They found that the overall mortality rate (including death from gastrointestinal events and from cardiovascular events) was similar in the two treatment groups. The rate of ischemic cerebrovascular events was also similar in these two groups at 0.2 %, whereas myocardial infarctions occurred in only 0.1 % of the participants in the naproxen group but at a significantly higher 0.4 % in the Vioxx group (95 % confidence interval for the difference, 0.1–0.6). There are five most common adverse events that led to the discontinuation of treatment, including dyspepsia, abdominal pain, epigastric discomfort, nausea, and heartburn. The researchers found there was a significantly lower rate of discontinuing treatment due to any one of the five adverse events in the naproxen group than in the Vioxx group (3.5 % vs. 4.9 %). These findings suggested that Vioxx is associated with a higher risk than naproxen.

In this example, objective treatment outcomes, i.e., the occurrence of upper gastrointestinal events and ischemic cerebrovascular events, have been collected to measure the relative effectiveness and safety of the two treatments. However, how participants evaluate and make trade-off between effectiveness and side effects have not been studied. Realizing this limitation, researchers have recently included additional measures that reflect participants' preferences, along with the traditional treatment outcome data, in the clinical trials analysis.

Bordeleau et al. (2010) studied a multicenter, randomized, crossover clinical trial to compare venlafaxine, a SNRI (selective noradrenergic reuptake inhibitor) antidepressant, with gabapentin, another existing drug, in treating hot flashes for women with breast cancer. Though there has been evidence that both are effective and well tolerated, the question of which drug is preferred by the patients remains unanswered. To answer this question, participant preferences were measured along with the self-reported incidence of hot flashes and the occurrences of various side effects. Sixty-six participants were randomly assigned to receive either venlafaxine or gabapentin, for the first 4-week period; after a washout period they would be crossed over to the other treatment for a second 4-week period. At the end of the study, participants were asked to complete a questionnaire regarding their preferred treatment. The crossover design and after-study questionnaire bring researchers with additional information that is unavailable in traditional clinical trials. Analysis results showed that both drugs reduced hot flash scores to a similar extent. However, side effects profiles were different between these two treatments: while venlafaxine was associated with increased nausea, appetite loss, constipation, and reduced negative mood change, gabapentin was associated with increased dizziness and appetite. Out of the 58 patients who provided preferred treatment data, a majority of 38 chose venlafaxine, 18 chose gabapentin, and 2 had no preference for either drug. Researchers also found that participants' preferences are correlated with the treatment effectiveness, since their preferred treatment is usually associated with a larger reduction in hot flash.

King et al. (2007) used a discrete choice experiment embedded in clinical trial to study patient preferences across various treatment attributes, including symptom control, its effect on daily activities, side effects, and convenience and cost of taking medication. The purpose of their multicenter, crossover, randomized controlled trial was to compare the efficacy and safety of three preventive asthma medications, including formoterol, a long-acting beta agonist (LABA), montelukast, a leukotriene antagonist (LTRA), and fluticasone, an inhaled corticosteroid (ICS). The study contained three treatment phases, each with a 6-week duration followed by a 2-week washout period. The discrete choice experiment was conducted after participants received either formoterol or montelukast in the first treatment phase. Participants were then randomly assigned to read alternative profiles of a hypothetical drug, which varied in treatment attributes, before they made the choice whether to continue with the current drug, to switch to the hypothetical medication, or to take no medication. Patients also reported experienced symptoms, side effects, and their daily activities while they were on one of the medications. Researchers estimated a random-coefficient multinomial logit model using the reported choice data.

They found that patients were more likely to choose drugs that allowed them to participate in daily activities and sports, with minimal symptoms, fewer side effects, and at a less cost. Based on the model estimates, simulations can be conducted to quantify and compare the impact of various treatment attributes. For example, the authors found that doubling the cost of the hypothetical drug from $50 to $100 would lead to a 2.6 % increase in demand for the current drug.

The above studies have modified the experiment design (e.g., crossover in trials) to some extent that is quite uncommon in industry practice. In a standard clinical trials setup, researchers have used information on participant compliance together with treatment outcomes to evaluate participants' preferences for treatment effectiveness vs. less severe side effects. Substantial attrition or noncompliance (i.e., drop out from the trial before the end of the study) from participants has been documented as a common problem that plagued many clinical trials (e.g., Efron and Feldman 1991). Clinical trial literature has traditionally treated attrition as a sample selection bias issue that can be addressed by various statistical methods (e.g., Frangakis and Rubin 1999). However, given that it is a choice made by participants, attrition may reflect their evaluation of treatments (Lamiraud and Geoffard 2007). For example, if we find that the attrition rate among participants in a treatment that is more effective in reducing symptom but also has more severe side effects is higher than the other drugs, this may indicate that side effects are more important than effectiveness in participants' evaluation. Therefore, attrition may reveal information regarding participants' preferences.

Built on this assumption, Chan and Hamilton (2006) constructed a structural economic model in which individual participants make utility maximizing decisions concerning dropout/compliance in a randomized clinical trial. They specified utility as a function of both "publicly observed" outcomes (i.e., the measured health status in the experiment) and side effects privately observed by participants. They also assumed that participants in the experiment have uncertainty regarding the treatment effectiveness and side effects. They would acquire information through their participation in the experiment to learn about these attributes and update their beliefs according to the Bayesian rule. The authors applied the model to analyze data from the AIDS randomized clinical trial ACTG 175 (Hammer et al. 1996). ACTG 175 was a large scale randomized double-blind clinical trial designed to evaluate the effectiveness of four alternative therapies in treating HIV patients with CD4 cell counts of between 200 and 500 mm^3, including 600 mg of zidovudine (AZT), 400 mg of didanosine (ddI), 600 mg of zidovudine plus 400 mg of didanosine (AZT + ddI), and 600 mg of zidovudine plus 2.25 mg of zalcitabine (AZT + ddC). The "publicly observed" treatment outcomes in the data were participants' CD4 counts[5] measured at the outset of the trial and then at weeks 8, 20, 32, …, 104 of the trial. Substantial attrition was observed in the ACTG 175 trial, as roughly half of participants dropped out from the trials by the end of the second year.

[5]CD4 count is a marker for the status of an individual's immune system, which has been widely used to measure the progression of AIDS in the patient.

Their estimation result showed that for many participants, AZT yielded the highest level of utility though it had the smallest impact of the publicly observed CD4 counts. This finding was in contrast with previous evaluations, which concluded that combination therapies were superior to using AZT alone because of the greater improvement in CD4 counts. Their results suggested that using the standard evaluation criteria alone may generate misleading conclusions regarding effectiveness of alternative treatments. They also found that AZT + ddC had the most severe side effects on average, although it had the highest impact on CD4 counts by the end of the trial; and AZT + ddi and ddI had rather mild side effects and positive impact on CD4 counts, therefore were the preferred treatment for the majority of patients. In addition, the authors also found substantial learning throughout the trial, suggesting that early attrition was primarily driven by side effects, while later dropout was by treatment effectiveness.

In a related study, Lamiraud and Geoffard (2007) also used participants' adherence to medication regimen to estimate their subjective preferences. They developed a binary choice model of participants' regimen adherence behavior as the result of trade-off between treatment effectiveness and side effects. They then estimated the model using data from CNAF3007, a multicenter, randomized Phase IIIB trial, to compare the safety and efficacy of two HIV therapies, a new simplified 4-pill daily or two-intake regimen (referred as CBV/ABC) vs. the standard 11-pill daily or 3-intake regimen (referred to as CBV/NFV). Health status measures such as viral load and CD4 counts, occurrence of treatment-related side effects, and treatment adherence were recorded for each participant at the beginning of the trial and then at weeks 4, 8, 16, 24, 36, 40, and 48 of the trial. Although the treatment effectiveness (measured by both antiretroviral activity and the rise in median CD4 counts) and the occurrence of side effects were both comparable between these two regimens, the percentage of compliant participants was higher in CBV/ABC group than in CBV/NFV group. The authors found that the probability of compliance would decrease when side effects occurred, and increase when a positive change in the CD4 count was observed, in the previous period. Using the estimated coefficients associated with the side effects occurrence and the change in CD4 count, they quantified patients' trade-off between treatment effectiveness and side effects, i.e., how severe should the side effects be for patients not to comply with a treatment and how effective should the treatment be for patients to adhere to a treatment despite of the side effects?

6.3 Measuring Treatment Effectiveness and Side Effects from Prescription Data

In this section, we will first discuss the limitations of using clinical trials data, which calls for further using post-marketing prescription data to address some important issues related to treatment evaluation. We then provide a review of related literature

that uses the post-marketing data. We discuss the data and method used in various studies. We then proceed to discuss the implications of these results for pharmaceutical marketing managers and for social planners and regulators.

6.3.1 Some Limitations of Using Clinical Trials Data

Although recent advancement in the literature has made it possible to investigate participants' subjective evaluation of treatment effectiveness and side effects, there remain some issues that have not been fully addressed using clinical trials data alone, calling for the use of post-marketing prescription choice data. First, in the real market environment, physicians and patients are faced with alternative drugs they can choose from. This choice set is different from the choices participants in clinical trials can make; therefore, analysis results based on clinical trials data may not be easily projected to how physicians and patients will choose in the real market. Also, when making prescription decisions physicians are exposed to marketing efforts such as detailing, sampling, and direct-to-consumer (DTC) advertising from pharmaceutical companies. Pharmaceutical companies are interested in understanding the impact of these activities on prescription choices, which cannot be studied using clinical trial data.

Second, it has been documented in the literature that, when new drugs are introduced, physicians and patients usually have large uncertainty in evaluating the potential treatment effectiveness and side effects. If patients are risk averse, physicians are less likely to prescribe them drugs of which the outcomes are uncertain. Many questions are likely to be asked by physicians when a new drug is introduced: Is the drug more effective or with fewer side effects compared with other existing drugs? Does the drug work better for patients with severe or mild conditions? Public domain information such as clinical trial reports may not be sufficient to address all these concerns. Physicians also rely on a variety of other information sources including marketing communication, such as detailing, learning from the feedback from their patients (Narayanan and Manchanda 2009), and/or recommendations from other physicians either formally or informally (Manchanda et al. 2008), to learn about these attributes. Understanding how various types of information sources help to reduce physician and patient uncertainty of important drug attributes is crucial from the policy perspective. Pharmaceutical firms typically spend a substantial fraction of their marketing budget on detailing, the role of which is a frequently debated topic in public policy. Many people argue that detailing distorts physicians' prescription decision because it is mainly persuasive in nature and call for regulating or even eliminating such activities. But if detailing can help physicians learn about drug attributes, restricting detailing would slow down the adoption of new innovative drugs and therefore benefit the incumbent drugs by raising the entry costs. If the new drugs are better than incumbents in either effectiveness or side effects, restricting detailing could negatively affect patients' welfare because patients would be less likely to be prescribed the new drugs. In addition, uncertainty

may also vary across multiple attributes, for example, a physician's uncertainty about a new drug's effectiveness might be higher or lower than his uncertainty on its side effects; as a result, the impact of uncertainty reduction on consumers' choice may be very different across these attributes. A pharmaceutical firm may want to focus its marketing communication on an attribute that physicians are most uncertain about and/or it has an advantage over others. This is an important strategic question in product positioning. To address this question, we need to understand the relative efficiency of alternative information sources in facilitating physician's learning of a drug's effectiveness and side effects, which calls for the use of prescription choice data under the real market environment rather than the clinical trial data alone.

Lastly, while pre-marketing clinical trials may be able to provide adequate evidence about the efficacy of a new drug relative a placebo or an existing drug, the full safety profile of a new drug is rarely known at the time of approval by the FDA (Hiatt 2006). This is mostly due to the limited number of participants and short duration in clinical trials. For example, even though the larger Phase III clinical trials typically involve several thousands of participants over a few years period, it may still be difficult to detect rare side effects when treating chronic conditions. Furthermore, clinical trials have become increasingly expensive because of the growing competition for participants and reliable contract research organizations (CROs). According to a recent survey from Cutting Edge Information (2011), in the 3-year period from 2008 to 2011, the average per-patient trial costs have risen 70 % across all development phases, with the largest increase of 88 % (from $25,280 per patient in 2008 to $47,523 in 2011) in Phase IIIa trials. Under this situation, expanding the scope of clinical trials may be financially prohibitive for pharmaceutical companies. In contrast, post-marketing prescription data provides an ample, efficient, and economical alternative for researchers to study rare side effects after the drug is being marketed (Okie 2005).

From a researcher's perspective, the main issue of using post-marketing prescription data is that treatment conditions are not controlled and patients who use different drugs are not randomly assigned. Consequently, one has to make model assumptions to infer the true effectiveness and side effects of prescription drugs on patients, and how these treatment outcomes are evaluated by physicians and patients.

6.3.2 A Review of the Learning Literature in Pharmaceutical Studies

A large number of studies in marketing and economics have investigated how physicians and patients learn about product attributes in the context of prescription pharmaceutical market. Ching (2010) constructed a model where physicians learn about the quality of a generic drug through patients' feedback in the presence of consumer heterogeneity in price sensitivity. He then estimated the model using aggregate sales data for 14 drugs with patent expired during the 4-year period from 1984 through 1987.

He found that patients on average had pessimistic prior expectation about the quality of generics, and the diffusion rate of generics for price-sensitive consumers was much faster than that for price-insensitive consumers.

In Narayanan and Manchanda (2009), the authors focused on physicians' learning about the quality of a new drug through marketing communication as well as past prescription experience using a physician-level panel data from the ED category. By adding a hierarchical Bayesian structure to the Bayesian learning model, the authors were able to estimate how responsiveness to detailing varied across physicians and over time. They found there was significant heterogeneity across physicians in their rate of learning. Their result also suggested that firms could increase their profit if they took these temporal and cross-sectional differences in detailing responsiveness into account while deciding on their detailing plan.

Chintagunta et al. (2009) considered a physician's learning about new drugs' efficacy from patient feedbacks (as revealed by patient satisfaction surveys) as well as from other information sources such as FDA updates, media coverage, academic articles, and pharmaceutical advertising, and applied the model to a patient-level panel data from the Cox-2 inhibitor category. They also distinguished across-physician learning of a drug's efficacy from the within-patient learning of the match between a patient and a drug. Their results suggested that different sources of information had varied impact on physician learning: patient satisfaction had a stronger impact on the learning of the drug–patient match than across-drug spillovers, news articles had a weak positive impact on Cox-2 drug sales, FDA updates did not have any impact, while academic articles had a strong negative impact.

More recently, Camacho et al. (2011) proposed an extension to a Bayesian learning model by incorporating a salience effect (that some pieces of information are easier to retrieve from memory than others) in physician learning about drug quality. They calibrated the model on a physician-level panel dataset of Dutch general practitioner prescription choices in the obstructive airways category. They found that feedback from switching patients received significantly more weight than feedback from other patients, a strong evidence for the existence of salience effects in physician learning. Their findings also suggested that salience effects slowed physicians' learning and the adoption of new treatments. Other papers that used post-marketing prescription choice data to study physician learning include Narayanan et al. (2005) and Ching and Ishihara (2010, 2012).

6.3.3 Using Post-marketing Prescription Data to Evaluate Effectiveness and Side Effects of Prescription Drugs

One common feature shared by the studies above is that they focus on how physicians learn about the overall quality of the drug and/or the match value between the patient and the drug. However, as we have discussed earlier in this chapter, it is important to understand how physicians and patients make trade-offs between effectiveness and side effects when deciding prescriptions. For a newly launched

drug, physicians and patients may have large uncertainty in these treatment outcomes. It is of great interest from the policy and managerial perspective to separately identify how physicians and patients evaluate treatment effectiveness and side effects of different drugs and how they resolve their uncertainties using information from various marketing channels.

To achieve this objective, researchers have used observed treatment outcomes in addition to prescription choice data. Crawford and Shum (2005) is a good example. In the paper, the authors proposed a dynamic match model of demand under uncertainty in which patients learn from experience about two distinctive treatment effects of alternative drugs: the symptomatic effect and curative effect. A drug's symptomatic effect impacts a patient's per-period utility directly via symptom relief and/or side effect, while its curative effect impacts a patient's probability of recovery. The authors used drug choices from patients to identify the parameters related to symptomatic effect and used observed treatment lengths conditional on different sequences of drug choices to identify the parameters related to curative effect. They estimated the model using a patient-level panel data in the antiulcer drug market. They found that existing drugs in the market are ranked differently along these two dimensions, suggesting a trade-off has to be made when patients decide on their treatments. They also found that learning from ones' own prescription experience can help patients and their doctors overcome the costs of uncertainty in this market: the uncertainty in each dimension was sharply reduced even after a single prescription.

Treatment outcome data may be difficult to collect. Furthermore, for those categories that only relieve symptoms (e.g., antidepressants or erectile dysfunction (ED) drugs), objective measures of treatment outcomes (e.g., blood or cholesterol count) are not observed. A different identification strategy, therefore, is required to separately identify the impact of treatment effectiveness and side effects. In Chan et al. (2013), the authors rely on an additional data source, self-reported reasons for switching drugs, as well as the observed treatment choice for each physician–patient pair to achieve such research objective. While the overall quality evaluation of drugs from physicians and patients can be inferred from treatment choices, self-reported reasons for switching help to identify effectiveness and side effects as well as the heterogeneity of their impacts. A drug that accounts for greater proportion of those switching out due to treatment ineffectiveness (side effects) implies that, compared with other drugs, more patients find this drug less effective (with severe side effects) than expected. Since the data also reports to which other drugs these patients switch, further inference can be made that drug switched into is more effective (with less severe side effects) for that particular patient. Hence the potential correlations of both treatment effectiveness and side effects across drugs can be estimated from the data. Self-reported consumer survey data was proposed by Manski (2004) to help understand the extent of consumer uncertainty. Berry et al. (2004) used the data of consumers' self-reported secondary choice in the automobile market to identify the correlation of consumer preferences for product attributes. The approach used in Chan et al. (2013) is similar to theirs. The authors developed a structural model of a physician maximizing a patient–physician joint utility function under uncertainty

when making prescription choice and explicitly modeled the conditions under which switching reasons were reported. In their model, physicians' uncertainty about treatment effectiveness and side effects of alternative drugs comes from two sources: first, treatment outcomes are heterogeneous across patients; and second, even the mean effectiveness and side effects may be unknown to physicians and patients, especially for those drugs that are new to the market. They assumed that physicians learn from patient feedback as well as from the pharmaceutical company's one-to-one marketing communication efforts such as the detailing, and they allowed the informational content of detailing visits differ across the two drug attributes. They estimated the model using a physician-level panel data from the ED category for a period from August 2003 to October 2004. There were three drugs in this category: Viagra was launched in March 1998, followed by two new drug entries in 2003, Levitra in August and Cialis in November.

Their estimation result showed that the two new drugs, Levitra and Cialis, had significantly higher mean evaluation in effectiveness than the existing drug, Viagra. However, Levitra had the largest variation in effectiveness, while Cialis had the largest variation in side effects, among the three drugs. Because of the smaller heterogeneity in physician and patient evaluations as well as the existence of a significant switching cost, Viagra still had a significant market share even after 1 year of the two new drug entries. These results coincided with the reality that Viagra positioned itself as the "safest" (as manifested through its smallest heterogeneity in side effects) ED drug while Cialis was promoted on the base of its maximum "effectiveness" among the three in their recent advertising campaign. An additional finding from the "what-if" experiments shed light on the direction for the pharmaceutical company's product improvement effort: it was critical for Levitra to increase the consistency in treatment effectiveness and for Cialis to reduce the variability in side effects, instead of improving the average effectiveness or side effects across patients only. Their results also showed physicians had a large prior uncertainty regarding the effectiveness of Levitra and side effects of Cialis. Detailing with or without meal was more effective in reducing the uncertainty of effectiveness among physicians compared with learning from patient feedbacks. Specifically, they found that just one detailing visit was sufficient in eliminating prior uncertainty of the mean effectiveness among physicians for both new drugs. In contrast, there still existed considerable amount of prior uncertainty in mean effectiveness even with feedback from ten revisiting patients. However, detailing was less effective in reducing the uncertainty of side effects. Roughly speaking, the informative role for side effects of one detailing with or without meal was comparable to that of one patient feedback. These results suggested that for sales representatives the provision of information about side effects should be the priority in their "messaging" strategies during their subsequent detailing visits. If it was difficult for sales representative to convey clear message regarding side effects because of multiple side effects and lack of clear documentation on the incidence of these during clinical trials, managers might want to switch to other methods such as free sampling through which patient trials hence quick patient feedbacks may be induced to reduce the prior uncertainty in side effects.

In another study unrelated to physician learning, Venkataraman and Stremersch (2007) constructed measures of treatment effectiveness and side effects based on the medical literature and information from the FDA drug approval database, then examined how these two drug attributes would moderate the effect of marketing efforts on physicians' prescription decisions. Using a physician-level monthly panel dataset in three therapeutic categories (including statins, gastrointestinal and coagulation drugs, and ED drugs), they found that marketing efforts had a more positive effect on prescriptions written and samples dispensed by physicians for drugs that are more effective or with fewer side effects. This finding was consistent with the notion that pharmaceutical companies' marketing efforts can facilitate physicians' uncertainty reduction in both attributes as shown in Chan et al. (2013).

6.4 Conclusions and Future Research

A consensus in the marketing choice literature is that consumers' evaluation of multiple product attributes explains a substantial part of the variations in brand choices across consumers. Understanding consumers' preferences over the attributes and how each individual product performs on these attributes is essential for firm's strategic decision-making. This is also true for the pharmaceutical industry. Treatment effectiveness and side effects have long been recognized as the two most important attributes to determine a drug's value. In this chapter, we discuss the importance of evaluating the impact of treatment effectiveness and side effects on prescription choices, followed by a summary of research on evaluating these two drug attributes using both clinical trials data and post-marketing prescription choice data.

There are several directions for the future research. First of all, there have been very few studies that have measured the impact of treatment effectiveness and side effects on prescription choices in different empirical contexts. Using a dataset for life-style drugs (ED drugs), Chan et al. (2013) found that side effects had a smaller impact on prescription choice than treatment effectiveness. It would be interesting to study life-saving drugs such as cancer or AIDS drugs. Conceptually, the impact of treatment effectiveness vs. that of side effects in these categories can be vastly different from the ED category.

Second, as we mentioned in the previous section, treatment outcome measures may be difficult to collect by pharmaceutical companies together with the prescription choice data. Recently, electronic medical record (EMR) system has been gaining tractions in the US healthcare industry. EMR tracks individual patients' entire medical and health history, including both prescription choices and treatment outcome measures. We believe that this type of data will provide researchers new opportunities to further study the subjective trade-offs across various treatment attributes in the real market environment.

Third, in the real market environment, patients may learn about new drugs through DTC advertising by the pharmaceutical companies, which could lead patients to request a particular drug. Future research can investigate how much

these patient-oriented advertising effort, together with detailing efforts that target physicians, would influence patient and physician's evaluation of the treatment effectiveness and side effects of the new drugs.

Finally, a few studies have investigated how pharmaceutical companies' marketing efforts such as detailing can help to reduce physicians' prior uncertainty in treatment effectiveness and side effects associated with a new drug. There is a lot more to be explored along this line of inquiry. For example, most of these existing studies are only partial analysis, focusing on the demand side. It is important to study under market equilibrium conditions how pharmaceutical companies compete in detailing, and perhaps also in other policies such as pricing and DTC advertising in the presence of physician and patient uncertainty of treatment attributes.

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Chapter 7
The Successful Launch and Diffusion of New Therapies

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Abstract The successful launch and diffusion of new drugs is an essential factor of survival for many pharmaceutical firms. Sophisticated managers in this industry are in need for decision support tools that they can implement to increase the success of a new and approved pharmaceutical drug. In this chapter we present a review of such strategic and analytical tools. The review is based on significant contributions by marketing scientists, and is organized according to the components of a *launch and diffusion decision chain* we define. This chain represents the sequence of decisions managers must make with regard to the launch and diffusion of new drugs. The first element of the chain includes decisions regarding the specific methods by which pharmaceutical firms can gauge the commercial potential of a new treatment over time. Second, as pricing and promotion are prime instruments for pharmaceutical firms to extract maximum value, we review the means by which a manager can decide to extract the new treatment's commercial potential and generate value for

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the firm either by stimulating unit sales or through per-unit pricing. Third, pharmaceutical firms often operate in multiple markets. We therefore present an overview of the strategies that can be used to leverage the new treatment's potential across countries taking into account the different regulations, spending power for healthcare, prescription practice, among other factors, of different geographic markets. We conclude by reviewing possible directions for future advances in methods across the three chain elements.

For many large pharmaceutical firms that sell branded drugs, the successful launch of new therapies remains the key to profitable growth. New therapies are essential in enabling pharmaceutical companies to overcome the challenge of generic substitution—the replacement of branded drugs with generic alternatives, at the initiative of either physicians or pharmacists—as the patents of older drugs in their portfolios expire. Generic drugs enter the market at much lower prices compared with the original branded drugs they replace, as generic drugs do not need to go through the risky, costly, and lengthy process of new drug development. Grabowski and Vernon (1992) show that an original brand typically loses half of its market share 1 year after patent expiration. Generic substitution is ever increasing in scope and speed, given government regulations in many countries that promote generic dispensing at the pharmacy, in an attempt to control drug spending. Granted, there are multiple ways in which pharmaceutical firms that produce brand-name drugs can fight the trend of generic substitution. Some companies (e.g., Pfizer) own their own generic subsidiaries, others (e.g., Bayer, Merck Serono) offer diagnostics and other types of services in addition to their drugs or try to convince patients or physicians to be brand loyal, for instance, through social media (e.g., Johnson & Johnson). Nevertheless, the successful launch of new branded drugs remains crucial to the survival of such pharmaceutical companies and continues to be their primary means of differentiation.

Seemingly at odds with pharmaceutical firms' dependence on the success of new treatments, the number of newly approved treatments is declining. Grabowski and Wang (2006) review the decrease in the number of newly approved molecular entities in the period 1982–2003. Grewal et al. (2008) estimate that only 1 out of 50,000 molecules that receive initial investigation develops into a marketable drug. In 2010, only 21 molecular entities were approved (Jack 2011). The cost of developing such new drugs is enormous, between $500 million and $2 billion. Government agencies such as the FDA and the EMEA are increasingly critical of new drug applications, and are specifically attentive to the effectiveness/safety tradeoff. Furthermore, in several domains the need for new treatment has diminished, as many common diseases have long been treatable with effective drugs with few side effects, such as antihistamines, statins, beta blockers, and antibiotics. Several areas, such as oncology, neurodegenerative diseases, and autoimmune diseases, remain in high need of new drug development from a societal perspective, because existing therapies are not sufficiently effective for a large proportion of patients. However, drug development in these areas has presented few breakthroughs. Thus, given the high strategic importance of the launch of new pharmaceutical drugs and the lower frequency at

Fig. 7.1 The launch and diffusion decision chain

which approvals for such drugs occur, the successful execution of a new product launch has gained importance in the pharmaceutical industry.

This chapter gives a broad overview of the strategic and analytical tools that pharmaceutical firms can use to increase the success of a new product launch, given that these firms have attained the enviable position of having a new drug approved by regulatory authorities. Marketing scientists have made significant contributions to thought leadership in this area, and we will review those contributions in the following sections (also see, Stremersch and Van Dyck 2009).

We organize our discussion according to the components of the *launch and diffusion decision chain*. This chain, depicted in Figure 7.1, represents the sequence of decisions that managers must make with regard to the launch and diffusion of new drugs.

The decisions include the following:

- Decisions regarding the specific methods for the assessment of a treatment's commercial potential. In step 1, we will review several ways in which pharmaceutical firms can gauge the commercial potential of a new treatment over time. Developing a clear vision of a new treatment's commercial potential is essential for making sound decisions in subsequent steps.
- Decisions aimed at optimally extracting the new treatment's potential. In step 2, we review the means by which a manager can decide to extract the new treatment's commercial potential and generate value for the firm, either by stimulating unit sales or through per-unit pricing. Pricing and promotion are prime instruments for pharmaceutical firms to extract maximum value.
- Decisions regarding the strategy that will be used to leverage the new treatment's potential across countries. Pharmaceutical firms are often global firms. Therefore, launch teams are global teams that consider a worldwide launch strategy to successfully diffuse their drug in as many markets as possible. However, the international realm is complicated in pharmaceutical markets. Different geographic markets have different regulations, spending power for healthcare, prescription practices, and the like, and therefore differ in their attractiveness to firms from a new drug diffusion perspective. Moreover, different geographic markets may not be independent. For instance, prices may spill over from one market to another, because of gray trade or because of government regulations. A pharmaceutical firm needs to take such spillovers into account in its launch strategy. An important characteristic of launch strategies in the pharmaceutical industry is that the launch of new pharmaceutical drugs is never a "sprinkler launch" (i.e., launching in all countries at once) but rather is always a "waterfall strategy" (i.e., countries are staggered one after the other). Note, however, that this does not imply that all

innovations are launched first in the USA or in even in the domestic market of the manufacturing firm. We review these considerations in step 3.

This review is based on an exhaustive search across major scholarly journals in marketing, economics, and health.

7.1 Step 1: Assessing the Potential of a New Treatment

Marketing scientists have developed several methods to assess the potential of new treatments. Broadly, we can discern six different methodological frameworks to evaluate the commercial potential of new treatments (for an overview of the main characteristics of each framework, see Table 7.1). These frameworks can be divided into two main categories, distinguished according to the level at which they study the acceptance of a new treatment. Models in the first category, comprising diffusion models and sales models, study new product acceptance at the level of a group of people (region, segment, total market), whereas the models in the second

Table 7.1 Methodological frameworks for assessing new treatments' commercial potential

	Dependent variable	Level of model	Type of data
Aggregate-level models			
Diffusion models	Number of adopters of the new drug (cumulative across time periods)	Across groups of physicians	Observed behavior in panels across time (e.g., IMS Health physician panel) or stated behavior gathered from surveys or interviews (e.g., the Coleman et al. 1966 Medical Innovation study)
Sales models	Amount of active ingredient of the new drug sold (per time period)	Across groups of physicians or pharmacies	Observed behavior (e.g., IMS Health pharmacy audits)
Disaggregate-level models			
Prescription count models	Number of new or total prescriptions written	Physician-level	Observed behavior (e.g., IMS Health physician panel)
Learning models	Utility of the new drug (choice likelihood)	Physician-level/ Physician-patient-level	Observed behavior (e.g., the IPCI panel of Erasmus MC)
Consideration and choice models	Utility of the new drug (choice likelihood)	Physician-patient-level	Observed behavior (e.g., IMS Health physician panel)
Conjoint analysis	Utility of the new drug (choice likelihood or preference)	Physician- or physician-patient level	Stated preference (e.g., experimental conditions imposed on a sample of physicians)

category study acceptance at the level of an individual person (Table 7.1). The former models are therefore called aggregate-level models, whereas the latter are disaggregate-level models.

Diffusion models capture and forecast the cumulative number of new adopters (i.e., the cumulative number of physicians prescribing the new drug for the first time), whereas sales (growth) models capture the amount of the new drug's biologically active ingredient that is sold in a given market or region. This distinction between diffusion models and sales (growth) models—i.e., the distinction between the types of data they rely on—is important. The estimation of diffusion models in the tradition of Bass (1969) is known to create estimation bias when estimated on sales data rather than cumulative adoption data (see Van den Bulte and Lilien 1997; Van den Bulte and Stremersch 2004).

A different type of method aims to predict the behavior of an individual physician (towards an individual patient) regarding a new treatment. Unlike aggregate-level models, models that are based on this approach rely on disaggregate-level data, evaluating the acceptance process of new drugs from the perspective of the individual physician or patient. We, here, focus on models that are estimated on experimental or behavioral data, not attitudinal data as often gathered in surveys. The use of such individual-level (disaggregate) models requires technical sophistication and programming skills, and they are mostly suitable for heterogeneous social systems, for social systems with unusual network structures, and for products involving complex adoption decisions (Muller et al. 2010). Accordingly, such models fit the complex and unique structure of the pharmaceutical industry very well. Four types of models can be used to assess treatment potential on the basis of disaggregate-level data: prescription count models, learning models, consideration and choice models, and conjoint studies.

Prescription count models predict the number of new prescriptions or the total number of prescriptions dispensed for a drug. These models' predictions are typically based on drug characteristics, past prescription levels, drug prescription levels of other physicians, and (own and competitive) detailing levels, among others. Learning models predict the utility physicians will perceive in a treatment for a particular patient. These models emphasize the dynamic nature of physicians' perceptions regarding the quality of a new drug, and the important role of these dynamics in the choice process. Physicians' perceptions are estimated according to the physicians' initial beliefs regarding the drug's quality and their eventual prescription behavior. Consideration and choice models use past observations of physicians' choice (i.e., prescription) behaviors to predict whether a physician will prescribe the new drug to a particular patient. Conjoint analysis predicts the utility of a new drug to a physician for a particular patient and derives the likelihood that the physician will prescribe the drug to that patient.

7.1.1 Diffusion Models

Typical models in the diffusion literature predict the dynamic process of new product adoption. The Bass diffusion model (1969) has been used extensively to

investigate diffusion patterns and to forecast demand. This model investigates the aggregate first-purchase growth process in a given social system. In this model, also called the mixed-influence model, an adopter of a new product is potentially subject to two types of influence: internal influence, i.e., influence that occurs within the social system, and external influence, i.e., influence that is external to the social system. Internal influence results from interactions between adopters (e.g., physicians or patients who have adopted in the past) and potential adopters (e.g., physicians and patients who will adopt in the future) in the social system. External influence includes all influence outside the social system, such as, for instance, commercial efforts by the firm (i.e., detailing, sampling, advertising, conferences, etc.).

The basic premise underlying the Bass model is that the conditional probability of adoption at a given time in a given social system is increasing in the portion of the social system that has already adopted the new product:

$$n_t = \frac{\mathrm{d}N_t}{\mathrm{d}t} = p(m - N_t) + q\frac{N_t}{m}(m - N_t) \tag{7.1}$$

where m represents the potential number of eventual adopters, N_t represents the cumulative number of adopters by time t, and n_t is the number of adopters at time t. The parameter q in (7.1) reflects the influence of past adopters (i.e., internal influence), and the parameter p reflects an influence that is independent of previous adoption (i.e., external influence). The internal influence parameter can reflect word-of-mouth effects between physicians (which also includes opinion leadership), as well as the adoption of common treatment standards across physicians. For a review of the literature on the Bass model and a meta-analysis of the estimates produced by prior research (including in the field of pharmaceuticals), see Van den Bulte and Stremersch (2004).

Several extensions of the original Bass model have been introduced over the past 4 decades in order to reflect a number of market complexities. Such extensions incorporate, for instance, the notion of the influence of marketing-mix variables on the diffusion process (Krishnan et al. 1999; Lehmann and Esteben-Bravo 2006; Mesak and Darrat 2002; Libai et al. 2005), product replacement and repeat purchases (Islam and Meade 2000; Lilien et al. 1981), substitution between generations (Bayus 1992; Danaher et al. 2001; Islam and Meade 1997; Mahajan and Muller 1996; Padmanabhan and Bass 1993), competition among products (Kim et al. 1999; Givon et al. 1995; Eliashberg and Jeuland 1986), and heterogeneity in the social system (Goldenberg et al. 2002; Moore, 1992; Van den Bulte and Joshi 2007).

Beyond its many applications across a wide variety of industries, the Bass model and its successors have been repeatedly used in the study of the diffusion of new medical treatments. Berndt et al. (2003), for instance, studied the diffusion of antiulcer drugs in the USA. They used the Bass (1969) model to characterize network effects in drug diffusion. In another diffusion study, Vakratsas and Kolsarici (2008) distinguished between early market and main market adopters in a diffusion model for a new pharmaceutical drug. This notion of differentiating between two segments of adopters is similar to the dual-market approach suggested for technological markets (e.g., Goldenberg et al. 2002; Moore, 1992). However, in the context of the adoption of a new pharmaceutical drug, Vakratsas and Kolsarici (2008) associate

this dual-market phenomenon with the early adopters being patients who have severe health problems and whose latent demand has accumulated prior to the new drug's introduction, whereas the later adopters are patients with milder conditions whose adoption may have been triggered by the launch itself.

Marketing scholars have also used diffusion models other than the Bass model to characterize market penetration of pharmaceutical drugs. For instance, Desiraju et al. (2004) examined the effect of market characteristics on the maximum penetration potential and diffusion speed for a new category of prescription drugs in both developing and developed countries, using a logistic specification as in Van den Bulte (2000). Van den Bulte and Lilien (2001) used a discrete-time hazard model to show that several studies analyzing the diffusion of the drug tetracycline confounded social contagion with marketing effects. That is, they showed that when marketing efforts were controlled for in diffusion models, contagion effects disappeared, underscoring the importance of controlling for potential confounds when studying the role of social contagion in new drug diffusion.

The breakthroughs discussed above have helped to provide a better understanding of the determinants of new drug diffusion. The developed models can be helpful in gauging the commercial potential of a new treatment in two main ways. First, after a new drug is launched, these models can assist in making predictions of the drug's future commercial potential (for instance, see Ofek's (2008b) application of the Bass model in forecasting the future diffusion of drug-eluting stents). However, these forecasts are most reliable only after the inflection point—the point at which the growth in the cumulative number of adopters starts to decline—has passed. A second way in which one can use these diffusion models is to *guesstimate* the commercial potential of a new drug using the diffusion path of a similar drug. Such a similar drug should resemble the focal drug in its product characteristics, and the diffusion process must occur in similar market conditions (see Ofek's (2005) application of the Bass model for this purpose in the case of e-books and the background note in Ofek (2008a); while some of us have used this method inside pharmaceutical firms, unfortunately, no pharmaceutical application exists in the public domain, to our knowledge).

7.1.2 Sales Models

Overall sales differ from adoption in that they encompass repeat purchases. Whereas in durable markets (e.g., microwave ovens or refrigerators), for instance, repurchase frequency is quite low, in many pharmaceutical markets (e.g., drugs for chronic conditions, such as high cholesterol or hypertension) the repurchase rate is very high. Given the high repurchase frequency in some markets, marketing scientists have also developed models to forecast sales rather than adoption. The development of models for sales rather than for adoption can assist in understanding the overall dynamics in the market, and such models can potentially provide insight into the relative roles of repeat purchase versus initial adoption in the sales of a new product. The development of market-level sales models to forecast the commercial potential of a new drug is also driven by the availability of data. Often, data on past sales are

more readily available than data on past adoption by physicians or by patients. One type of sales model, using observations of aggregate sales, explicitly accounts for the trial and repeat-purchase process by identifying distributions for trial rates and for repeat-purchase rates (Hardie et al. 1998; Shankar et al. 1998). Parametric sales models typically rely on the assumptions that there is a linear relationship between the model variables and that the repeat-purchase rate for a given brand is constant. Shankar et al. (1998), for instance, propose a model in which the sales of a new product are decomposed into trial and repeat purchases as follows:

$$S_t = T_t + \rho \mathrm{CT}_{(t-1)} \tag{7.2}$$

where S_t represents the sales of the new product at time t, T_t represent the trial purchases at time t, $\mathrm{CT}_{(t-1)}$ represent the cumulative trial purchases until $t-1$, and ρ is the repeat-purchase rate. The authors further model trials as affected by both contagion and marketing-mix effects.

Several researchers have implemented trial-repeat models to investigate sales growth of new pharmaceuticals, incorporating, for instance, the influence of detailing visits (i.e., sales calls by pharmaceutical representatives), word-of-mouth effects, and competition (Ding and Eliashberg 2008; Hahn et al. 1994; Lilien et al. 1981; Rao and Yamada 1988; Shankar et al. 1998).

The validity of the interpretation of trial-repeat models critically hinges upon the validity of the models' identifying assumptions with regard to the trial-repeat-purchase process. Therefore, in forecasting the sales of new drugs, other scholars have preferred semi-parametric methods, which do not entail any assumptions on the underlying purchase process. For instance, Stremersch and Lemmens (2009) used regression splines to model new drug sales across the world. This flexible approach can be viewed as a compromise between linear regression and nonparametric regression sales models. The advantage of splines compared with other specifications lies in the fact that splines do not impose any assumption (linear, quadratic, or cubic) regarding the interactions among explanatory variables over time. Such flexibility is important in the case of sales growth models of pharmaceuticals. Stremersch and Lemmens (2009) investigated the role of regulatory regimes in explaining differences in the sales growth of new drugs across 55 countries all around the world. Their model is of the following form (with REG_{rt} representing r regulatory conditions and OTHER_{pt} representing p other variables, such as other country or drug characteristics):

$$sales_{it} = \beta_{rt} \times REG_{rt} + \beta_{pt} \times OTHER_{pt} + \varepsilon_{it} \tag{7.3}$$

The general idea behind splines is to represent the evolution of a smoothly varying function through a linear combination of basis functions. These functions are usually polynomial functions of low degree. The time-varying coefficients of any explanatory variable of drug sales (such as the REG or OTHER vectors in (7.3)) can then be expressed as follows (Stremersch and Lemmens 2009):

$$\beta_t = \beta_0 + \beta_1 t + \sum_{k=1}^{K} u_k^{\beta} (t - k_k)_+ \tag{7.4}$$

Where K is the number of linear spline basis functions, and k_k is the truncation point or knot where the broken lines are tied together. The combination of linear spline basis functions described in (7.4) gives a piecewise linear function called a spline.

Additional sales-derived metrics have previously been developed and can be used to build forecasting models. One such metric is new product takeoff, which refers to the first strong increase in sales after an initial period of low sales. The metric of takeoff has been developed for and applied to high-tech products and durables (Agarwal and Bayus 2002; Golder and Tellis 1997; Tellis et al. 2003; Van Everdingen et al. 2009), although it has not been tested, let alone used for forecasting purposes, in pharmaceutical markets. Another sales-based metric is third-quarter sales level, which Corstjens et al. (2005) proposed as a good measure for the ultimate success of new drugs. According to their logic, third-quarter sales could be used as a predictor for long-term commercial success.

The use of sales models in forecasting is similar to the use of diffusion models. First, like diffusion models, sales models can be used to make forecasts once the product is available in the market, and initial sales patterns can be used to reliably calibrate the model. Often, at least 1 year of monthly data needs to be available to be able to achieve a reliable calibration of the model. Second, one can use the pattern of sales growth of another molecule to predict the growth pattern of a soon-to-be launched molecule that is similar in terms of clinical support and market conditions (e.g., market structure and spending).

7.1.3 Prescription Count Models

The number of prescriptions written for a given drug is essentially a count variable with a considerable number of zeroes and a relatively small number of frequently occurring outcomes (Manchanda et al. 2005). Thus, the distribution across physicians of a new drug's prescriptions can be captured in individual-level prescription count models. Accordingly, several marketing scholars have used such models to investigate physicians' prescribing behavior and the factors affecting it. The standard count model is the Poisson regression model. In this model, the conditional mean and variance are specified as identical.

$$\Pr(\mathrm{RX}_{pt} = k \mid \lambda_{pt}) = \frac{\lambda_{pt}^{k} \exp(-\lambda_{pt})}{k!} \tag{7.5}$$

In this equation, λ_{pt} is the mean prescription rate, p represents the physician, and t represents the time period. Manchanda and Chintagunta (2004) use a Poisson model to examine the influence of detailing on the number of prescriptions written. The Poisson parameter in their model is allowed to be physician-specific and a function of detailing efforts, and the effect of detailing is also allowed to be physician-specific and a function of the characteristics of detailing directed to the physician, observed physician characteristics, and unobserved factors.

The negative binomial (NBD) regression model is another count model widely used in pharmaceutical marketing. One of the main advantages of the NBD

regression model is its ability to accommodate a wide range of over-dispersion degrees. An NBD distribution with mean $\lambda_{pt}^{\mathrm{RX}}$ and over-dispersion parameter α^{RX} is represented by:

$$\Pr(\mathrm{RX}_{pt} = k \mid \lambda_{pt}^{\mathrm{RX}} \alpha^{\mathrm{RX}}) = \frac{\Gamma(\alpha^{\mathrm{RX}} + k)}{\Gamma(\alpha^{\mathrm{RX}})\Gamma(k+1)} \left(\frac{\alpha^{\mathrm{RX}}}{\alpha^{\mathrm{RX}} + \lambda_{pt}^{\mathrm{RX}}} \right)^{\alpha^{\mathrm{RX}}} \left(\frac{\lambda_{pt}^{\mathrm{RX}}}{\alpha^{\mathrm{RX}} + \lambda_{pt}^{\mathrm{RX}}} \right)^{k} \tag{7.6}$$

This flexible count model has been used in several studies investigating physicians' prescribing behavior (e.g., Manchanda et al. 2005; Stremersch et al. 2013; Venkataraman and Stremersch 2007). In these studies, the most common specification for the conditional mean of the number of prescriptions is a log-link function that specifies the log of the mean of the conditional distribution as linear in the parameters.

In the case of new pharmaceutical drugs, time dynamics in the adoption process can be integrated into the NBD regression model through the specification of the conditional mean. Specifically, the mean number of prescriptions can be modeled as a function of the number of time periods, *t*, since the introduction of the new drug, as follows:

$$\ln(\lambda_{pt}^{\mathrm{Rx}}) = \beta_{0p} + \beta_{1p} t + \gamma_p \bar{X}_{pt} + \zeta_{pt}^{\mathrm{Rx}} \tag{7.7}$$

where $\bar{X}_{pt}$ includes a set of time-varying physician-level covariates such as the volume of detailing to the physician. Moreover, time in this specification can also take a nonlinear form.

Count models can be used for prediction purposes in at least two ways. First, they allow extension of the horizon for the prescriptions a physician writes. Once the model parameters are estimated on past data, one can calculate predictions of future states for each physician in the data set given the physician's past behavior. For instance, the number of detailing visits the firm expects the physician to receive can be used to predict the expected number of prescriptions for that physician, on the basis of the estimated model parameters. In other words, knowing the prescription history of a given physician for periods 1 through *T* (but not for any time after *T*), researchers can develop probabilities for some future time period $T + t$. Once these individual predictions are aggregated across all physicians in the data set for each time period in the investigated timeframe, they provide a predicted pattern of the total number of prescriptions. The aggregated predictions can serve as a diagnostic tool that depicts not only to what extent a new drug is expected to be prescribed across physicians, but also the differential effects that various factors, such as marketing efforts or the prescription volume of other physicians (e.g., word-of-mouth) or opinion leaders, have on this process. Second, "analogical" count models can be used in a similar fashion as "analogical" diffusion models, discussed above. In essence, given two drugs (drug A and drug B) that are similar in terms of category, administration method, etc., one could use response parameters retrieved for drug A (e.g., the responsiveness of new drug prescriptions at the physician level to detailing over time) to forecast physicians' responsiveness to drug B. This forecasting strategy works better for "follow-on" drugs (non-bioequivalent drugs in the same therapeutic category) than for radically new

drugs. As an example, given that Nexium was a clear follow-on drug of (Pri)Losec, one could have used physician response parameters of time, detailing, etc. on historical data on (Pri)Losec to estimate physician response to Nexium.

7.1.4 Learning Models

Learning models in particular exploit the uncertainty physicians perceive regarding the quality of a new pharmaceutical drug. Physicians reduce their uncertainty about the quality of a new drug over time on the basis of feedback from patients as well as the firm's marketing efforts. Several studies have specified models to capture physicians' learning with regard to new pharmaceutical drugs as these drugs diffuse into the market (Camacho et al. 2011; Coscelli and Shum 2004; Crawford and Shum 2005; Narayanan et al. 2005; Narayanan and Manchanda 2009). Coscelli and Shum (2004) suggest that the slow diffusion time of a new pharmaceutical drug in an existing product category is due to slow learning by risk-averse physicians. The only source of information in their model is patient feedback. Narayanan et al. (2005) investigated how the role of marketing communication for new products changes over time in the presence of learning. They specified a learning model in which marketing communication by firms as well as physicians' accumulated usage experience contribute to physicians' learning about a new drug. Narayanan et al. (2005) found that marketing efforts by pharmaceutical companies—i.e., detailing—have a primarily indirect effect (i.e., learning) in the early stages of the new drug's life cycle and a primarily direct (i.e., persuasive) effect at later stages. Narayanan and Manchanda (2009) find significant heterogeneity across physicians in learning rates and show that there are asymmetries in the evolution of physicians' responsiveness to detailing over time. Chintagunta et al. (2009) suggest that the information physicians retrieve from patients who were prescribed a new drug is subsequently used in the physicians' learning process to update their beliefs regarding both the drug's overall quality and a patient's idiosyncratic match with the drug. Their results suggest that physicians are influenced by many sources of information, including patient satisfaction, Medline articles, reports in the mass media and direct-to-consumer advertising (DTCA).

Camacho et al. (2011) developed a generalized quasi-Bayesian learning model that allows for decision-making biases that occur in physician decision making. In essence, they argue that physicians can retrieve some pieces of information from memory more easily than they can retrieve others. They show that physicians' belief updating, and thus the speed of their new drug adoption process, is strongly influenced by the salience of patient feedback. They find that negative patient feedback—feedback from patients whom the physician needed to switch to a different drug—receives 7–10 times more weight than positive feedback does in the physician's quality belief formation. The authors show that this effect greatly reduces the speed of diffusion of the new drug.

Firms can use learning models to gain knowledge about patterns in physician adoption of new drugs, and they can subsequently take such patterns into account

when planning the launch and forecasting the sales of a new pharmaceutical drug. The model by Camacho et al. (2011) can even be used to adjust predictions downwards after taking into account early switch-outs of patients from the new drug to other drugs in the market. Their model can also be used to predict, using counterfactual experiments, what would happen if a firm could reduce the number of patients abandoning the new pharmaceutical drug shortly after its launch. In addition, one can use the estimated parameters of a learning model for a given drug to predict the speed at which physicians would switch patients to a new, similar drug.

7.1.5 Consideration and Choice Models

In most diffusion models, the diffusion process is viewed as a single-stage, binary-state process in which at any point in time, individuals are either adopters or non-adopters. A few diffusion studies consider diffusion as a multistate, macro-flow process and thus take into account heterogeneity in customers' pre-adoption states, e.g., by incorporating awareness stages (Dodson and Muller 1978; Kalish 1985; Mahajan et al. 1984) or consideration stages (Weerahandi and Dalal 1992). However, in these models, heterogeneity is not reflected at the individual adopter level but rather at the aggregate level. To address heterogeneity among consumers in pre-adoption states, one can also build an individual-level model that separates different stages in the adoption process. For instance, Landsman and Givon (2010) proposed an individual-level model of a two-stage process of the diffusion of a service. In the first stage, customers decide whether to "consider" joining the service. This (Consideration) stage is modeled by a hazard model. Customers who decide to consider the service move on to the Choice stage, wherein they choose among the service alternatives and an outside No Choice option. This stage is modeled by a conditional multinomial logit model.

The model proposed by Landsman and Givon (2010) was developed for services or durable goods outside the pharmaceutical industry. Taking into account the unique features of the pharmaceutical market environment (Camacho et al. 2010; Stremersch and Van Dyck 2009), one could also apply such a model to these markets at the physician level. In this setting, in contrast to the setting of a new service, once a new drug is introduced, physicians can prescribe either the new drug or one of the other therapeutic alternatives already existing in the category. Accordingly, we must distinguish between physicians' initial adoption decision (the decision to first prescribe the drug) and their consequent process of integrating the new drug into the choice set until the new drug reaches its ultimate share in the category.

The time-dynamic process of initial adoption can be represented using a proportional hazard model, where the hazard function is decomposed into two multiplicative components:

$$h_{pt} = h_{p0t} \cdot \psi(X_{pt}) \tag{7.8}$$

The first component, h_{p0t}, defines the baseline hazard function. This function reflects the longitudinal patterns in the duration time dynamics. The second

component is a function of a vector of physician and/or market covariates that affect the adoption hazard rate. Thus, $\psi(X_{pt})$ adjusts h_{p0t} up or down proportionally to reflect the effect of the covariates.

The post-adoption stage can be modeled as a physician-level *choice* process, where P_{pjt} represents the probability that a physician p chooses drug j ($j=1, \ldots, J$) at time t, conditional on drug j's adoption by physician p by t. This probability can be specified as a multinomial logit model:

$$P_{pjt} = \frac{e^{V_{pjt}}}{\sum_{j=1}^{J} e^{V_{pjt}}} \tag{7.9}$$

where V_{pjt} is the deterministic part of the utility obtained from choosing drug j at time t. V_{pjt} can be specified as a function of a set of covariates that can characterize the drug, the physician, or the combination of both, and a *time dynamic* element affecting physician choice of the new drug (Coscelli and Shum 2004). To explain the dynamic adoption process, at least some covariates in the two model functions must vary over time.

7.1.6 Conjoint Analysis

The methods we have reviewed so far only use observed data either from the new treatment's own prescribing behavior or from the past prescribing behavior of other drugs that have been available in the market for a longer time. They do not use so-called primary data. Nonetheless, the use of primary data in the estimation of the commercial potential of a new pharmaceutical may yield valuable insights. Conjoint analysis is a particularly useful method to assess physicians' and patients' preferences and unmet needs before the launch of a new drug. Conjoint analysis is a method to estimate the structure of consumers' preferences, given their overall evaluations of a set of alternatives that differ with respect to several attributes. The main advantage of this research tool is that it can be used before a new product enters the market. Since its introduction (Green and Rao 1971), conjoint analysis has been widely adopted by marketing scientists and practitioners as a method for preference measurement. Conjoint analysis can assist firms in developing and launching new products, as it can be used to integrate knowledge on potential adopters' expected reactions to these products. This ability facilitates prelaunch sales forecasts for a new product, thus avoiding the high costs and time investments required for the use of test markets. Conjoint analysis is most appropriate when new levels of attributes are being introduced or when new attributes can be described well to potential customers (Urban et al. 1996). Figure 7.2 describes the different steps in setting up a conjoint study.

The basic premise of conjoint analysis is to present physicians or patients with several variations of attribute levels for a new product and to assess their choices, rankings, or ratings. This is typically done in a survey setting (Cattin and Wittink

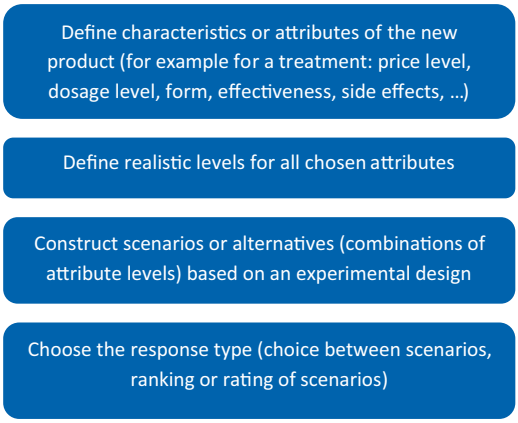

Fig. 7.2 Setting up a conjoint study

1982). Recently, web-based methods, together with efficient algorithms and more powerful computational capabilities, have yielded new interactive conjoint methods that generate more accurate knowledge with far fewer questions compared with traditional methods (Dahan and Hauser 2002; Hauser and Toubia 2005; Toubia et al. 2003, 2004).

By executing a conjoint analysis, companies observe the importance of the different attributes to physicians or patients as well as the preference for specific levels of these attributes. The complex payment structure of the pharmaceutical industry complicates the ability to assess market sensitivity to the price of a new pharmaceutical drug. In many cases, one of the attributes in a conjoint study is price (or, the co-pay of the patient), as incorporating this attribute allows companies to make statements about patients' or payers' willingness to pay or physicians' willingness to prescribe. In a conjoint study, every product—which is a combination of attribute levels—gets assigned a value based on assessments of attribute-level preferences. By letting consumers evaluate different products, conjoint studies enable inferences to be made with regard to the expected market share of different products. Furthermore, conjoint analysis also allows companies to discern different segments in the markets. Segments are groups of respondents that attach similar importance to attributes and share a preference for specific attribute levels. This type of information has proven to be very valuable when developing a new product and forecasting the demand for that product (Dolan 1990). To forecast the demand for a new product, the results of the conjoint analysis are incorporated into a model based on mathematical representations of each consumer's preferences alongside the specific attribute composition of the product. An aggregate-level diffusion or sales model can then be used to aggregate these individual forecasts into an overall prediction of the new product's sales (Gupta et al. 1999; Lee et al. 2006; Roberts et al. 2005; Urban et al. 1990).

The complex structure of demand in the case of pharmaceutical drugs forces pharmaceutical firms to identify patients' needs, either through direct means or through the mediation of physicians. Accordingly, prelaunch sales forecasts for new

products must consider several dynamic factors such as the discovery of new uses for the drug, the drug's dosing, efficacy, and side effects, and the price of the drug. Conjoint analysis can provide pharmaceutical companies with this type of information.

Several studies have focused on conjoint analysis in the context of healthcare. Kontzalis (1992), for instance, proposes a model to forecast the potential market share of a new pharmaceutical drug for Sandoz Pharma AG. The model considers physicians' decision-making process, taking into account their attitudes and needs as well as the drug's clinical profile. In this paper, the author first identified the key attributes physicians consider important in selecting drugs that treat certain conditions, and then, using a conjoint analysis, measured the relative importance of each attribute. Specifically, for the therapeutic category investigated in this study, the attribute "low irreversible toxicity" was found to be 3 times more important than of the attribute "low side effects," while the latter was found to be 5 times more important than of the attribute "easy to administer." In the next step of the study, the author simulated the therapeutic category market shares based on the clinical profile of the new product and its competitors.

In another study, Kellett et al. (2006) used a conjoint analysis to investigate patient preferences for acne vulgaris treatment. The conjoint analysis examined five different attributes of such treatment: form, storage, product life once opened, method of application and regimen. Although this research was conducted with the purpose of enhancing patient compliance, it demonstrates the applicability of patient-based conjoint analysis in predicting the adoption of new pharmaceutical drugs.

Conjoint analysis has also been used to assess the tradeoffs young girls make between various aspects of HPV vaccination, such as protection against cervical cancer, protection duration, risk of side effects and age of vaccination (de Bekker-Grob et al. 2010a). De Bekker-Grob et al. (2010b) have also looked at patients' preferences for both labeled and non-labeled screening tests. Kruijshaar et al. (2009) examined the trade-off patients make between the burden of testing and the expected health benefits in the context of regular endoscopic surveillance. Studies such as these guide managers as well as policy makers in the pharmaceutical industry.

If one of the product attributes affecting customer preferences is price, conjoint analysis can assist pharmaceutical firms in assessing patients' willingness to pay and thus provide them with a valuable tool in determining the price of a new drug. Singh et al. (1998) have conducted a conjoint analysis among patients for growth augmentation therapy. One of the five attributes they assessed was the yearly out-of-pocket cost of the drug ($100, $2,000, or $10,000). Their findings suggest that cost is among the most important factors in patients' preferences, outweighed only by long-term side effects. Moreover, once the utility partworths are derived from the conjoint analysis, the preference trade-offs among the different drug attributes can be used to assess consumers' willingness to pay for different drug profiles, as well as to simulate market shares given those profiles for different price levels.

7.2 Step 2: Extracting the Potential of a New Treatment

In assessing the potential of a new treatment, pharmaceutical companies gain insight into the types of decisions they need to make to extract value from the new treatment. Marketers have studied two main methods of extracting the commercial potential of a new treatment: setting the price of the new treatment and increasing unit sales through promotional expenditures.

Many studies (e.g., Kremer et al. 2008; Mizik and Jacobson 2004; Stremersch et al. 2013; Venkataraman and Stremersch 2007) have looked at the effect of promotional expenditures (e.g., DTCA, direct-to-physician advertising, detailing) on demand for pharmaceutical drugs, obtaining mixed results. Pricing strategies of new treatments have been studied to a lesser extent (e.g., Berndt 2000; Ekelund and Persson 2003; Lu and Comanor 1998). Researchers have also shown increasing interest in the threat of generic substitution and its consequences for the pricing of drugs (Frank and Salkever 1997; Hariharan et al. 2013).

Pharmaceutical companies' decisions regarding drug price levels and promotional expenditures, which are crucial for extracting value from the commercial potential of a new treatment, are often a source of controversy in the pharmaceutical industry. In the following subsections we discuss each of these two types of decisions.

7.2.1 Pricing New Treatments to Maximize Profits

Pharmaceutical companies' pricing decisions with regard to new treatments are often cause for debate. Opponents of current price levels claim that the prices of new drugs are too high given the low marginal cost of producing them. Hence, they conclude that high price levels of new drugs only serve companies' profit motives (Berndt 2000). However, pharmaceutical companies state that these prices are justified given the high research and development (R&D) costs and the high risk involved in the development of a new drug (Lu and Comanor 1998). Furthermore, industry executives claim that in many international markets, drug prices are no longer sufficient to reward companies for taking these high risks. Indeed, sufficiently high price levels are necessary to guarantee a society's access to innovative life saving drugs in the future (Santerre and Vernon 2005). Economists support this claim by showing that innovation is threatened by low price levels (DiMasi et al. 2003). Notably, however, pricing decisions have been found not to depend exclusively on past R&D expenses (Verniers et al. 2011; Vernon et al. 2006; Wagner and McCarthy 2004).

Lu and Comanor (1998) examined drivers of launch prices of new drugs relative to the average prices of existing brand-name substitutes (in the same categories) in the USA over the period 1978–1987. Unsurprisingly, they found that drugs with a larger therapeutic potential were priced higher than drugs that constituted smaller therapeutic advancements. Furthermore, a higher number of branded substitutes

decreased the launch price level of a new drug in the category. "Follow-on," or "me-too," drugs have more difficulty obtaining a higher price because they have to demonstrate their superiority in comparison with existing substitutes (DiMasi and Paquette 2004). DiMasi (2000) studied price levels of new entrants in an existing therapeutic class in the USA and found that 65 % of the observed drugs had an introductory price that was 14 % lower than the category's average price. Ekelund and Persson (2003) also studied new drugs' launch prices in Sweden, where regulations are stricter than in the USA, between 1987 and 1997. Similarly to Lu and Comanor (1998), they found that the extent of a drug's therapeutic innovation positively affects its relative introductory price. However they found that, competition does not influence launch prices. In addition to the extent of therapeutic benefit and number of substitutes, another factor influencing price is therapeutic indication: drugs indicated for acute conditions have larger premiums than those indicated for chronic illnesses (Ekelund and Persson 2003; Lu and Comanor 1998).

The evolution of new drugs' prices over the product life cycle—or price dynamics—has also received some attention. Lu and Comanor (1998) observed a price-skimming strategy, i.e., a high introductory price and then a decrease in price level, for drugs that constitute a substantial therapeutic advancement, whereas they found that pharmaceutical companies apply a penetration pricing strategy—low introductory price and then an increase in price level—for drugs that offer a small therapeutic gain (Lee 2004). Price increases were smaller if more brand-name substitutes were available in the market. In contrast to Lu and Comanor, who studied pricing strategies in the USA, Ekelund and Persson (2003) observed higher relative introductory prices and a price-skimming strategy across all drugs in the regulated country Sweden. The main source for the differences between the results of Lu and Comanor (1998) and those of Ekelund and Persson (2003) is likely the difference in the regulatory environments in the USA and in Sweden. Regulators in Sweden seem to compensate the pharmaceutical manufacturers' limitation of a price cap by allowing a relatively high introductory price before price decreases, and competition seems to matter less in a regulated country.

Many countries worldwide enforce price regulations, and a pharmaceutical company in such countries can only launch a new drug once price negotiations with local health regulators have ended. Price regulations can include price cap mechanisms that limit the price a new drug can attain. For example, a country's public health administration might enforce an ex-manufacturer price cap, i.e., a maximum price or reservation price that a manufacturer can charge to the wholesaler of a pharmaceutical product (Danzon et al. 2005). Belgium, Greece, and Portugal are examples of countries with strict ex-manufacturer price regulations. Verniers et al. (2011) find no direct effect of these price regulations on launch price. When setting a launch price, pharmaceutical companies often also take into account whether a new drug will get reimbursement or not.

At the moment of patent expiration in the product life cycle of a drug, generic drugs—drugs that are bioequivalent to the brand-name drug—enter the market. This generic entry poses a challenge for brand-name pharmaceutical companies, as generic manufacturers' drugs enter the category at lower prices. Morton (1999)

states that prices of generic drugs are 30–50 % lower than brand prices, and that these prices decrease further after introduction as the number of generic manufacturers increases. In addition, generic entry may also affect branded drugs' prices. Caves et al. (1991) found that prices of branded drugs fall when generics are introduced. This could be a strategy of branded manufacturers to safeguard their market share. However, Frank and Salkever (1997) and Lexchin (2004) found that branded drug prices may increase when generic entry occurs. Brand-loyal customers could drive this result, as these customers are willing to pay more for the branded drug, whereas other customers will choose the cheap generic drugs. On average, the price of an off-patent drug is lower than that of the patented version because of market competition. Danzon and Chao (2000b) find that generic competition is significant in countries that do not have strict regulations, such as the UK, the USA, and Germany. Generic competition is much fiercer in regulated countries such as France and Italy.

7.2.2 Promoting New Treatments to Maximize Unit Sales of a New Treatment

Pharmaceutical firms use several types of marketing tools, including free samples, detailing visits, professional magazine advertising, and DTCA to support the launch of new treatments. An important challenge marketing scientists have had to overcome is how to calculate the optimal allocation of marketing investments.

When a pharmaceutical firm launches a new treatment, it typically spends the largest portion of its marketing budget on physician detailing visits. Accordingly, numerous marketing research studies have focused on the effectiveness of these visits. Early endeavors by marketing scholars in this field used aggregate data to examine the effect of detailing visits on drug sales (Lilien et al. 1981; Parsons and Vanden Abeele 1981). In the past decade, several studies have used panel data to investigate the effect of detailing visits on the demand for pharmaceutical drugs (e.g., Kamakura et al. 2004; Gonul et al. 2001; Manchanda and Chintagunta 2004; Venkataraman and Stremersch 2007). While some of these studies (e.g., Gonul et al. 2001) find that detailing has a positive and significant effect on the number of prescriptions, other studies find that detailing has only a very modest effect (Mizik and Jacobson 2004; Stremersch et al. 2013; Venkataraman and Stremersch 2007) or even no effect (Rosenthal et al. 2003) on prescriptions or sales.

One possible explanation for these contradicting findings is that brands may in fact differ in the extent to which their detailing efforts evoke physicians' response (Leeflang et al. 2004). Venkataraman and Stremersch (2007) find that drug characteristics are a source for brand-specific differences in physicians' responsiveness (as reflected in their prescription behavior) to marketing efforts by pharmaceutical firms. Specifically, they find that physicians tend to be more positively affected by detailing visits when the drug is more effective or has more side effects. Typically, detailing visits for a newly launched drug are effective, as physicians still have a great deal of uncertainty with regard to the effectiveness, side effects, and safety of

the new drug. Gradually, this uncertainty declines due to past detailing visits or patient feedback that allow the physician to learn (see discussion of learning models above). As a result, detailing visits become increasingly ineffective. A general lesson for the pharmaceutical industry is to maximize their detailing spending at launch and shortly afterward, and to cut the detailing budget when the new drug starts maturing. Typically, models find that pharmaceutical managers may underspend at launch or shortly afterward, whereas they may overspend in maturity.

Narayanan et al. (2005) suggest that this variation in findings regarding detailing effectiveness is rooted in the difference between the role of detailing at the introduction stage of a drug versus its role in subsequent stages. In early stages of the drug's life cycle, physicians' experience with the drug is limited, and they are likely to be uncertain about its efficacy. Thus, in the introductory phase, detailing is assumed to have a primarily indirect effect by helping physicians reduce their uncertainty about the efficacy of the drug. However, as physicians learn about the drug and gain experience with it, they have less uncertainty about the drug's efficacy, and the effect of detailing becomes more direct (i.e., reminder effects influencing preferences through goodwill accumulation).

Another important aspect of the effectiveness of detailing visits is the information content that is provided in sales calls. Kappe and Stremersch (2013) investigate the responsiveness of physicians to information provided across different drug attributes. They also examine whether firms present positively biased information to physicians, and whether this bias has an influence on the responsiveness of physicians. In their study, they use data on the drug attributes presented in detailing visits, and they find that pharmaceutical firms do not provide information on the right product attributes at their optimal frequency. They also find that detailing visits that include discussion of positively biased information in the long run have a lower detailing effectiveness. These results imply that firms must optimally adjust their messaging in order to improve physicians' responsiveness to detailing.

Pharmaceutical firms' spending on DTCA has increased dramatically in recent years, from less than $1 billion US dollars in 1996 to $4.3 billion in 2010 (AdAge 2011). This increase has drawn attention from both practitioners and marketing scholars, who have made efforts to analyze the effects of DTCA on demand and the ROI from such marketing activities. As in the case of detailing, academic studies on the effect of DTCA on prescriptions yield contradictory results. Some studies claim that DTCA spending has a large effect on prescriptions (Atherly and Rubin 2009; Bell et al. 1999; Fischer and Albers 2010; Iizuka and Jin 2005; Koch-Laking et al. 2010; Kolsarici and Vakratsas 2010; Ling et al. 2002; Meyerhoefer and Zuvekas 2008; Weissman et al. 2004; Wilkes et al. 2000), whereas others claim it has no effect, or a very limited one, on brand-level prescriptions (Calfee et al. 2002; Donohue and Berndt 2004; Manchanda et al. 2008; Rosenthal et al. 2003; Stremersch et al. 2013; Zachry et al. 2002). Kremer et al. (2008) even find that DTCA has a negative effect on prescriptions in the fields of skin disease, neurology, and psychiatry. Another set of studies on DTCA focuses mainly on studying the ROI from such marketing activities by pharmaceutical firms (Wittink 2002; Narayanan et al. 2004). These studies find that the ROI for DTCA is quite low. Narayanan et al. (2004) further find a lower level of ROI for DTCA than for

detailing. None of these studies, however, focuses on the role of DTCA in supporting newly introduced pharmaceutical drugs (which may be one reason for the small effect found by prior studies).

Sample dispensing by physicians is rarely addressed in academic studies despite being an important physician decision. From the perspective of a pharmaceutical firm, samples that are dispensed by physicians may lead to prescribed long-term treatment (Morelli and Koenigsberg 1992). Thus, sampling can be a valuable tool to support the launch of new pharmaceutical drugs, especially for chronic conditions. Venkataraman and Stremersch (2007) find that physicians' prescription behavior in response to firm's marketing efforts and to patients' requests may differ from their sample-dispensing behavior in response to such factors. They also find that when a marketed drug is more effective or has more side effects, physicians tend to provide more samples in response to firms' marketing efforts.

7.3 Step 3: Leveraging the Potential of a New Treatment Across Countries

The international realm brings interesting challenges to global pharmaceutical launch teams. Probably among the most important challenges are differences across countries in new drug sales growth and the interdependence of international launch timing and pricing, generating a need to develop sophisticated global launch strategies.

7.3.1 Variance in the Market Potential and Speed of Diffusion Across Countries

Marketing research on international growth of new products in various industries has identified several key drivers of variation across countries in market potential and diffusion speed (Dekimpe et al. 1998; Gatignon and Robertson 1989; Helsen et al. 1993; Stremersch and Tellis 2004; Talukdar et al. 2002; Tellis et al. 2003; Van den Bulte and Stremersch 2004; Van Everdingen et al. 2009). For instance, the wealth of a country was found to have a positive effect on the diffusion process in terms of reducing the time before the country tries the innovation and speeding up the diffusion within the country (Van Everdingen et al. 2009). Other studies show that additional country characteristics, such as national culture, affect new product growth differentially across the product's life cycle (e.g., Stremersch and Tellis 2004; Tellis et al. 2003). Moreover, several studies have found evidence for cross-country learning effects (Dekimpe et al. 2000, Dekimpe et al. 1998; Mahajan and Muller 1994). Countries that introduce an innovation later than others seem to have faster within-country diffusion patterns.

Desiraju et al. (2004) examined the relative attractiveness of various countries in terms of maximum penetration potential and diffusion speed for a new category of

prescription drugs across both developing and developed countries. Their results, which are consistent with earlier findings from outside the pharmaceutical industry, indicate that developing nations tend to have lower diffusion speeds and lower maximum penetration levels compared with developed countries. They also find that per capita expenditures on healthcare have a positive effect on diffusion speed, and that this effect is stronger among developed countries. Stremersch and Lemmens (2009) have investigated the role of regulatory regimes in explaining international sales growth of new drugs, while controlling for introduction timing, economic and cultural factors, among others. In their paper they used a time-varying coefficient model to analyze the sales of 15 new molecules in 34 countries. Stremersch and Lemmens (2009) found that differences in regulation substantially contribute to cross-country variation in sales, emphasizing the importance of incorporating local regulatory constraints into pharmaceutical manufacturers' global launch plans. For instance, drug volumes were found *ceteris paribus to be* higher in countries with manufacturer price regulation, and lower in countries with DTCA or prescription budget restrictions. In addition, this study confirms that the cultural and economic characteristics of countries affect their attractiveness to pharmaceutical firms.

Table 7.2 displays the early sales volume (less than 3.5 years after launch) and late sales volume (more than 3.5 years after launch) for a sample of the following brands across 15 molecules (molecule name in parentheses; several molecules are marketed under multiple brands): Lipitor (atorvastatin), Baycol/Lipobay (cerivastatin), Lescol (fluvastatin), Crestor (rosuvastatin), Vesicare (solifenacin), Detrol (tolterodine), Caverject/Muse/Viridal (alprostadil), Uprima/Ixense (apomorphine), Viagra/Revatio/Caverta (sildenafil), Cialis (tadalafil), Levitra (vardenafil), Clarinex (desloratadine), Elestat (epinastine), Allegra/Telfast (fexofenadine), Mizollen (mizolastine). For each country Stremersch and Lemmens (2009) have calculated the percent deviation from the mean sales level. In countries where this deviation is high, the molecule reaches high sales levels compared to the mean sales level across all countries. Correspondingly, in countries where this deviation is low, the molecule reaches only low sales levels compared to the mean sales level across all countries. From Table 7.2, we can conclude that new molecules in the USA, Sweden, Norway, and Japan reach high sales levels. New molecules reach only low sales levels in many developing countries, such as Mexico, Eastern European countries, the Philippines, and South American and African countries. Some countries show very fast adoption (very high early sales level as compared to the late sales level): Sweden, Netherlands, and Belgium. Other countries show very slow adoption (very low early sales level as compared to the late sales level): Australia, Norway, and United Kingdom.

7.3.2 International Launch Timing and Pricing

Research on international launch of new drugs has identified several drivers of launch timing (Danzon et al. 2005; Kyle 2006, 2007; Lanjouw 2005; Verniers et al.

Table 7.2 Variation in early and late sales growth of a sample of 15 new molecules, launched between 1994 and 2004[a]

Early sales (<3.5 years after launch) per 1,000 inhabitants			Late (>3.5 years after launch) sales per 1,000 inhabitants		
Country	% Dev. from mean	Rank	Country	% Dev. from mean	Rank
North America	*79*			*74*	
U.S.	270	1	U.S.	305	1
Canada	87	8	Canada	94	9
Puerto Rico	34	17	Puerto Rico	−18	23
Mexico	−74	39	Mexico	−87	45
Oceania	*44*			*77*	
Australia	70	10	Australia	153	3
New Zealand	18	20	New Zealand	1	21
Europe	*23*			*17*	
Western Europe	*65*			*56*	
Sweden	202	2	Norway	163	2
Luxemburg	188	3	Sweden	139	5
Norway	114	5	Luxembourg	106	6
France	100	6	Greece	99	7
Netherlands	98	7	United Kingdom	97	8
Greece	75	9	Finland	77	10
Belgium	70	11	Portugal	56	11
Germany	61	12	Spain	49	12
Spain	56	13	Netherlands	42	13
Finland	54	14	Ireland	35	14
Portugal	42	15	Switzerland	32	15
Switzerland	31	18	Belgium	26	17
Italy	21	19	France	25	18
Austria	4	22	Germany	18	19
Ireland	1	23	Denmark	10	20
United Kingdom	−1	24	Austria	−1	22
Denmark	−15	25	Italy	−26	24
Eastern Europe	*−65*			*−66*	
Slovakia	−27	27	Slovakia	−28	25
Hungary	−51	30	Hungary	−33	27
Estonia	−64	34	Czech Republic	−60	31
Czech Republic	−65	35	Estonia	−78	40
Lithuania	−77	40	Poland	−81	43
Poland	−82	43	Lithuania	−88	48
Latvia	−86	48	Latvia	−92	51
Asia	*−27*			*−35*	
Japan	139	4	Japan	146	4
Korea	37	16	Korea	29	16
Saudi Arabia	6	21	Lebanon	−31	26
United Arab Emirates	−21	26	Turkey	−42	28
Lebanon	−31	28	Kuwait	−52	29

(continued)

Table 7.2 (continued)

Early sales (<3.5 years after launch) per 1,000 inhabitants			Late (>3.5 years after launch) sales per 1,000 inhabitants		
Country	% Dev. from mean	Rank	Country	% Dev. from mean	Rank
Kuwait	−40	29	Israel	−53	30
Israel	−56	31	Saudi Arabia	−61	32
Turkey	−68	36	United Arab Emirates	−69	35
Jordan	−83	45	India	−77	39
India	−84	46	Jordan	−80	41
Philippines	−94	53	Philippines	−96	52
South America	*−80*			*−79*	
Venezuela	−58	32	Uruguay	−63	33
Chile	−72	37	Chile	−64	34
Argentina	−74	38	Argentina	−70	36
Brazil	−79	41	Venezuela	−80	42
Uruguay	−82	42	Brazil	−86	44
Ecuador	−88	49	Colombia	−87	46
Colombia	−91	51	Ecuador	−87	47
Peru	−93	52	Peru	−91	50
Africa	*−80*			*−83*	
Tunisia	−60	33	Egypt	−72	37
South Africa	−82	44	Tunisia	−75	38
Egypt	−86	47	South Africa	−89	49
Morocco	−90	50	Morocco	−97	53

[a]Based on joint work of Stefan Stremersch and AurélieLemmens

2011). Kyle (2007) investigated the effect of price regulation on the number of new drug launches and the timing of launch and found that price regulation causes pharmaceutical companies to delay launch and leads to fewer launches. She also finds that drugs are 1.5 times more likely to be launched in countries that share a language border with the country in which the headquarter of the pharmaceutical company is located (Kyle 2007). In addition to these effects, Kyle (2006) also investigated other drivers such as the number of competitors, corruption index of a country, and administrative costs in a country. Danzon et al. (2005) examined launch timing of new drugs in 25 countries worldwide and observed an effect of expected drug price and expected market size (the data they evaluated included lagged average price and market size of drugs in the same therapeutic class). After controlling for a home country effect and global experience, the researchers found that pharmaceutical companies launch fewer new drugs and that they launch them at a later time in countries with a lower expected drug price and lower expected market size. Lanjouw (2005) also focused on drivers of launch timing and showed that price regulation tends to lower the launch speed, whereas she found mixed results for patent protection regulation (results were dependent on the specifics of the regulation).

When launching a new drug in an international context, pharmaceutical companies also need to decide on the launch prices in different countries. Like launch time, launch price is an important determinant of the evolution and distribution of cash flows across time and countries. As different countries have different characteristics (regulation, population size, GDP per capita, number of competitor drugs, etc.), launch prices are expected to differ across countries. Some studies have looked at drug prices across countries, without explicitly focusing on launch price. Chintagunta and Desiraju (2005) studied drug price levels across five geographic markets and showed that the USA is less price sensitive than European markets. Danzon and Furukawa (2003) examined drug prices in nine countries and showed that Japan and the USA have the highest drug prices. Other countries' drug prices are 6–33 % lower than drug prices in the USA. Danzon and Chao (2000a) examined bilateral drug price indexes between seven countries and found that older molecules had lower prices in countries with strict price regulations than they did in less strictly regulated countries. Price differences on a worldwide level have been the cause for parallel trade, which occurs when a third party purchases drugs in lower-priced countries and then resells them in higher-priced countries (Onkvisit and Shaw 1989). Although prices are quite heterogeneous across countries, many countries worldwide (mainly in the European Union) have an external reference pricing regulation. This regulation requires that, before launching a drug in a certain country, the pharmaceutical company supplies that country's health regulators with information on the drug's prices in selected foreign countries. Regulators then cap prices on the basis of that information (Dukes et al. 2003; Verniers et al. 2011).

Several studies have examined drivers of launch timing, and other studies have looked at differences in international launch prices. Verniers et al. (2011) investigated 58 molecules in 50 countries worldwide to empirically evaluate the regulatory drivers of both launch timing and launch price. They examined the effect of ex-manufacturer price control, profit control, internal reference pricing regulation, external reference pricing regulation, pharmacoeconomic evidence, and patent protection strength on launch price. Although they did not observe a direct effect of regulation on launch price, they did find an effect of regulation on launch timing. Apparently, regulatory restrictions are more useful to regulators in constraining the price of mature drugs rather than the price of newly launched drugs (Stremersch and Lemmens 2009; Verniers et al. 2011).

Table 7.3 presents the mean lead or lag in launch window (the launch window is defined as the difference in months between the first launch worldwide and the subsequent launch in a specific country) and the percent deviation from the mean price at launch for countries across seven world regions. Column 3 in Table 7.3 shows each country's deviation from the mean launch price across drugs. This is calculated according to the following steps: (1) construct the mean launch price for each drug across the countries; (2) calculate the percentage of deviation of the country-specific price from the mean price over all countries; (3) average these percentages of deviation for each specific country over all drugs launched in that country. A negative deviation for a given country means that a drug is typically launched at a relatively

Table 7.3 Mean lead (−) or lag (+) in launch window and % deviation from mean price at launch by world region and country[a]

World region and countries	Mean lead (−) or lag (+) in launch window (in months)	% Deviation from mean price at launch per gram
North America	*−8.95*	*37.87*
USA	−17.17	37.79
Canada	−7.50	−1.57
Puerto Rico	−7.21	93.09
Mexico	−3.94	22.16
Western Europe	*−5.81*	*−8.15*
Germany	−15.59	−9.17
Denmark	−10.65	−5.35
U.K.	−9.82	−0.14
Austria	−9.13	−9.92
Switzerland	−8.97	0.21
Ireland	−8.08	−5.22
Sweden	−7.11	−8.48
Netherlands	−6.95	−6.93
Finland	−6.44	−4.39
Norway	−5.87	3.83
Spain	−4.03	−17.22
Belgium	−3.45	−13.61
Luxemburg	−2.22	−12.78
Portugal	−1.66	−11.47
Italy	−1.01	−13.26
France	−0.46	−12.44
Greece	2.06	−12.21
South America	*−0.43*	*7.93*
Brazil	−6.79	14.43
Argentina	−6.36	0.89
Colombia	−3.12	33.67
Chile	−2.27	−8.19
Venezuela	1.97	17.49
Uruguay	3.95	12.72
Peru	4.29	−4.20
Ecuador	4.91	−3.39
Oceania	*0.10*	*−8.02*
Australia	−1.55	−11.82
New Zealand	1.75	−4.21
Asia	*5.16*	*11.01*
Philippines	−2.17	−12.15
Japan	6.89	47.89
Korea	10.75	−2.71
Eastern Europe	*8.74*	*−1.62*
Czech Republic	5.03	1.58
Estonia	5.21	−3.51
Hungary	5.68	−5.54
Poland	8.91	1.71
Latvia	9.55	−5.78

(continued)

Table 7.3 (continued)

World region and countries	Mean lead (−) or lag (+) in launch window (in months)	% Deviation from mean price at launch per gram
Slovakia	12.77	0.78
Lithuania	14.02	−0.61
Africa and the Middle East	*14.51*	*−13.31*
Kuwait	4.42	−1.81
South Africa	5.14	−26.11
United Arabic Emirates	6.49	4.33
Lebanon	6.77	−16.32
Jordan	12.37	−7.89
Egypt	17.86	−29.10
Saudi Arabia	19.40	−13.37
Morocco	20.88	−8.67
Tunisia	37.28	−20.82

[a]Based on the work of Isabel Verniers, Stefan Stremersch, and Christophe Croux

low price in that country, whereas a positive deviation indicates that a drug is typically launched at a relatively high price in that country.

Table 7.3 shows that the USA, Germany, and Denmark experience the largest lead in launch. Tunisia, Morocco, and Saudi Arabia experience the largest lag in launch. North America and Western Europe show similar (small) launch delays. Launch delays are largest in Eastern Europe, Africa, and the Middle East. There is a marked difference in launch timing between Western Europe (fast) and Eastern Europe (slow), despite many of these launches having occurred recently. Puerto Rico, Japan, and the USA have the largest positive deviation from the average launch price worldwide, whereas Egypt, South Africa, and Tunisia show the largest negative deviation from the worldwide average launch price. North America, South America, and Asia show positive deviations from the worldwide average launch price, while the other world regions—including Europe—show a negative deviation from the average launch price worldwide (Verniers et al. 2011).

When a pharmaceutical firm launches a drug in multiple countries worldwide, it needs to decide on the sequence of countries in which the launch will take place. As the launch price is a decision that is being made simultaneously, Verniers et al. (2011) examined whether launch timing is interrelated with launch price. They found that launch timing has a curvilinear effect on launch price, whereas launch price has a U-shaped effect on launch timing. This means that launch occurs fastest at moderate price levels. One can therefore infer that for pharmaceutical companies, a tradeoff is being made between the amount of time left under patent protection and the price needed to recoup R&D investments. Health regulators make a tradeoff between access of new drugs to society and the level of health expenditures.

7.4 Future Research on Launch and Diffusion Excellence

While the above overview shows that much work has been done in marketing science towards assessing the potential of new treatments, extracting value from a new treatment, and leveraging the value of a new treatment across countries, much work still remains. Below, we review some of the themes we consider important.

7.4.1 Future Research on Assessing the Potential of a New Treatment

Over the past 2 decades, marketing scholars have pointed out the need for a more elaborate framework for the study of diffusion processes that takes into account the usage of an introduced innovation (Anderson and Ortinau 1988; Hahn et al. 1994; Lewis and Seibold 1993). Several models in the life sciences, marketing, and economic literature have considered the process of post-adoption learning about a new drug (e.g., Camacho et al. 2011; Coscelli and Shum 2004; Hahn et al. 1994; Narayanan et al. 2005). These models, however, do not specifically account for physicians' initial adoption decisions and the factors that influence them. Furthermore, the models focus on the development of market shares rather than on drug sales and do not fully integrate patient behavior into the modeling framework. A promising avenue for future research is therefore to develop an individual-level model that integrates both the role of time dynamics in physicians' adoption decision processes and the role of patient compliance in the sales patterns of new drugs. This can be done by integrating information on refill prescriptions for previously diagnosed patients, corresponding to patients' compliance with therapeutic regimens, into an individual-physician-patient adoption model.

In addition, more work is needed that integrates the richness of primary data with the behavioral regularity identified in secondary data (such as from physician prescription panels). Integrating or fusing such data sources can yield great value, particularly for pharmaceutical companies have demonstrated the usefulness of primary and secondary data fusion in examining policy shifts in detailing by pharmaceutical firms. They found that when the market leader in a drug category dramatically reduces detailing, all firms in the category make more money, and the category shrinks only to a minor extent. Similar models can be developed for pharmaceutical forecasting, integrating information from conjoint analysis and information on past physician behavior from physician tracking panels.

Finally, there is a need for more work that examines the adoption of marketing science models by pharmaceutical managers. While marketing scientists have developed "heavy artillery" to assess the commercial (future) potential of new drugs, little of that artillery is used in practice. Rather, managers typically use linear or nonlinear extrapolation as well as traditional conjoint models. Examining the reasons that underlie the limited usage of sophisticated models in practice can yield important insights that can lead to better model development in the future.

7.4.2 *Future Research on Extracting the Potential of a New Treatment*

Pharmaceutical firms spend considerable sums on marketing activities and in particular on detailing visits. Over the past decade, some US states have initiated legislation limiting marketing spending by pharmaceutical firms, mostly in response to the growing concern regarding the effects that excessive marketing budgets might have on the costs of drugs. In the state of California, for instance, a new bill was signed in 2004 (going into effect in June 2005) requiring pharmaceutical firms to adopt a *Comprehensive Compliance Program* (CCP) that includes policies on marketing interactions with health care professionals. This program implements limits on gifts and other incentives to medical or healthcare professionals. More specifically, the CCP includes "specific annual dollar limits on gifts, promotional materials, or items or activities that the pharmaceutical company may give or otherwise provide to an individual medical or health care professional." In other parts of the world, governments have begun to take increasingly restrictive actions with regard to pharmaceutical marketing. An interesting question to investigate is whether legislation concerning the marketing of drugs alters the supply of detailing and/or the impact that marketing efforts have on the physician's final choice. More specifically, one may wonder whether such restrictions restrain the diffusion of new drugs in physician and patient populations. Another related development is the pending shift to virtual detailing, currently under experimentation in several major firms. What is the difference in effectiveness between a virtual versus a real-life detailing visit in promoting new drugs to physicians?

On the patient side, there is growing evidence suggesting a fundamental shift in the role of the patient in the medical decision-making process (Camacho et al. 2010). Specifically, there is evidence for more participatory decision-making involving patients and their physicians, in which both parties bear responsibility for medical decisions that concern the patients. This change indicates a dialogue between physicians and their patients, wherein physicians apply their medical knowledge in order to best suit their patients' needs and preferences (Emanuel and Emanuel 1992; Epstein et al. 2004). Stremersch et al. (2013) find additional evidence for such participatory decision-making interactions. They find that drug requests, especially those made to primary care physicians and to a lesser extent to specialists, have a substantial influence on brand prescriptions. Nowadays, digital and social media (e.g., Twitter, Facebook, PatientsLikeMe) are an important factor in drug requests in countries around the world. We know very little about the role of digital and social media in the diffusion of new drugs.

In terms of pricing new treatments, it would be beneficial to develop more insight into the evolution of price over the life cycle of a new drug. Lu and Comanor (1998) and Ekelund and Persson (2003) examined price dynamics in the USA and Sweden. However, more interesting insights could come from studying pricing strategies across multiple countries. In addition, the influence of regulation throughout the life cycle of a drug has also remained unexamined so far. Verniers et al. (2011) showed

that regulation does not influence launch price but conjecture this not to be true for prices across the product life cycle. In addition, all studies so far have focused on the ex-manufacturer drug price (e.g., Verniers et al. 2011), which is the price charged to wholesalers. However, it is crucial to also understand the proportion of the drug price that is truly paid by the patient. Data on copayment for drugs and reimbursement levels could provide useful insights. In addition, volume and bundle discounts are increasingly offered to payers. This is another topic that, to our knowledge, has not been the subject of systematic inquiry.

7.4.3 Future Research on Leveraging the Potential of a New Treatment Across Countries

To optimize their profits at a global level, pharmaceutical companies need to account for the extent to which the price of a drug in one country has an effect on the price of the same drug in other countries. There may be different reasons for such cross-country spillovers of price, such as the geographical proximity of countries, the trade relationships between countries, and the extent to which countries enforce a cross-country reference pricing system. Governments often see price spillover as a way to reduce or maintain drug prices at justifiable levels. To stimulate such spillover, many (European) governments have regulations in place by which they require companies to submit their products' prices in a predefined set of reference countries. The prices in this predefined set of reference countries are used to derive a reference price (often the minimum or average price across all reference countries). In both cases, the reference price becomes a ceiling price, and a drug's price can typically not exceed it (Gregson et al. 2005). Most reference pricing systems are asymmetric, in the sense that countries that are included in a specific country's reference set do not necessarily include that specific country in their own reference set. Governments and insurers (commonly referred to as "payers") consequently take prices in other countries into consideration in their own price negotiations with the firm. Managers need to account for price spillover, as agreeing to an excessively low price in one country may "infect" the price levels they obtain in other countries, and thus impact their global profits. So far, no rigorous model exists to optimize pharmaceutical managers' decisions on global pricing, even though this issue is the focus of thriving consulting businesses. Such models would also provide pharmaceutical companies with an optimal launch sequence across countries.

The successful launch and diffusion of new drugs remains the life blood of many pharmaceutical firms. While it is clear from our review that some questions are answered by past research in marketing science, it is equally clear that sophisticated managers are short of decision support tools (i.e., marketing models) that they can implement successfully to make a difference in their respective markets. We hope the present chapter has provided a stimulus for the development of such tools.

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Chapter 8
Pharmaceutical Lifecycle Extension Strategies

Eelco Kappe

Abstract The combination of higher costs of drug development and an increasing share of generics has lead pharmaceutical firms to focus on alternative strategies to make profits. An important development in the pharmaceutical industry is the focus on strategies that increase the returns from an already approved drug. Firms have various possibilities to extend the lifecycle and profitability of a branded drug, before and after its patent has expired. These lifecycle extension strategies can be divided into marketing strategies (pricing, promotion, divestiture, differentiation, over-the-counter drugs, and branded generics), R&D strategies (new indications, reformulations, combination drugs, and next-generation drugs), and legal strategies (generic settlements and patenting). For example, when the patent of the blockbuster drug Prilosec was about to expire in 2001, its manufacturer was pursuing many different lifecycle extension strategies concurrently. Already 6 years before patent expiry its legal, marketing, and R&D experts had started with the development of over 50 different strategies to soften the impact of the patent expiry, such as a next-generation product, introducing branded generics, and improving the patent protection of the product. This chapter provides a comprehensive framework to classify the various lifecycle extension strategies, gives an in-depth overview of the research on the different strategies, and identifies gaps in our knowledge on these strategies to guide future research.

The pharmaceutical industry is heavily spending on developing new prescription drugs, which are protected by patents to enable firms to recoup their research and development (R&D) costs. When the patent on a branded drug expires, generic drugs enter the market to compete based on price. Dimasi et al. (2003) estimate the development costs of an average drug at $802 million in 2000. While the costs of

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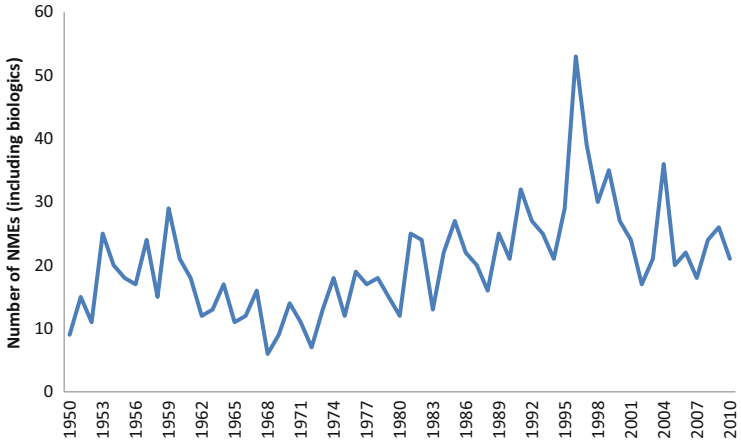

Fig. 8.1 The number of new drug approvals between 1950 and 2010 is relatively stable

new drug development have risen enormously over the last 60 years, the number of newly approved drugs has remained relatively stable (see Fig. 8.1; Cockburn 2007; Munos 2009). In 2008, the pharmaceutical industry spent $50 billion on R&D and 21 new drugs have been approved in the United States (Munos 2009).

At the same time, the share of generic drugs has increased substantially. The generic share of prescription drugs in the United States has risen from 18.6 % of unit sales in 1984 to 78 % in 2010 (Forden 2011; Frank 2007b). The current generic share is comparable for most other countries with high drug sales, although in some countries like France, Italy, Japan, and U.K. the generic share is 50–60 % (Danzon and Furukawa 2008). The rise of the generic share has several reasons. The growth of managed care organizations (MCO) and health maintenance organizations (HMOs) have increased the emphasis on generics. Pharmacy benefit managers (PBMs) act as managers for reimbursement for firms and HMOs and stimulate the usage of generic drugs. In several countries—such as the United States, Canada, and Belgium—insurers have introduced tiered copayments (or partial reimbursement rates) and generics have the lowest copayments. Pharmacists have been incentivized to prescribe more generics, due to higher margins (Grabowski and Vernon 1992). Many countries and all states in the United States have now laws in place that permit pharmacists or make it compulsory for them to substitute a branded drug by a generic if one is available (Vivian 2008). Hellerstein (1998) reports that, in 1995, pharmacists already substituted generics in half of the cases when the doctor prescribed a branded drug. An extensive literature has discussed the determinants (e.g., Grabowski and Kyle 2007; Grabowski and Vernon 1992; Hurwitz and Caves 1988; Saha et al. 2006; Scott Morton 2000) and consequences of generic entry (e.g., Caves et al. 1991; Hurwitz and Caves 1988; Reiffen and Ward 2005; Saha et al. 2006). This literature shows that the number of generic entrants decreases the generic price. The number of generic entrants is mainly driven by market size, pre-patent expiry advertising, and the ease of manufacturing. The generic share increases in the extent of HMO coverage and is larger in hospital markets. In addition, most

	Short-term Impact	Medium-term Impact	Long-term Impact
Marketing	Pricing Promotion Divestiture	Differentiation	Switch to OTC Branded generics
Research and Development		New indications Reformulations	Combination drugs Next generation Products
Legal	Generic settlements	Patenting strategy	

Fig. 8.2 Pharmaceutical lifecycle extension Strategies classified according to their impact. *Source*: Adapted from Sandner and Ziegelbauer (2008)

studies find that generic entry decreases the total market size of the molecule, branded prices increase after generic entry, and marketing expenditures decrease before and after patent expiry.

The combination of higher costs of drug development and an increasing share of generics has lead firms to focus on alternative strategies to make profits. An important development in the industry is the focus on strategies that increase the returns from an already approved drug. Firms have various possibilities to extend the lifecycle and profitability of a branded drug, before and after its patent has expired. These lifecycle extension strategies can be divided into marketing strategies, R&D strategies, and legal strategies (see Fig. 8.2).[1] In this chapter, I discuss these pharmaceutical lifecycle extension strategies and focus on providing an overview of prior academic research and directions for future research.[2]

Marketing strategies to extend the lifecycle of a branded drug include the pricing of the drug before and after patent expiry, the promotion strategy, differentiation strategies, the divestment of a drug, the introduction of branded generics, and making the drug available over-the-counter (OTC). Marketing strategies can be executed relatively quickly compared to other lifecycle extension strategies. The price of the branded drug before and after patent expiry is important as generics enter the market with substantially lower prices and margins than the branded drug (Frank and Salkever 1997; Grabowski and Vernon 1992). When the number of generics increases the generic prices approach marginal costs (Reiffen and Ward 2005). The branded manufacturer may decide to decrease its price to face head-to-head competition with generics, or maintain or even increase its price to focus on the

[1] Another consequence of the increasing market share of generics is that many branded manufacturers have recently moved into the generics industry via acquisitions.

[2] There are plenty of cases written about specific lifecycle extension strategies. For example, Kvesic (2009) discusses various lifecycle extensions of nifedipine (Adalat, Procardia) over a 30-year period, such as new indications, new dosages, a combination drug, etc. Chandon (2004) is another excellent case, discussing the strategies used by Clamoxyl in France to fend off generics.

price-insensitive segment of the market and benefit from its brand equity (Frank and Salkever 1992). At the same time, the firm has to decide on the promotion for the branded drug around patent expiry (Berndt et al. 2003). The branded drug has enjoyed a legal monopoly during its patent-protection period and likely has built substantial brand equity and goodwill (Caves et al. 1991; Hurwitz and Caves 1988). Around patent expiration, the firm must decide on whether to keep investing in this brand equity, focus the promotion on specific segments of the market, or largely cut the promotion. The marketing department of the firm can also decide to differentiate the branded drugs from generics by providing additional value to its product, without obtaining a new patent (Chandon 2004; Kvesic 2008). For example, they can offer extra service to their product or produce a different flavor of the drug. Furthermore, firms can decide to divest or milk their product (Kvesic 2008).

The introduction of branded generics and switching a drug to become available OTC require a long-term commitment of a firm and may bring a healthy stream of revenues over a longer period of time. Branded generics are cheaper versions of the branded drug that build on the branded drug's name and are marketed or licensed by the manufacturer (Berndt et al. 2007). This allows the firm to capture a share of the generic profits and possibly increase the equilibrium price of generics, which in turn may lead to a higher share for the branded drug (Kamien and Zang 1999; Reiffen and Ward 2007). A firm can also opt to make the drug available to consumers by getting OTC approval (Berndt et al. 2003; Ling et al. 2002). This option is limited to drugs that have a low potential for abuse and have proven to be reasonably safe and well tolerated. OTC drugs make up 28 % of the unit prescriptions in the United States (Danzon and Furukawa 2008).

R&D strategies require more time to execute, but potentially have a long-term impact on the sales of the drug. The advantage of R&D into extensions of an existing drug is that it can benefit from the information obtained from past clinical trials (O'Connor and Roth 2005). This makes drug development more efficient and decreases the development costs and risks substantially (Chong and Sullivan 2007; Fleming and Ma 2002). New indications and reformulations are frequently used R&D strategies to extend a drug's lifecycle (Dubey and Dubey 2009). Upon approval, both can extend the monopoly period of the branded drug for several years. Increasing the number of approved indications also expands the potential market for the drug. In 2004, 84 % of the top 50 prescription drugs had obtained additional indications after approval (Sandner and Ziegelbauer 2008). Reformulations use the same active ingredient as the original drug, but provide substantial improvements to the drug that make the drug more effective, reduce side effects, or provide patients with more convenience. Between 1989 and 2000, 65 % of the approved drugs in the United States were reformulated versions of existing drugs (Hong et al. 2005). Firms can also opt for combination drugs, which are two or more drugs (i.e., pills, injections, patches, or inhalers) combined into one drug (i.e., pill, injection, patch, or inhaler) (Herrick and Million 2007). In 2009, worldwide sales for combination drug were over $30 billion. Combination drugs require more substantial R&D investments, but can receive their own patent. Similarly, firms can develop a next-generation product that is based on a drug already on the market, but qualifies

for a new patent as it consists of a new molecule (e.g., Nexium is the next-generation product of Prilosec).

Legal strategies are also widely used to extend the lifecycle of a drug and have a short to medium-term impact on the sales of the drug (Burdon and Sloper 2003). As the branded drug's lifecycle is mainly determined by the period without generic competition, firms use various legal strategies to deter generic entry. These comprise patenting strategies, where firms heavily protect their drug with multiple patents, and settling with generic manufacturers to postpone generic entry. For example, the average number of patents on a drug has seen a fivefold increase from 1995 to 2005 (Frank 2007b).[3]

The overall strategy of a branded firm around patent expiry often combines multiple strategies discussed above. These are not independent from each other and to decide on and execute these strategies knowledge from different departments in the company is needed, requiring the formation of cross-functional teams. For example, the development of a reformulation of a drug requires R&D input, a marketing plan, and support from the legal department on patenting and trademarking. Some lifecycle strategies require many years to develop (e.g., combination drugs due to new clinical trials), while others can be implemented overnight (e.g., price change). An active lifecycle strategy can start already before the launch of a new drug (e.g., see Fig. 2 in Kvesic (2009) for various extensions of nifedipine).

A manufacturer has invested heavily in successful drugs that near patent expiry. In 2008, $50 billion was spent on R&D, not only to get drugs approved to the market, but also to continuously support drugs that are on the market. In addition, substantial amounts are spent on marketing drugs by informing and educating doctors, patients, etc. When the patent on a drug expires, the drug has built various assets that can be leveraged to extend a lifecycle.

To decide which lifecycle extension strategy a firm should pursue for a particular drug, a firm should evaluate its own assets and the assets of the drug. These can be divided into *reputational assets* and *knowledge assets* (Teece et al. 1997). Reputational assets come from the brand and the company's name. After patent expiry, the branded drug can benefit from its brand equity and trademarks. These give a quality signal to doctors and patients and lower informational costs (Landes and Posner 1987). This can be used to slow down the impact of generics and can be used for line extensions to leverage market power and brand equity from one market or product to another. The firm also has knowledge assets. Some of them are protected by patents, but most are due to the firm's extensive experience in the market and in the development of the drug. These knowledge assets comprise expertise in technical areas, manufacturing, marketing, knowledge of doctor and patients, and a good network. These knowledge assets should also be carefully evaluated and used to decide on alternative lifecycle extension strategies. For example, this knowledge may help to identify new potential market applications for the branded drug.

[3] Another strategy sometimes used by firms is to corner supply, whereby the manufacturer makes an exclusive contract with suppliers of scarce ingredients, prohibiting competitors to produce generics. I will not further discuss this strategy as it is questionable from a legal perspective.

In this chapter I focus on strategies that build on a drug that is already on the market and do not cover various related topics. These include a discussion of the general R&D process (e.g., Ganuza et al. 2009) and the budgets set for R&D (e.g., Weiss et al. 2009). In addition, I refrain from discussing the technical aspect of the R&D process and an in-depth discussion of legal strategies. However, I will discuss the R&D and legal strategies at a more general level, as they are important strategies in themselves and because they are also closely related with the other lifecycle extension strategies.

Patent expiration has consequences for many different market players: Branded manufacturers, generic manufacturers, doctors, patients, insurers, pharmacists, and the government. I focus mainly on the consequences of patent expiry for branded manufacturers and will not extensively discuss the impact for the other players.

Finally, I limit the main discussion to pharmaceutical drugs and not discuss strategies for biologics. Biologics are still relatively new and regulations concerning generic biologics (also called biosimilars) are in flux (Engelberg et al. 2009; Frank 2007a; Kozlowski et al. 2011). The end of this chapter will briefly discuss implications for biologics.

I continue by discussing the regulatory environment for prescription drugs, which is essential to understand the rest of the chapter. Then, I discuss the determinants and impact of generic entry. Next, I discuss the various lifecycle extension strategies in more detail and give specific recommendations for future research on them and I end with a conclusion and some more general recommendations for future research.

8.1 Regulatory Environment

New drugs are often protected by multiple patents. Patents allow firms to extract monopoly rents from their product for a limited period of time, often in return for high R&D investments. The total time a drug is on the market without facing generic competition is referred to as the market exclusivity period (e.g., Grabowski and Kyle 2007). Upon approval of a drug in the United States, its patents are listed in the Orange Book of the Food and Drug Administration (FDA).[4] The most important patent on a drug protects the molecule. Internationally, the norm is that a patent lasts for 20 years from the date of application. However, after patenting firms need to test and prove the safety and efficacy of the drug to receive market approval from the national regulatory bodies. Both patents and drug approval by the regulatory body are needed to sell drug without liability (Bhat 2005).[5] The time between patent filing

[4] http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[5] The market approval of a drug is regulated by the regulatory body of a country. In the U.S. this is the Food and Drug Administration (FDA), in Europe the European Medicines Agency (EMA), and in Japan the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). These agencies control the three largest pharmaceutical markets.

Table 8.1 Overview of pharmaceutical terminology and abbreviations

Abbreviation	Explanation
ANDA	Abbreviated new drug application: contains data that provides for the review and ultimate approval of a generic drug product. These are not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, a generic applicant must scientifically demonstrate that its product is bioequivalent.
Bioequivalence	The absence of a significant difference in the rate and extent to which the active ingredient/moiety in pharmaceutical equivalents (i.e., same active ingredient, dosage form, route of administration and strength) becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.
NDA	New drug application: an application for a new drug approval containing data from specific technical viewpoints for review, including chemistry, pharmacology, medical, biopharmaceutics, and statistics. If the NDA is approved, the product may be marketed.
NME	New molecular entity: an active ingredient that has never before been marketed in any form.
OTC	Over-the-counter: drugs classified as safe and effective for use by the general public and which can be obtained without a doctor's prescription.
sNDA	Supplemental new drug application: an application to allow a firm to make changes in a product that already has an approved NDA.
SPC	Supplementary patent certificate: extension of a patent used by the European Union.

and market approval can be substantial and shortens the patent-protected time of the branded drug on the market. Regulatory bodies often compensate for the lost time, as a result of clinical testing, by extending the patent or the market exclusivity period. In Europe, for example, a supplementary protection certificate (SPC) can be obtained extending the patent for a maximum of 5.5 years (Table 8.1 provides an overview of pharmaceutical terminology and abbreviations used in this chapter).

I discuss the US regulations in more detail. In 1984, US congress passed the Hatch-Waxman Act—also known as the Drug Price Competition and Patent Term Restoration Act—which regulates the competition between branded and generic drugs. It marks an important change in the US pharmaceutical market and applies to all pharmaceuticals, except antibiotics, and biotechnology products. I discuss two important parts of the Act.[6]

Title I allows generic drug makers to file an abbreviated new drug application (ANDA), which involves a bioequivalent of a branded drug whose patent expires. Compared to before the Act, generic drug makers do not have to prove the safety and efficacy of the drug anymore, which involves substantial costs and creates high barriers to entry. The Act required generic manufacturers to only show bioequivalence of their drug.

[6] See for the complete law: Public Law 98–417.

Bioequivalence is typically shown by measuring and comparing the absorption of the branded and generic drug in the blood stream in around 30 healthy volunteers (Bhat 2005; Dubey and Dubey 2009). Testing for bioequivalence is 18 times cheaper than also repeating the safety and efficacy tests (Bae 1997). The costs to prepare an ANDA are about $1 million (Hemphill and Sampat 2011). The first generic manufacturer that successfully files an ANDA is granted an exclusive marketing period of 180 days for the drug among generic manufacturers. The Act also allows firms to test the patented drug before patent expiry and specifies a process to resolve a patent dispute between a branded and generic manufacturer.

An ANDA must contain one of the four certifications with respect to each patent listed for the branded drug. A Paragraph I, II, and III Certification involve the assurance that respectively: (1) no patent for the branded drug is filed, (2) the patent on the branded drug has expired, (3) the approval of the ANDA is only sought after the patent on the branded drug has expired. A Paragraph IV Certification involves a claim of a generic manufacturer that the patent on the branded drug is invalid or will not be infringed (Bulow 2004; Hemphill and Sampat 2011). After an ANDA is filed by a generic manufacturer, based on a noninfringement claim, branded manufacturers can file a patent-infringement suit within 45 days. The FDA cannot approve the ANDA until a court invalidates the infringement or 30 months elapse (Bhat 2005). In 2003, the Medicare Prescription Drug, Improvement and Modernization Act (MMA) passed the senate to prevent branded manufacturers to exploit former law to delay generic entry. For example, firms started multiple patent-infringement litigations, which all provided a 30-month stay of generic drug approval. The new Act allows a maximum of one such extension. Higgins and Graham (2009) report that, between 1992 and 2000, branded firms started an infringement suit to 72 % of the Paragraph IV challenges and the branded drug manufacturer won these litigations in 58 % of the cases. They also report that the number of paragraph IV challenges has increased substantially after 2000.

Title II of the Hatch-Waxman Act grants additional market exclusivity to branded drugs for the time lost due to FDA drug review. On average, the additional market exclusivity granted is 2.5–3 years with a maximum of 5 additional years or 14 years from the original FDA approval date. Newly approved drugs get a minimum of 5 years market exclusivity. Firms need to apply for the extension within 60 days of market approval.

In all US states and many other countries there are generic substitution laws for pharmacists, allowing them or making it compulsory to substitute the branded prescription by a bioequivalent generic (Vivian 2008). This leads to a higher generic share. In some states patients first need to give their consent prior to the generic substitution by the pharmacist, leading to a lower substitution rate (Shrank et al. 2010).

8.2 Generic Entry

When the patent on a drug expires, generic drugs can enter the market. These generics have substantially lower prices than the branded drug before patent expiry and take a large share of the market. Hellerstein (1998) finds that almost all doctors prescribe both generic and branded versions of the same molecule if a generic is

available. They report substantial heterogeneity across doctors in the frequency of branded vs. generic prescriptions.

The impact of patent expiry in the pharmaceutical industry is widely investigated. Regulations play an important role in the outcomes of patent expiry and in the U.S. the Hatch-Waxman Act in 1984 has changed the dynamics after patent expiry substantially. See for a comprehensive study on patent expiry before the Hatch-Waxman Act (Statman and Tyebjee 1981). Below, I focus mainly on patent expiry and generic entry after the Hatch-Waxman Act. Table 8.2 gives an overview of the empirical studies into patent expiry. I start by describing the characteristics of generic entry, followed by the consequences of generic entry.

8.2.1 Determinants of Generic Entry

The time until generic entry is uncertain, because the approval time of an ANDA is uncertain. Branded manufacturers also do not know the exact patent expiry date, as patents can be challenged before the original patent expiry date. Generics entering the market are often considered a commodity, with little differentiation between them. Hence, the number of generic entrants largely determines their price, with more entrants implying a lower price.

The extent and speed of generic entry after patent expiry differ across products and markets. Scott Morton (2000) finds that the most important factor determining the number of generic entrants is the revenue of the branded drug before patent expiry (see also Grabowski and Vernon 1992; Hurwitz and Caves 1988; Saha et al. 2006). Sometimes a drug is in a niche category and no generic enters, e.g., between 1987 and 1993, 40 % of the drugs faced no generic competition within 2 years after patent expiry (Bae 1997). Hurwitz and Caves (1988) also find that branded drugs with a longer market exclusivity period and higher pre-patent expiry promotional expenditures face fewer generic entrants.

Hudson (2000) investigates the impact of generic entry in four different countries: the U.S., the U.K., Germany and Japan. He largely confirms the findings of earlier studies based on US data and finds that larger markets face more generic entrants and faster generic entry.

Grabowski and Kyle (2007) find in a recent large-scale study, based on 251 drugs that lost their patent between 1995 and 2005, that drugs face generic entry more often over time and that more successful drugs face more generic entrants and a smaller market exclusivity period.

8.2.2 Consequences of Generic Entry

Generic entry has a large impact on the market. It leads to drastic changes in the average price of a molecule as cheap generics enter and the demand for the branded drug largely shifts to generics. Below, I discuss the consequences of generic entry and also discuss how it influences the promotional expenditures and total market size.

Table 8.2 Overview of empirical research on generic entry

Article	Goal	Period	Sample	Findings
Hurwitz and Caves (1988)	Investigate the impact of the goodwill of a branded drug on generic market share and the impact of the generic price and promotion on the branded drug's share	1978–1983	29 Oral drugs	Drugs that are on the market for a longer time before patent expiry have a higher post-patent market share, due to a higher amount of goodwill built. Higher pre-patent expiry promotional expenditures also increase post-patent market share. Higher branded prices increase the share of generics.
Caves et al. (1991)	Identify the patterns displayed by branded and generic drugs' prices, market shares, and quantities sold, as well as branded drugs' advertising	1976–1987	30 Drugs	Generic entry leads to a small decrease in the branded price. The price of the generic drugs decreases with the number of generic competitors. The total share of generic drugs increases with the number of generic drugs available, but remains relatively small. The advertising expenditures start decreasing 2 years before patent expiry, decrease substantially upon generic entry, and in the number of generic drugs.
Grabowski and Vernon (1992)	Investigate the impact of generic entry on generic and branded drug prices, as well as the determinants of generic entry	1983–1987	18 Drugs with yearly sales above $50 million before patent expiry	On average, branded drugs lose half of their market share in the 2 years after patent expiry. Prices of branded drugs rise in response to generic entry and generic prices decrease in the number of generic entrants. There are no significant barriers to generic entry and the expected profitability of generic entry is driving the number of generic entrants.
Frank and Salkever (1997)	Price response of generic and branded drugs to generic entry	1980–1991	32 Drugs	Brand-name prices increase after generic entry and more generic drugs leads to lower generic prices, but do not decrease branded prices. The net effect is a decrease in the average price of a molecule.
Bae (1997)	Determine factors that influence the speed and likelihood of generic drug entries	1987–1994	81 Drugs	Higher sales for the branded drug lead to faster generic entry. Generic entry is slower for branded drugs with few or many competing brands in the same therapeutic market. Chronic drugs face increased generic competition than drugs for acute illnesses.

Ellison et al. (1997)	Compute own and cross-price elasticity between branded and generic drugs	1985–1991	4 Drugs (anti-infectives)	A two-step decision process, where in the first step the doctor prescribes a chemical compound and in the second step the pharmacist dispenses a generic or branded version, sometimes in conjunction with the patient and often constrained by the law, insurers, etc. They find high demand elasticity between generic substitutes (bioequivalent, but produced by different firms) and a smaller, sometimes significant, demand elasticity between therapeutic substitutes (chemically distinct, but used to treat similar conditions).
Scott Morton (2000)	Entry decisions of generic firms into markets opened up by patent expiration	1986–1992	98 Drug-form combinations (of 81 drugs)	Pre-expiration brand revenue is the most important determinant of generic entry. Oral solids and drugs for chronic diseases also attract more entry. Regulatory stringency at the FDA deters entry. Increasing the number of consumers with elastic demand increases generic entry. Branded advertising is not barrier to entry by generic firms in the United States.
Berndt et al. (2003)	Pricing and marketing for branded drugs around patent expiration	1988–1999	4 Drugs (H_2-antagonists)	Branded drugs increase their price and decrease their marketing expenditures after patent expiry. The marketing expenditures already decrease 2 years before patent expiry. Prices of OTC drugs are lower than the branded drug's price, but higher than generic drug prices.
Wiggins and Maness (2004)	Determine the relationship between price and the number of generic sellers	1984–1990	98 Anti-infective drugs	Generic prices fall rapidly moving from one to multiple sellers and continue to decrease even when there are numerous sellers. The generic price decreases by 83 % moving from 1 to between 6 and 15 sellers and another 52 % when the number of sellers rises above 40. As entry of generic manufacturers increases, both the prices of branded and generic incumbent drugs decrease.
Hong et al. (2005)	Test whether market entries of new extensions are associated with market success of original branded drugs and whether branded drugs exhibit price rigidity to generic entry only when they are extended	1985–1995	27 Drugs	Drugs that achieved market success before patent expiry are 16 times more likely to be extended than unsuccessful drugs. Price rigidity is observed for drugs with extensions, but not for drugs without extensions.

(continued)

Table 8.2 (continued)

Article	Goal	Period	Sample	Findings
Reiffen and Ward (2005)	Understand how competition evolves in the generic drug industry	1985–1995	31 Drugs	The rents in the generic industry increase during the first 5–10 months after patent expiration and then decrease as more firms enter. In markets with higher expected rents, more firms enter and they enter faster. In large markets, the margins on generics will eventually become close to zero.
Saha et al. (2006)	Understand the interactions between generic entry, prices, and market shares	1992–1998	40 Drugs	The number of generic entrants is a key determinant of generic market share and generic-to-brand price ratio. Blockbusters face more generic entrants, lower generic prices, and higher generic penetration. The extent of HMO coverage increases generic market share. Generic entries lead to a small decrease in price of the branded drug (0.2 % per additional entrant) and no evidence of entry-deterrent pricing is found.
Gonzalez et al. (2008)	Study how doctors and doctor characteristics impact competition among molecules in a therapeutic class, when one of the drugs loses its patent and generics enter	1998–2000	Panel data on patent expiry of fluoxetine	Generic entry decreases the number of prescriptions for the molecule that loses its patent, but increases prescriptions for non-bioequivalent branded competitors. Detailing-sensitive doctors switch from the drug that loses its patent to other branded alternatives, while price-sensitive doctors switch from the drug losing patent to generic alternatives.
Regan (2008)	Study the effect of generic entry on post-patent price competition	1998–2002	18 Oral solid drugs for chronic conditions	There is strong price competition between different generics, but not between branded and generic brands. The price of branded drugs increases in the number of generic entrants, while average generic price decreases.
Ching (2010)	Investigate the dynamics of demand for prescription drugs after patent expiration	1984–1987	14 Drugs	Brand-name price elasticities of demand are often less than one and increase over time. Patients are risk averse and have a negative prior about the quality of generic drugs. Branded drugs should set their prices before patent expiry lower than expected by a myopic firm (that does not take learning about generics' quality into account) in order to decrease the learning for the quality of generics.

Notes: Two important regulatory changes may have substantial impact on the results in different time periods: (1) the Hatch-Waxman Act in 1984, (2) the change in the regulations on DTCA in 1997.

Hurwitz and Caves (1988) investigate the impact of generic entry on the market share of the branded drug. They find for a sample of 29 drugs, expiring between 1978 and 1983 (before the Hatch-Waxman Act), that the share of the branded drug after generic entry is proportional to the time of that drug on the market (goodwill stock) and its promotion. The goodwill and promotion are less effective for hospital markets than pharmacy markets.

Caves et al. (1991) provide a descriptive analysis of the impact of generic entry in the United States for 30 drugs. They investigate the speed and fullness with which generic entry erodes the sales of the branded drug losing its patent. They analyze the period 1976–1987 and hence most patents in their sample expired before the Waxman-Hatch Act. They find a small decrease of the branded drug's price as the number of generic entrants increases. The price of generics decreases with the number of generic competitors. The total generic share increases with the number of generic drugs available, but remains relatively small. They find that when the generic price is about half of the branded price, generics attain a 25 % market share 5 years after patent expiry.

Grabowski and Vernon (1992) analyze prices and market shares of 18 high-sales drugs facing their first generic competition between 1984 and 1987, after the Waxman-Hatch Act. They find that overall market prices decline sharply in the first 2 years after patent expiry. During that period branded prices increase by 11 % (see also Berndt et al. 2003), exceeding inflation. Generic prices are substantially lower and keep decreasing with additional generic entrants. Two years after patent expiry, the average generic share is 49 %.

Wiggins and Maness (2004) find that generic and branded prices decrease in the number of entrants. They test this for a single therapeutic category (anti-infectives) and argue that this focus allows them to control for cost and demand differences across therapeutic categories. However, their results may partly be driven by the characteristics of the therapeutic class under consideration.

Reiffen and Ward (2005) investigate generic prices in reaction to generic entry using a structural model. Based on 31 drugs facing generic entry, they find that the number of generic entrants and the speed of generic entry increases with market size. They report that the price for the first generic is 20–30 % above long-term marginal costs, but generic prices begin to approach marginal costs when ten or more generic competitors have entered.

Saha et al. (2006) empirically investigate for 40 drugs the interactions among generic entry, prices, and market shares. They claim to be the first to analyze these three variables using a simultaneous estimation procedure to address the endogeneity between them. The price and share of generics are simultaneously determined. The number of generic entrants is a key determinant of generic market share and the generic-to-brand price ratio. They also find that the extent of HMO coverage increases generic market share.

Another reason for the decreasing market share of the branded drug is that its promotional expenditures decrease substantially around patent expiry (Caves et al. 1991). Berndt et al. (2003) investigate the marketing expenditures of branded drugs around patent expiry. They find for four H_2-antagonist drugs that marketing expenditures between 24 and 1 months before patent expiration are 20–59 % lower than the amount spent between 48 and 25 months before patent expiry. The amount spent

on marketing in the first 2 years after patent expiry is even lower. This decrease in marketing expenditures is confirmed by Huskamp et al. (2008) and Iizuka (2004).

The market size can also change due to generic entry. Gonzalez et al. (2008) investigate how doctors change their prescription behavior in a therapeutic category when one of molecules (a branded drug) goes off patent. Due to the introduction of generics, the average price of the molecule that loses its patent decreases. In line with Caves et al. (1991) they find that, despite the lower price for the molecule, total prescriptions decrease as some doctors switch to other branded and more expensive molecules.

The literature on generic entry has mainly investigated the US market as it is the biggest and least regulated pharmaceutical market in the world. However, these results are not directly generalizable to other countries due to differences in the regulatory context. For example, many European countries have reference price systems, prohibiting branded drugs to increase prices after patent expiry. Hudson (2000) studies the impact of generic entry on sales in multiple countries. He confirms several results of earlier studies on US data and finds that, except for the U.K. market size and the price of the branded drug increase the speed with which the branded drug loses its market share. In addition, he finds that the impact of generics is greater in the U.S. than in Germany, the U.K., and Japan. This can either be due to the US regulations or because the United States has the biggest market size among these countries. Lexchin (2004) analyzes price changes of branded drugs after patent expiry in Canada and finds no significant changes. Aronsson et al. (2001) find for the Swedish pharmaceutical market that lower generic prices substantially decrease branded market share.

8.2.3 Summary of Generic Entry

The impact of generic entry on branded sales has substantially increased in the United States after the passage of the 1984 Hatch-Waxman Act. As generic drugs are a commodity, the main determinant of their impact is the number of generic entrants, which in turn decreases the generic price. This is mainly driven by market size, but pre-patent expiry advertising and the ease of manufacturing also influence the number of generic entrants. The generic share increases in the extent of HMO coverage and is larger in hospital markets. Generic entry decreases overall market size for that molecule due to a substantial decrease in marketing.

Hence, the number of entrants largely determines the generic price, but the literature is not converged on the effect of generic entry on branded prices. While most studies find that branded prices increase (e.g., Berndt et al. 2003; Grabowski and Vernon 1992; Regan 2008), some studies find decreasing prices after generic entry (e.g., Caves et al. 1991; Wiggins and Maness 2004). These differences warrant a large-scale study analyzing price changes of branded drugs after patent expiry. It is valuable to explore the product and market moderators that explain the changes in branded prices after patent expiry.

The literature is consistent on firms decreasing their marketing expenditures before and after their patent expires (Berndt et al. 2003; Caves et al. 1991). The literature is also consistent on a decreasing market size for the molecule after patent expiration (Caves et al. 1991; Gonzalez et al. 2008), though this may not hold for current markets due to the advent of stronger managed care pressures.

8.3 Marketing Strategies

Firms of branded drugs that face patent expiration have different marketing tools to retain sales and soften the impact of generic entry. They can make their product attractive by the price, promotion, and by differentiating it from generics, to either limit the generic share directly or by deterring generic entry (Scott Morton 2000). A firm can also decide to divest its drug around patent expiry. In addition, the firm can introduce a branded generic or an OTC version of the drug. I discuss these marketing-related strategies in turn below.

8.3.1 Pricing

When the market exclusivity period for a drug ends, lower-priced generics enter the market. The branded drug manufacturer can react by decreasing the price to compete directly with the generics (e.g., Chandon 2004). For example, they can decrease the unit price or give volume discounts to large distributors or pharmacies. They can also maintain or increase the price and focus on the price-insensitive segment of the market, although price increases are not an option in countries where the price is regulated (e.g., Europe). In the United States the most common reaction of branded firms to generic entry is a price increase.

Frank and Salkever (1992) explain the price increase of branded drugs in response to generic entry by dividing the market into two segments. They show theoretically that a price increase after generic entry can be explained by optimal firm behavior. They distinguish a segment that is price insensitive (or brand loyal) to the branded drug and a price-sensitive segment. The price-insensitive segment can consist of patients of doctors in fee-for-service practices, while the price-sensitive segment consists of hospitals, HMOs and Medicaid patients. They conclude that generic entry decreases the price elasticity of the demand for the branded drug and hence a price increase for the branded drug is optimal (this is extended and confirmed by Regan (2008), who incorporates the payment type of the patient for the drug). In a later paper Frank and Salkever (1997) confirm these predictions empirically. Gonzalez et al. (2008) use doctor-level data from the U.K. to study the patent expiry of Prozac. They confirm the existence of two doctor segments: a marketing-sensitive segment that prescribes less of the molecule losing its patent and switches to the more heavily marketed alternatives, and a smaller price-sensitive segment that starts prescribing the cheaper generics.

Hong et al. (2005) find that the price rigidity of branded drugs after patent expiry is due to the introduction of line extensions of the branded drug. As line extensions are closely related to the branded drug that loses its patent, the manufacturer sustains the price of the branded drug to increase the demand for its extension. This is in line with Kadiyali et al. (1996), who find that line extensions decrease the original product's cross-price elasticity to competitors.

Ching (2010) finds evidence that myopic firms would set their price after patent expiry higher than long-term oriented firms, who take the learning about generic quality into account. A lower price for branded drugs decreases learning about the quality of generics.

8.3.2 Promotion

Manufacturers use the period in which the branded drug is protected by a patent to build the brand equity of the drug without direct competition of bioequivalent generics. Traditionally this brand equity is build among doctors using detailing, sampling, and journal advertising. The increase in direct to consumer advertising (DTCA) since 1997, when the regulations on DTCA have been loosened, has allowed firms to also actively build brand equity among patients. The resulting goodwill concerns differences in quality between the branded and generic drug and induces doctors to keep on prescribing branded drugs when generics are available (Caves et al. 1991; Hurwitz and Caves 1988). These quality differences can arise by a higher quality control for branded manufacturers as generic manufacturers have fewer reputational assets to lose from lower quality control. Also quality perceptions of properties of branded drugs can be higher, such as formulation and stability. For example, branded drugs are perceived higher in effectiveness and lower in side effects, though the difference in quality perceptions has decreased over the last 40 years (Ganther and Kreling 2000; Hassali et al. 2009).

Hurwitz and Caves (1988) find that advertising before and after patent expiry preserves the branded drug's market share, because it builds brand loyalty. Higher brand equity slows down the impact of generic entry (Kvesic 2008). However, while most branded drugs lose market share quickly after patent expiry, for some brands it pays off to keep marketing their brand, such as Intal and Coumadin (Parece et al. 2004), especially when the technology is complicated and the brand's sales are relatively low.

Rizzo (1999) finds that advertising decreases price sensitivity and thereby inhibits generic entry. Königbauer (2007) finds that over-investing in advertising before patent expiry has the potential to deter entry, but decreases social welfare. Scott Morton (2000) empirically investigates whether branded advertising creates a barrier to entry for generic drugs after patent expiration. She distinguishes between informative and persuasive advertising. The latter merely persuades consumers of product differentiation between the brand and generic, while almost none exists, and may create a barrier to entry for generic firms. In contrast to earlier work investigating the relation between advertising and generic entry, she treats advertising as

endogenous. She finds that when endogeneity is ignored, branded advertising deters entry. However, when correcting for endogeneity, advertising creates a barrier to entry by generic firms. This is in contradiction to the findings of earlier work.

Ellison and Ellison (2011) investigate strategic entry deterrence just before drugs lose patent protection. Using a sample of 63 drugs that lose their patent between 1986 and 1992, they find that investments to deter entry are nonmonotone in market size. For small markets, no investments are necessary to deter entry, while for large markets entry deterrence is impossible. Incumbents in medium-sized markets have lower advertising levels and are more likely to reduce their price and advertising near the patent expiry date.

In addition to patents, trademarks are available to protect the drug. They offer less intellectual property protection than patents, but may be renewed indefinitely. Trademarks can refer to the drug's name, color, shape, etc. and signal quality and goodwill and reduce consumer search costs. The patent period gives firms time to develop trademarks in a monopoly market to retain the drug's value even after patent expiry. For example, AstraZeneca successfully transferred the trademark of Prilosec (with the trademark: the purple pill) to its follow-up drug Nexium (the purple pill with racing stripes).

8.3.3 Differentiation

Firms can retain branded sales after generic entry by differentiating their drug from generics, which may justify their higher price. They can do that by providing more value of their drug than generics without extending the patent of the drug. They can introduce new flavors, new coatings, improved packaging, easy-to-swallow pills, or patches (Chandon 2004; Kvesic 2008). This can be supported by providing doctors with free samples, which are typically not provided by generics. Another innovative approach is to offer other support services, such as a hotline for doctors. Branded manufacturers can also market the brand with a different message to patients or doctors, without actually changing the drug's properties.

8.3.4 Divestiture

When a firm is not expecting a bright future for the drug after patent expiry, it can divest or milk the drug (Chandon 2004; Kvesic 2008). This is a viable alternative if a firm wants to free resources for other drugs in its portfolio. It involves cutting the drug's marketing and R&D expenditures and selling or licensing the drug to another firm. The branded manufacturer may also increase the price targeting brand loyal customers and maximize short-term profits. Alternatively, a firm can milk the drug by focusing on segments where it has the biggest advantage over generics (e.g., hospitals, marketing-sensitive doctors).

8.3.5 Branded Generics

The first generic obtaining US market approval through an ANDA obtains a 180-day exclusive marketing period for the drug. This temporary monopoly in the generics market allows the first generic to obtain large profits. However, during that period, branded manufacturers are allowed to introduce their own generics. The branded manufacturer needs no FDA approval to enter the market with a so-called branded generic—also referred to as authorized generic, pseudo-generic, or fighter brand. Large pharmaceutical firms often control subsidiaries that produce and market generics or they license the drug to a generic firm to compete against other generics (Chandon 2004; Kvesic 2008).

Branded generics are a regularly used strategy of pharmaceutical firms, especially outside the United States, to either deter generic entry or to capture a share of the generic profits (Berndt et al. 2007; Kamien and Zang 1999; Kong and Seldon 2004). Berndt et al. (2007) argue that there are two effects of branded generics on the price of generics. In the short run, competition increases in the generics market as branded generics are allowed to enter during the 180-day exclusivity period for the first generic manufacturer. This results in a lower generic price during that period. In the long run, branded generics can deter entry, leading to higher long-run equilibrium prices for generics. In small markets, branded generics may even discourage generic manufacturers to submit an ANDA. Hollis (2003) finds for the generic market in Canada that branded generics have a substantial deterring effect on subsequent generic entries in medium-sized markets. Reiffen and Ward (2007) also find that branded generics deter entry in small and medium-sized markets. Depending on the market size they decrease the number of generic entrants by 1.7–2.4. They also find that branded generics increase equilibrium prices; on average, long-term generic prices increase by about 1 % after the entry of a branded generic. This price increase leads to higher profits of the branded drug, up to 3.2 %. Berndt et al. (2007) find that branded generics only lead to higher long-term prices when less than five generics enter the market, which is rarely the case in practice.

Kong and Seldon (2004) conclude in a theoretical study that introducing branded generics to deter entry is only in specific instances a profit-maximizing strategy. They suggest that firms should mainly introduce branded generics in large markets to capture part of the profits from the generics market.

Branded generics are often the first generic in the category and can benefit from a first-mover advantage. Grabowski and Vernon (1992) find that the first-moving generic has long-term advantages over followers. Reiffen and Ward (2007) report that the first generic entrant earns 19–27 % of total generic sales, while, on average, 14 generics enter.

8.3.6 Switch to OTC

The regulatory body sometimes allows drugs with a proven safety under self-medication circumstances to be available over the counter. Similar to prescription

drugs, in the United States, the FDA regulates the approval and marketing claims for OTC drugs and they require an approved label with drug facts for patient education. There are two different forms of OTC products: (1) those that may only be dispensed after a pharmacy employee has assessed the needs of the patients and has given some patient education, (2) those that are just like any other consumer product and are freely available in store. In case the OTC drug has a new indication, dosage, or form, it is eligible for 3 years of market exclusivity.

OTC products make up 28 % of unit prescriptions in the United States, comparable to other countries (Danzon and Furukawa 2008). The advantage of OTC drugs is that they can have high sales for a prolonged period of time. For example, Listerine is available for over 100 years and still successful. The number of prescription drugs approved for OTC usage has risen since the 1990s (Ling et al. 2002). Older classes of H_2-antagonists (e.g., Tagamet, Zantac) and antacids are well-known examples of prescription drugs that are converted to OTC. In Europe, switching a prescription drug to OTC can be a good strategy as then it can then be advertised to consumers (Kvesic 2008). However, also in the United States where DTCA is allowed for prescription drugs, OTC products are heavily advertised.

An OTC drug has the potential to expand the market for its molecule. In addition, it has two opposing effects on the manufacturer. It can cannibalize sales of the branded drug, but the firm can also benefit from spillover effects between the prescription and OTC drug. Often, the cannibalization is limited to a certain extent as OTC drugs are mainly available in lower dosages, while higher dosages are still prescription only. Spillover effects between the OTC and prescription drug are also likely, as OTC drug can benefit from the brand equity of the prescription drug and the firm can benefit from spillover effects in promotion.

Berndt et al. (2003) explore the effects of making prescription drugs available over the counter for four drugs in the H_2-antagonist category. They focus on the impact of OTC switches on the sales of the branded prescription drug and the joint sales of the OTC drug and the branded prescription drug. They find that the amount of cannibalization and the spillover effect between the OTC and the prescription drug varies across brands, depending on whether generic alternatives are available for that drug.

Ling et al. (2002) find spillover effects of marketing prescription drugs on OTC drug sales, but not vice versa. These spillover effects are found for detailing and not for DTCA. They also find an order-of-entry effect for OTC drugs. Later entrants in the OTC market compensate for this by spending a higher percentage of their sales on marketing.

8.3.7 Summary of Marketing Strategies

Marketing strategies to fend off generic entry are relatively easy to implement and mainly have a short-term impact. Pricing and promotion can decrease the extent of generic entry in a limited way. Price decreases to deter entry are infrequent in

practice and promotion has been found to deter entry in medium-sized markets. After patent expiry, firms often maintain or increase the branded drug's price and focus on the price-insensitive customers to retain a profitable market share. Research to date on pricing and promotion mainly describes the rationale behind branded price changes around patent expiry. Future research is warranted on the optimal pricing and promotion of a branded drug around patent expiry, balancing both its competitive effects on generic and branded competitors and its effect on entry deterrence. Empirical studies on the profitability of these strategies are also welcome. Future research can also focus on the impact of trademarks before patent expiry on the post-patent success of a branded drug and how this influences its pricing and promotion strategy.

Research into differentiation strategies and divesting the drug is limited to case evidence. Future research can focus on the impact of various differentiation strategies on sales for the branded product. It is also valuable to investigate theoretically and empirically the optimal pricing and promotion path to divest a drug. This is especially relevant when a firm has multiple related products that may cannibalize each other.

The introduction of branded generics has two potential effects on the market. First, they can deter entry, but its effect on long-term prices is limited and works mainly in small to medium-sized markets. Second, a branded generic can provide the branded manufacturer with a profitable share of the generics market. The latter applies mainly to large markets with many generic entrants. Further research is necessary on branded generics' influence on the branded drug and on how to price and market both. Furthermore, it is valuable to investigate whether preannouncements of branded generics is an effective entry deterrence mechanism.

Switching a prescription drug to OTC status is a viable alternative for some drugs. The challenge for empirical analysis on the impact of such a switch is that different datasets need to be combined, prescription drug sales and OTC sales, which are collected by different data providers (Berndt et al. 2003). This is an important reason for the lack of research in this area and interesting questions remain to be answered to assess the impact of switching a drug to OTC status. For example, how to price the OTC drug compared to the branded drug and compared to possible generic alternatives. What is the optimal moment to switch to OTC? How does brand equity transfer from the prescription drug to the OTC drug? Should the OTC brand name be related to the prescription drug?

8.4 R&D Strategies

R&D strategies build on an existing drug in the market. Development strategies mainly build on reputational assets, as they are extensions of an existing drug. They make use of a patent extension or extended market exclusivity of several years. They improve on convenience for the patient, increase drug effectiveness, reduce

side effects, or are approved for new indications. Research-oriented strategies build more on the knowledge assets of a firm, require extensive research, and new drugs resulting from this strategy often qualify for a new patent on the molecule.

Ganuza et al. (2009) show that pharmaceutical firms target their R&D on small innovations, such as product-line extensions. This is driven by the low sensitivity of demand. Indeed, a large part of newly approved drugs are line extensions.

8.4.1 New Indications

As existing drugs have known pharmacokinetic profiles and side effects, new indications for them are relatively cheap to develop. The process of finding new uses for the drug outside current indications is sometimes referred to as drug repositioning and requires additional clinical testing (Ashburn and Thor 2004). The new indications have the advantage of starting with a Phase II trial which saves almost 40 % of the costs of clinical testing (Chong and Sullivan 2007). New indications enlarge the market potential of a drug and can extend the market exclusivity period up to 3 years through a sNDA (Bhat 2005; Dubey and Dubey 2009; Kvesic 2008). It is a widely used strategy and 84 % of the top 50 drugs in 2004 has obtained additional indications after approval (Sandner and Ziegelbauer 2008).

One specific way for firms to extend the market exclusivity period of a drug by 6 months is to investigate, before patent expiry, the effectiveness of the drug in children. This pediatric exclusivity is independent of the success of the study and must be requested by the FDA (see for the guidance document: FDA 1999). Upon request, this is a standard move for successful drugs. Firms can increase the chances of receiving such a request by proposing pediatric studies to the FDA. For example, sildenafil (Viagra) was initially developed for angina, but in 1998 approved for erectile dysfunction, and in 2003 for pulmonary arterial hypertension under the brand name Revatio. In addition, the manufacturer tested the drug on a rare lung disorder for children to receive an additional 6 months of pediatric exclusivity.

Huskamp et al. (2008) find that promotional expenditures of drugs in the selective serotonin reuptake inhibitor (SSRI) category increased after approval for a new indication. Depending on the new indication, firms increased either detailing or DTCA expenditures.

New indications are usually marketed under the same brand name and hence the brand equity of the drug can be leveraged to the new indication. If the new indication is very different from current indications, firms can opt to market it under a new brand name (e.g., Viagra and Revatio, both sildenafil; Zyban and Wellbutrin, both bupropion; Proscar and Propecia, both finasteride; Prozac and Sarafem, both fluoxetine). Drugs with multiple indications have an increased chance of competing in different markets and to a different set of competitors. Firms should then carefully consider the pricing of the drug in order to be competitive in the various markets.

8.4.2 Reformulations

Reformulations of a drug use the same active ingredient as the original drug, but the formulation is changed to improve compliance, side effects or efficacy. This strategy can involve new forms or dosages and requires new clinical tests. Reformulations have a shorter approval path than NMEs (Fleming and Ma 2002) and upon approval receive at least three additional years of market exclusivity through a sNDA (Bhat 2005). Reformulations often involve technical challenges, which sometimes can be patented, making it harder for generic firms to copy or design around.

Time-release versions of a drug are a popular reformulation and make up 8 % of unit sales of prescription drugs in the United States (Danzon and Furukawa 2008).[7] They ensure a slow and controlled release of the drug in the body and provide the advantage of fewer dosages per day (compared to instant-release formulations) and fewer side effects. Other emerging technologies are site-specific drug delivery, depot formulation, and inhalation drug delivery (Dubey and Dubey 2009).

Sixty percent of newly approved drugs are reformulations (Dubey and Dubey 2009; Huskamp et al. 2008; Sandner and Ziegelbauer 2008). The cost of introducing a reformulation is estimated to be $10–50 million (Bhat 2005). The reformulation typically builds on the brand name of the original drug (e.g., Effexor XR is a reformulation of Effexor). When the reformulation is approved, only the reformulation receives the additional market exclusivity. Hence it is important for firms to differentiate their reformulation from the original drug and switch patients to the reformulation in order to benefit from the additional market exclusivity. Huskamp et al. (2008) find that promotional expenditures for the original brand decrease substantially when a reformulation is introduced.

8.4.3 Combination Drugs

Combination drugs are an increasingly popular lifecycle extension strategy (e.g., Advair, Caduet, Vytorin), with worldwide sales in 2009 of over $30 billion. Combination drugs are two or more active ingredients that are physically or chemically combined to produce a single pill, inhaler, injection, or patch (Herrick and Million 2007). In some circumstances, firms are allowed to co-package drugs (Evans and Salinger 2007); however, this is more common for OTC drugs. Combination drugs are often based on two or more ingredients already on the market and qualify for a new patent. It is required for approval that the combination drug provides an improved treatment for at least some type of patient, compared to the single components. The approval process of a combination drug depends on the

[7] Time-release technology is also referred to as sustained release (SR), sustained-action (SA), extended release (ER, XR or XL), controlled-release (CR), modified-release (MR), or continuous-release (CR).

experience with the single components. If the single components are already approved, drug agencies move more swiftly. For example, the FDA may allow the combination drug to start testing in Phase III.

While empirical research on the sales success of combination drugs is lacking, they can be considered as a form of product bundling (Stremersch and Tellis 2002). Bundling can be done to leverage market power from one to another market, but also to provide a quality signal, which lowers the informational costs for customers.

8.4.4 Next-Generation Drugs

An alternative way to use R&D to build on an existing drug is to develop next-generation drugs. Their development builds on the mode of action and pharmacology of the first generation product and needs to demonstrate significantly improved properties. It changes the underlying chemical structure of the active ingredient and requires a NDA.

Research on the success and marketing of next-generation drugs is lacking and evidence on their effectiveness to extend the product lifecycle of a drug is limited to case studies (e.g., Conley et al. 2006). However, in press these strategies are widely debated. On the one hand, the next-generation drug can build on the brand equity of the previous generation drug, while on the other hand it may need to differentiate itself enough to induce customers to switch. Two well-known examples are Nexium and Clarinex. Claritin is the first generation product and a metabolized version of the drug was approved to the market as an NME (Fleming and Ma 2002). The next-generation drug was named Clarinex, clearly positioning it as the "next Claritin." Nexium is a successful single-isomer version of first generation drug Prilosec; however, it was positioned as a new drug. The link between the two drugs was made through the trademark "the purple pill" and Nexium was strongly differentiated from Prilosec in the marketing communications.

8.4.5 Summary of R&D Strategies

New indications and drug reformulations are frequently used lifecycle extension strategies. New indications require no change to the existing product and usually keep the same brand name. One challenge for new indications is that the set of competitors for a product may change to which a firm should adapt. In case the new indication is very different from existing indications, a firm may consider marketing it under a new brand name. Reformulations build on an existing drug and brand name. They are line extensions and firms typically shift their promotional expenditures from the original drug to the reformulation.

While widely used in practice, research into the success of new indications and reformulations is limited and worthwhile for future research. The optimal timing of the introduction of a reformulation and new indication is also a very important open question, especially in relation to the patent expiry date of the original drug.

The research strategies that require a longer-term investment, such as combination drugs and next-generation drugs, have almost not been researched in the academic literature. While a substantial literature exists on how to develop this kind of drugs, I have identified no study that evaluates the impact of the pricing and promotion of these drugs on market success. While the number combination drugs is relatively large (over 100 in the last decade), the number of next-generation drugs is more difficult to identify and classify. Both provide interesting marketing problems as they are strongly related to the components of the combination drug or the previous-generation drug, which are already on the market. The challenge for research is to identify how firms should price and promote such a portfolio of interrelated drugs, taking into account spillover effects and cannibalization. Another major challenge is how to position a next-generation drug compared to the original drug. Some have chosen to explicitly position the next-generation drug as a new product (e.g., Nexium), while others have positioned it more as a reformulation (e.g., Clarinex, Glucovance).

8.5 Legal Strategies

A drug consists of its main active ingredient and excipients to make the active ingredient work, delay its absorption in the body, and create the taste of the oral drug. Both the active ingredient and the excipients can be patented and firms use these to protect their intellectual property. The United States Patent and Trademark Office (USPTO) grants three types of patents: (1) utility patents to protect new processes, machines, articles and compositions of matter, (2) plant patent to protect new asexually reproduced plants, (3) design patents to protect novel ornamental designs of manufactured articles. New drugs usually receive utility patents. The active ingredients of drugs are patented long before market approval, typically when Phase II testing starts. This involves the composition of matter and protects the constituent elements of a drug and their specified chemical formulas. However, other patents are used as well to protect the branded drug, such as the different formulations used in treatment (chemical variants), methods of manufacture, methods of administration, and specific indications of use. However, often generic firms can "design around" such patents. Infringements on the composition of the matter claim (or chemical claim) are easier to detect than on the other type of patents.

8.5.1 Patenting Strategies

Firms can extend the lifecycle substantially by having a good patenting strategy (see Burdon and Sloper 2003 for various examples). In 2005, firms had an average

of ten patents on a drug, compared to an average of two patents in 1995 (Frank 2007b). As a result the length of the nominal patent period for branded drugs has increased (Hemphill and Sampat 2011). At the same time, Hemphill and Sampat (2011) find that the fraction of drugs receiving patent challenges has increased; they are challenged sooner, and drugs with higher sales are challenged more often. Bruce (2003) provides various patent cases for pharmaceuticals. Patents also deter entry as the costs to invent around, license, or challenge the patent can be large (e.g., in the software industry, Cockburn and MacGarvie 2011).

8.5.2 Generic Settlements

Manufacturers can settle with a generic manufacturer that challenges the patent on the branded drug, to drop the patent challenge or delay generic entry (Bulow 2004). These settlements involve a payment of the branded manufacturer to the potential generic entrant. These are also referred to as sweetheart deals and can be very profitable. It works especially for the first generic manufacturer that has a 180-day exclusive marketing period. There is a clear incentive for branded manufacturers to pay the generic manufacturer to delay entry, due to the higher margins for the branded drug. These settlements are highly disputed by the antitrust authorities (e.g., FTC) and society, but are not immediately forbidden by law. Several cases have been in court, with mixed outcomes (Forden 2011; Frank 2007b).

8.5.3 Summary of Legal Strategies

The biggest part of the profits from pharmaceutical drugs is earned during the period in which the drug is protected by patents. Hence, firms can extend the patent on a drug or delay generic market entry to obtain extra profits. There are two main ways of delaying generic entry (see Shuchman (2006) for a case discussion of these strategies for Plavix). Over the last 15 years, firms have adopted a strategy of multiple patents to protect a branded drug, increasing the market exclusivity period of the drug, and firms are involved in settlements with generic manufacturers to postpone their market entry. Research comparing the return on these legal strategies to other lifecycle extension strategies would help firms to make tradeoffs on which strategy to prioritize.

8.6 Conclusion and Suggestion for Future Research

Lifecycle extension strategies in the pharmaceutical industry are becoming a popular way for pharmaceutical firms to make profits. While lifecycle extension strategies have existed for some time, the rising costs of developing a new drug and the

increasing impact of generics, has lead firms to increasingly focus on lifecycle extensions. The academic literature reviewed in this chapter has focused mainly on the determinants and consequences of generic entry. Strategies to extend the drug's lifecycle have received less attention. Further research in these areas is warranted to increase our understanding of how various strategies work, which strategies are successful, and why they are successful. Future research can utilize the enormous amounts of data available on drugs. The FDA Orange book contains detailed information for each branded and generic drug, including the approval and expiry date for every patent, the manufacturer, the form of the drug, line extensions, and combination drugs. The FDA website contains information on extra indications and label changes for every drug. Organizations such as the Tufts Center for the Study of Drug Development and the Kaiser Family Foundation have extensive data available on, respectively, approved drugs in the United States and Europe, and health outcomes. Data providers like IMS Health, Kantar Media, and Wolters Kluwer have detailed information on sales, price, and marketing expenditures. While detailed information on sales and marketing is often limitedly available, publicly available data at a more aggregate level is provided by, for example, IMS Health and http://www.drugs.com.

Marketing strategies to extend the lifecycle of drugs nearing patent expiry can benefit from the extensive literature on marketing strategies in other industries. Insights on optimal pricing, promotion, and divestiture paths can be derived using theoretical models and dynamic empirical models. However, a large cross-sectional research on various moderators of pricing and promotion strategies around patent expiry is necessary. Such as study should explore how the success of these marketing strategies depends on the competitive landscape, trademarks of the branded drug, brand loyalty, chronic or acute disease, insurance type of patients, etc. Branded generics are a longer-term strategy which has already received some attention in the literature, but a large-scale empirical study that measures its impact in practice is valuable. Switching a prescription drug to become available over the counter requires the combination of different data sources and is a topic with ample opportunities for future research.

For the R&D strategies, many open areas for future research exist. In addition to extra research on the what-question—what strategy should a firm use and what is the impact of such a strategy—the when-question is very important. When should a firm implement the reformulation or combination drug to maximize the return on investment? Is it optimal to make a combination drug available when the single components are still under patent, or should a firm launch it near the patent expiration date of a single component? Research on the market impact of reformulations, combination drugs, and next-generation product is lacking in general. They are all a form of line extensions and questions on brand name, spillover effects in marketing, and cannibalization are important for future research to address.

Legal lifecycle extension strategies are also widely used by pharmaceutical firms. Marketing research can benefit from an improved understanding and clear outlining of how the regulations on patent extensions and market exclusivity impact firms decisions.

The discussion on pharmaceutical lifecycle extension strategies in this chapter has focused on nonbiologic drugs. These differ substantially from biologics due to their complexity, which makes biologics more expensive and it is harder to produce therapeutically equivalent generic versions of them. However, the number of approved biologics is rising substantially and their share of pharmaceutical sales is increasing (Munos 2009). Regulations on the approval of biologics that are biosimilar to drugs already on the market, is not well established yet and little research exists on their impact. In 2005, the EMA has published guidelines for biosimilars that give product-specific guidelines for their approval. In 2009, US congress has passed the Biologics Price Competition and Innovation (BPCI) Act, allowing the FDA to approve biosimilars. The FDA is currently working on guidelines for an approval path for biosimilars (Kozlowski et al. 2011). The guidelines will be stricter than the approval of generic nonbiologics. However, when the patent on a biologic expires, biosimilars will enter if the market is attractive enough. Compared to nonbiologics, production and entry costs of biosimilars are higher, limiting the number of generic entrants. Hence, in the future biologics are still likely to face less competition after patent expiry, making them an attractive alternative to nonbiologics and a very important topic for research.

Most strategies to extend the lifecycle involve interdisciplinary knowledge on marketing, R&D and regulations. This makes it challenging to investigate various lifecycle extension strategies in-depth. The marketing and economics literature have largely overlooked the impact of R&D and legal strategies. Plenty of research exists on the technical issues around R&D strategies and the legal issues surrounding the regulations and law on drugs, but is not discussed in detail here. Research on pharmaceutical lifecycle extension strategies would benefit from researchers or interdisciplinary research teams that are able to jointly assess the impact of marketing, R&D, and legal strategies. Finally, research on pharmaceutical lifecycle extensions would benefit tremendously from a study comparing the impact of the various strategies. One way to do that is to collect information on the various strategies and some moderators and relate those to the stock returns of pharmaceutical firms.

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Chapter 9
Patent Expiry and Pharmaceutical Market Opportunities at the Nexus of Pricing and Innovation Policy

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Abstract This paper explores the academic literature and empirical evidence associated with the strategic and tactical opportunities available to pharmaceutical firms confronted with the loss of patent protection on their branded drug. The marketing dimensions of product innovation, pricing, and brand equity options are considered together with exclusivity options available through government regulators such as the US Food and Drug Administration. These options are then considered in the context of the legal monopolies available to innovators through the policy lenses of intellectual property. This paper further explores the maxim that sustainable competitive advantage for pharmaceutical innovators is realized at the nexus of marketing choices, intellectual property, and regulatory regimes. Separate examples in gastrointestinal and neurological medications will be used to explore how the various options might be integrated together and used in a time sequenced, longitudinal manner to extend the market advantages and earnings levels of the original pharmaceutical compound innovation. Areas of potentially fruitful future academic research are described.

9.1 Introduction

A central, chronic challenge of the major pharmaceutical firms is the sudden loss of revenue that coincides with patent expiry on multibillion dollar product. The sales curves for such products takes on a "shark fin" or patent cliff like character with dramatic growth of revenue followed by a rapid decline due to the market entry of

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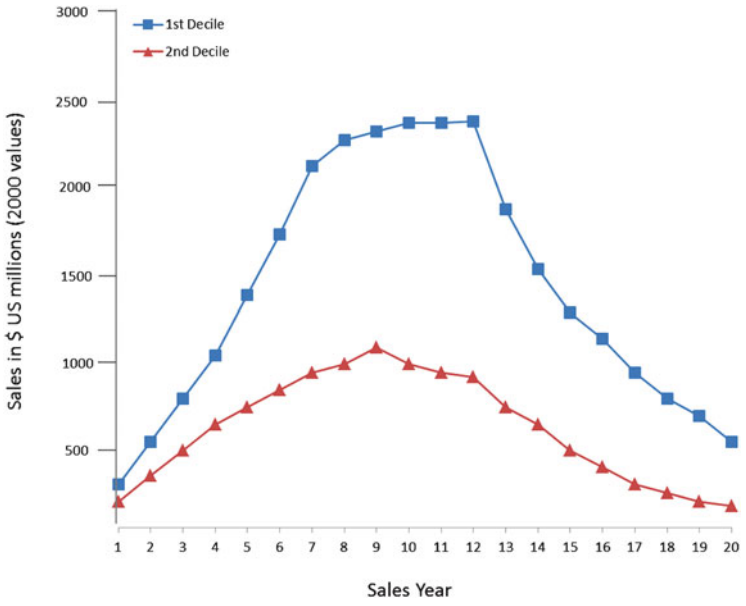


Fig. 9.1 Worldwide sales profiles of 1990–1994 new drug introductions, from Grabowski et al. (2002)

multiple price-based competitors' once patent and other market exclusivities are exhausted. Figure 9.1 is a graphic depiction of these sales dynamics created from longitudinal drug sales data both pre and post patent expiry (Grabowski et al. 2002).

The declining of this curve is most dramatic when the original innovator of a multibillion dollar drug is confronted with generic competition, an undifferentiated, bioequivalent product emulator that competes solely on price. More generally, these sales dynamics are experienced in those markets where imitation of the original innovator and price-based competition occur. This phenomenon is acute in those contexts where price is relatively unregulated such as that for prescription drugs in the United States (US). What does the academic and professional literature tell us about the efficacy of marketing management options that can be pursued to avoid the literal downside of patent expiry in pharmaceutical markets? This article is an attempt to address the chronic challenge of patent expiry revenue loss and the management of price-based competition from generics.

A pervasive challenge and management opportunity in this context is the sequenced planning and execution of options in a proactive and or reactive sense that can be used to slow down or even avoid the loss in revenues associated with the market entry of generic emulators or other forms of price-based competition. To examine this challenge, this article will present an interdisciplinary perspective on the management of marketing, intellectual property, and policy options that are specific to the pharmaceutical patent expiry event.

After summarizing a broad list of patent extension and or market exclusivity options, this article considers the relevant literature on pricing of pharmaceuticals

both pre and post expiry. We then briefly investigate how promotional activities and newer product branding actions such as advertising and product configuration impact the behavior of patients exposed to such innovations. We further consider other bodies of literature to learn how researchers beyond the management academy view intellectual property options and how they may be integrated to sustain the market premiums of the original innovation beyond the end of the patent life. Finally, we will examine how these theories are applied in two distinctly different pharmaceutical product categories, namely the markets for gastroesophageal reflux disease and neurological medicines. Reflecting on these findings the article will offer observations useful to practitioners and researchers.

9.2 Literature Review

What does the academic and professional literature say about the options that pharmaceutical marketing professionals have when they are planning for the inevitable market entry of generic price-based competition?[1] In order to address this question we will first explore the general rules of the market game from the perspective of regulatory measures, property-based exclusions and licensing options and other tactics that can be deployed to slow down the entry of the generics. Related literature on pre and post expiry pricing (Jain 2010; Eliashberg and Jeuland 1986; Kamien and Zang 1999) promotion, e.g., advertising and effects of direct to consumer (DTC) media and product extensions, new disease indications, new molecules etc. and pill color or packaging will then be reviewed. The relevant literature on value transference, an integrated approach to sustaining the differences associated with the innovation of the original molecule, will be discussed. Finally the execution of the above pharmaceutical marketing options will be examined in a number of contexts.

9.2.1 The Ground Rules of Pharmaceutical Competition

A selection of the literature characterizing the options that pharmaceutical marketing professionals may consider when anticipating the market entry of generic competition is given in Table 9.1. In what follows the tactical implications of each option listed in the table are discussed.

[1]To address this question it is helpful to consider the marketing mix management variables of product, price, promotion, and place (Kotler 1988). In the pharma context the place variable is constrained to the dispensation system of established prescribers (doctors) and dispensers (pharmacists) in most countries. The mix variables that have the potential to be varied and hence managed are product (alter or improve the formulation/extend), promotion (DTC advertising and aggressive detailing to doctors), and or price. In the context of the US market, product, and promotion activities are both government regulated and require considerable advanced planning.

Table 9.1 Summary of pharmaceutical product life cycle extension strategies and tactics with source literature

Strategy	Protection/exclusivity	Duration	Logic/tactics/how to	Source
FDA review extension	Patent term extension	Normally between 2.5 and 3 years (max. 5 years)	FDA approval delay related. Apply for extension once approval for NDA is granted	FDA (2003)
Fighting ANDA "Evergreening"	Patent litigation	Up to 30 months	File more Orange Book patents to trigger the repeated use of 30-month stay provision to delay the generic introduction for many years	FTC (2002); Higgins and Graham (2009)
Reformulate active ingredient	Composition claim patent	3 years	Phase development efforts for improvements to patented compounds	Yoshitani (2007)
Conducting pediatric studies	Patent supplementary marketing exclusivity	6 months added to existing exclusivity periods	Conducting trials on children	FDA (1999, 2009)
Orphan drug act	Marketing exclusivity	Up to 7 years	Gain marketing exclusivity by developing product variations specifically targeting diseases with <200,000 people in the USA	DHHS (2001)
New indications	SNDA marketing exclusivity	3 years per indication	Expand use to extended exclusivity for other uses	Glover (2007)
Introducing OTC formulas	Trademark/marketing exclusivity	Indefinite/up to 3 years	Gain approval for OTC, then build market through DTC advertising	Brass (2001); Berndt et al. (2003)
License manufacturing process	Process claim patents	Life of patents	License process claim patents to generic manufacturers to capture some value in the generics market	Common sense
New pill mechanisms	Composition claim patent	Life of patents	Improve convenience or efficacy through reformulation	Bhat (2005); Harris (2002)
Non-pharmaceutical claims on chemical	Method of delivery	Life of patents	Develop new dosage forms or introduce new methods of delivery (capsules instead of pills)	Bhat (2005)

Pharmacogenomics	New patent	Up to 3 years	AstraZeneca could classify effectiveness and side effect reactions regarding human genetic variations or claim a new method-of-use for certain subtypes	Lichter and Kurth (1997)
Introducing a branded (or "authorized") generic	Market through "first mover advantage"	Limited duration	Go to market with "branded" or authorized Generic to get first mover advantage. At the same time raise price of branded products to capture additional margins from brand sensitive buyers	FTC (2009)
Cornering key ingredients	Supply chain exclusivity	Life of exclusivity	Cornering supply of key ingredients e.g., by exclusive contracts	Harris and Rundle (2000); Harris (2001)
Introducing a generic	Market through "first mover advantage"	Limited duration	Go to market with Generic to get first mover advantage. At the same time raise price of branded products to capture additional margins from brand sensitive buyers	Mehl (2006)
Produce for generic companies	Legal/contract	N/A	Use existing manufacturing capacity to make and sell to generic companies	AstraZeneca (2008)
Pay generics to delay entry	Legal/contract	Limited duration	Pay generic companies explicitly to not produce competing products	Rosenthal (2002); FTC Staff Study (2010)
Petitioning patients, doctors, and congress	Legal	Limited duration	Unlikely that Congress will grant any more substantial patent extensions in near future. AZ could apply for an extension under the General Agreement on Trade and Tariffs (GATT) legislation	Hensley (2001); Paige (1997)

(continued)

Table 9.1 (continued)

Strategy	Protection/exclusivity	Duration	Logic/tactics/how to	Source
Trademark purple color and other recognizable attributes	Trademark and trade dress	Indefinite	Build strong brand image related to use of the drug and gain association with color and benefits	Palczuk et al. (2004)
Maintain strong marketing and sales force presence	Business practices (no formal protections)	Indefinite	Maintain a strong brand recognition to keep patients asking their doctors for Prilosec or related drugs	Manchanda et al. (2003)
Exit	N/A	N/A	Cash out. Save competitive battle, shift resources	N/A

The 1984 Drug Price Competition and Patent Term Restoration Act also known as the Hatch Waxman act is US-based legislation intended to balance the interests of branded drug manufacturers, generic drug companies and consumers. This legislation provides a number of options for pharmaceutical companies to extend some or all of the regulatory market exclusivity of their original patented molecule (Mossinghoff 1998). An important option facilitated by Hatch Waxman allows those drug innovating entities with an approved new drug application (NDA) to recover some of the patent term that may have been lost due to clinical trials and or NDA prosecution delays at the government agency that reviews and adjudicates NDAs. In the United States the Food and Drug Administration processes and adjudicates NDA's (Boone 2009). Patent term extensions under Hatch Waxman are limited to 5 years maximum and are frequently less. The application for and prosecution of an extension is a process with many technicalities that must be carefully managed in order to realize the formal extension of the patent term (Boone 2009).

The Hatch Waxman legislation also encourages the rapid entry of generic firms with a "bioequivalent," undifferentiated product by limiting their legal liability for developing or using the molecule during the term of the molecule patent in preparation for patent expiry. To promote the prompt entry of multiple generic firms post expiry, a 6-month market exclusivity period is granted to the first approved auxiliary new drug application (ANDA). This 6-month period of generic marketing exclusivity has the effect of providing for a limited period of duopoly pricing between the first ANDA approved generic company and the incumbent NDA drug provider. During this period of limited competition, the first ANDA approved can earn an abnormally large return on the investment. In theory, this opportunity will motivate ANDA applications from multiple generic sources such that there will be price-based competition amongst a plurality of generic providers within 1 year of formal patent expiry (Mehl 2006).

Hatch Waxman further encourages generic providers to pursue an ANDA application at any time during the term of the patent on a particular molecule if the generic manufacturer believes the molecule patent to be invalid. If this type of application is challenged in court by the incumbent drug firm/NDA holder, a 30-month ANDA approval delay will be triggered at the FDA (Higgins et al. 2009). In theory, this statutory 30-month delay is anticipated by those generic companies that submit a patent challenging ANDA more than 30 months before formal patent expiry.[2] Additional market exclusivity advantages for developing a new chemical entity and other improvements via a supplemental new drug application (SNDA) are also provided for in the act.

Beyond the Hatch Waxman specific options available to incumbents or generic firms, the FDA grants a range of marketing exclusivities to incumbent firms who address certain unmet needs in the market place. More specifically, those NDA

[2]This type of ANDA is sometimes referred to as a Paragraph IV certification in the pharmaceutical literature.

holders that undertake clinical studies examining the efficacy of their drug in pediatric populations are granted an additional 6 month marketing exclusivity beyond the expiration of their patent or the expiration of any other FDA granted marketing exclusivity grant that may be in place (Li et al. 2007; FDA 1999, 2009). During the exclusivity term, no ANDA application will be approved. Hence the period of time for premium pricing absent direct price-based competition from bio-equivalent generics is effectively extended by 6 months.

The Orphan Drug Act (ODA) of 1983 (Haffner et al. 2002) promotes research into markets of underserved patient populations such as orphan diseases. An orphan disease by definition has a small (<200,000) target patient population. This limited market will not justify the required investment in clinical trials needed to prove the efficacy of the drug. Hence independent of patent rights, the FDA grants up to a 7 years of marketing exclusivity to any firm who will file an NDA or supplemental new drug application (SNDA) with data that proves an improvement in the efficacy of existing treatment of an Orphan Disease. More recently the FDA has provided expedited reviews of applications for Orphan Drug status (Burton 2011). The success of the US-based ODA has inspired similar legislation elsewhere (Haffner et al. 2002).

Beyond the above options, the SNDA procedure (Glover 2007) can be used to realize 3 years of additional marketing exclusivity for an approved drug that can be demonstrated to have efficacy for treating a new disease indication.[3] Three additional years of exclusivity will be granted to the first SNDA approved for an over the counter (OTC) nonprescription use of a previously approved prescription drug.

Scientific advances such as pharmacogenomics coupled with companion diagnostics lead to opportunities for more market segmentation of an existing patient population (Lichter and Kurth 1997; Lindpaintner 2002). To the extent that the genetically specific treatment can be resolved in an existing population with the efficacy and novelty required to establish patentability, new patents may be realized on both the diagnostic and any reformulation that addresses the subtype population.

Finally, the incumbent NDA approved drug company can introduce a generic version of their branded drug at any time before or after patent expiry (Laurent 2008). An ANDA is not required since it will be the same molecule and from the same source as the drug approved in the original NDA. Some scholars suggest that this leads to a better market for all consumers (Jain 2010; Kamien and Zang 1999). While this approach would seem to make sense according to economic models, it is rarely done in the United States but has some traction in other markets such as Canada (Hollis 2005).

[3]Three years or additional marketing exclusivity granted for each new approved indication.

Aside from regulatory and or patent actions,[4] additional steps to delay generic entry include:

1. Monopolizing the supply of key ingredients (Labaton 2000). Note this approach works better for larger bioactive molecules (Coan and Ellis 2001).
2. Lobby congress to grant patent term extensions (Schacht and Thomas 2002; Paige 1997). Very unlikely this will be possible going forward.
3. Pay the generics to not enter the market once they have an approved ANDA (Gold 2001; Rosenthal 2002).

An incumbent pharmaceutical companies marketing power can also be extended by clever brand and trademark management (Conley and Szobocsan 2001). Drug brand equity such as color or shape that is developed pre patent expiry may be used to move or transfer the prescription preferences of a brand loyal population from the original drug to a new patented drug (Conley et al. 2008). The brand equity thus acts as an agent of transference to migrate the brand loyal population to the new drug.[5]

9.2.2 Perspectives from the Economics and Legal Literature

In discrete industries like chemicals and pharmaceuticals, the leveraging of intellectual property rights can be very effective. The pursuit of multiple intellectual property regimes (patents + marks + copyrights + secrets etc.) can be coordinated over the life cycle of a particular offering to build and sustain the functional advantages of the original offering. Using large scale survey methods examining companies from a variety of industries in Europe, Japan, and North America, Granstrand

[4] Beyond the FDA marketing exclusivities outlined above, incumbent firms also have the options to extend their pre-expiry market advantages through patents that are invented and filed subsequent to the original molecule patent. While scaling to production there may be new inventions and process patents on the methods of fabrication that are relevant to efficient scale production of the NDA approved drug. These process patents will have an expiry date years beyond that of the molecule patent and are listed on the FDA orange book (orange book reference here). All interested generic providers who may file an ANDA can see the process patents related to the NDA approved drug via orange book (available online). Generic firms need to certify in their ANDA application that production of the bioequivalent product that they seek to have approved has avoided the infringement of valid orange book patents (Hill 2005).

Patents on reformulations of the active ingredient can also lead to market place exclusivities of a sort, at least to the extent that patients using the older formulation can be switched to the new, patent protected formulation pre-expiry of the older formulation patent (Yoshitani 2007). This tactic is central to life cycle planning for a portfolio of products or for a drug offering in a particular class and may play into pricing strategies.

[5] Appropriately defined brand equity such as color or pill shape can be registered as a trademark (see Table 9.2) with a life that can be indefinite assuming continuous use of the mark (Conley and Orozco 2005). These same trademark rights can be bundled into licensing agreements that can have regional and or global specificity to help with the controlled expansion of the drug to multiple markets (Downing 2003).

(1999) observed that companies typically concentrate their activities on patents when thinking of intellectual property and do not consider the possibilities of using more than just patents. Through focused case studies on IBM, Coca Cola, and others, he observed that intellectual property rights regimes, when managed and coordinated may compliment and substitute each other in terms of market place advantage and increase the firm's total asset value, summarized as "multiprotection systems and total IP strategies" (Granstrand 1999).

Economists Allegrezza and Guard-Rauchs (1999) highlighted the distinctive features of trademarks that in theory allow companies to appropriate the rents or margins from product innovations (especially when linked with patents) for an unlimited time. The property monopoly beyond the patent life would be limited to trademark source identity rights but would indeed live as long as the mark is used and conceivably beyond the life of any particular limited life patent, copyright, or secret. These researchers use survey techniques to examine the trademarking behavior of a broad grouping of over 2,500 companies from within the Benelux countries. The results of this study also show that Benelux firms applying for trademarks tend to have high R&D expenditures and a larger workforce, similar to results of studies on patents. Factors such as trademark awareness within a company, likelihood of product imitation, and the level of competitor monitoring also seem to have a significant effect on awareness. The relation between patents and trademarks is not directly accounted for in his survey. Differentiation of products combined with an enduring brand loyalty, higher market entry barriers, and market positioning within a certain product sector are suggested to enable the registrant to higher margins and returns. This is also shown by the relationship between a product and the providing firm via a registered symbol (ensured by trademark protection) which compliments the protection of an innovation through patents. The Registration of trademarks (only used by half of the companies surveyed in his study) offers the necessary juridical possibilities to shield the differentiation legally against unfair competition as patents enable the registrant to protect technology innovation.

In the legal management literature, Conley and Scozoboscan (2001) characterized the proactive management of multiple IP regimes across the life cycle of an offering in a manner that sustained the value of the initial innovation as *value transference*. In theory transference could occur from any limited life regime, patent to trademark or copy right to trademark. Case study examples discussed include the branding of the omeprazole molecule invention (patent) as the purple pill (trade dress, mark) and the securing of the original image of Disney's Snow White (copyright 1937) [6]as a Character Mark (2001 application).[7]

In the law review literature, Parchomovsky and Siegelman (2002) focus on "leveraging patents though trademarks": the combination of patents and trademark protection may have two main benefits for a firm: the exclusivity secured by the patent might lower the marketing costs of creating a strong brand and simplify the

[6]Copyright on Disneys original animated version of the Snow White story dates back to 1937.

[7]Disney's image of the Snow White registered as a US trademark in 2005.

establishment of brand loyalty by locking out competition. Their main focus is on "leveraging patents though trademarks": the combination of patents and trademark protection may have two main benefits for a firm: the exclusivity secured by the patent might lower the marketing costs of creating a strong brand and simplify the establishment of brand loyalty by locking out competition.

Explanatory case studies on Round-Up, NutraSweet, Tagamet, Zovirax, and Bayer Aspirin show that a former patentee's loyal customers are willing to pay a premium price on an off-patented product, even though competing products on competitive price levels are available. Therefore those companies were able to shift profits ensured by from the formerly patent protection to the trademark, enabling those companies to charge premium prices even though the patent has expired.

This leads these legal scholars to the hypothesis that a long-term interested patentee also taking future profits into account (after the patent expired) will charge less than the maximum monopolistic prize during the patent period and invest more in product quality to build up brand loyalty. To test this hypothesis they constructed a stylized two-period model: during the first phase the patent protection enables companies to maximize their profits. When the patent protection is expiring in the second phase, companies need to build up and rely on brand loyalty and trademark protection to insure competitive results, without exploiting the above mentioned full monopoly power a patent grants. Finally Parchomovsky and Siegelman (2002) expand the above mentioned theory to trade secrecy and copyrights, suggesting that this would create comparable synergy effects.

In independent work that follows similar logic, Jenneweins (2005) assumption is that brand equity might be combined with patents (referred to as technological protection) to build a "multi-layer, complex intricate shield" protecting against competitors and imitating products. To support his argument he presents two in depth case studies one on Bayer Aspirin and another on Cisco Systems, showing how these companies were able to build and tighten their dominant market positions over time even when the protection by patents expired. Starting with these case studies he develops a life cycle model showing how intangible technological assets may interact with brand equity to create an enduring protection, ensuring significant margins, and market shares.

9.2.3 Pharmaceutical Marketing Mix Models

Given the pharmaceutical landscape ground rules and opportunities described above and summarized in Table 9.1, what does the literature say about marketing mix variables (product, place, promotion, price) that can be managed when an incumbent drug manufacturer is confronted with patent expiry?

The least regulated variable of the marketing mix in the US context is price. Post expiry competition from generics that enter a pharmaceutical market is what drives down the incumbent's sales revenue curve as illustrated in Fig. 9.1. Postlaunch and pre-expiry Lu and Chomanor (1998) found that the extent of therapeutic advance of

a particular remedy is a strong determinant of its market price with some compounds commanding 2 or 3 times the price of existing treatments. Drugs with a largely duplicative effect and less of a therapeutic gain are priced comparatively at launch.

In a practical review of the pharmaceutical pricing question, Kolasa (2009) suggests this is a simple matter of perceived benefits of the drug determined in conjunction with what the doctor is willing to prescribe and or the consumer (or their insurance company) is willing to pay.

On the question of dynamic drug pricing in the face of competitive entry from generics, the marketing literature is less developed. Eliashberg and Jeuland (1986) use time period economic models to analyze dynamic pricing strategies for incumbents based on their "myopia" with respect to the anticipation of competitive entrants. Their models explore the optimal pricing strategy of a firm that introduces a new product first and anticipates competition in the future. Their model explores two temporal periods one during the monopoly period, and another during the duopoly period. Also considered is the effect of a second entrant during the duopoly period. Their findings indicate that for those firms that anticipate competitive entry and are hence "non-myopic," it is better to price the drug higher than those firms that do not anticipate competitive entrants (characterized as "myopic").

From the economics perspective, Kamien and Zang (1999) use analytical models to examine pricing options for firms that approach patent expiry. As previously described, most incumbents have the opportunity to introduce their own generic into the market at any time, including pre-expiry. The branded drug may stay in the market and experience a price increase while the "own generic" can be sold at a substantial discount (Jain 2010). As modeled, the pre-expiry first mover introduction of a discounted "own generic" coincident with a price increase on the incumbent branded drug can lead to a market-expanding effect. Both brand loyal and cost conscious consumers are reported to benefit from this kind of two pronged approach. This approach while appealing in theory does not fully consider the potential impact of the cannibalization on sales of the branded drug by the "own generic." In the context of the histamine blocker antacid medicines market the launch of a cheaper OTC variant post expiry was viewed to cannibalize sales of the branded drug (Berndt et al. 2003, 2007).

Jain (2010) describes an integrated product and pricing methodology to address the challenges of cost-based competition also known as the "sandwich" approach (Jain 2010). Figure 9.2 illustrates the fundamentals. An innovator enjoys an incumbent position with the associated *quality* and *price* attributes of its offering (q, p). Price-based competition enters the market at time t_{entry} offering products of similar quality q but at a discounted price, p–. If the original innovator has the ability to differentiate its offerings on the quality dimension, it can launch products with both higher (q+, p+) and lower (q–, p–) price/quality attributes relative to the original offering. If the incumbent can maintain the low price (p–) position, it effectively sandwiches the competition's maneuverability on quality and price, locking them into middle market segments. The "sandwich" approach works for companies that proactively anticipate cost-based competition (generic entry in pharmaceuticals) and companies that are surprised and must react. The author further explains how this approach has been employed in multiple market environments (Jain 2010).

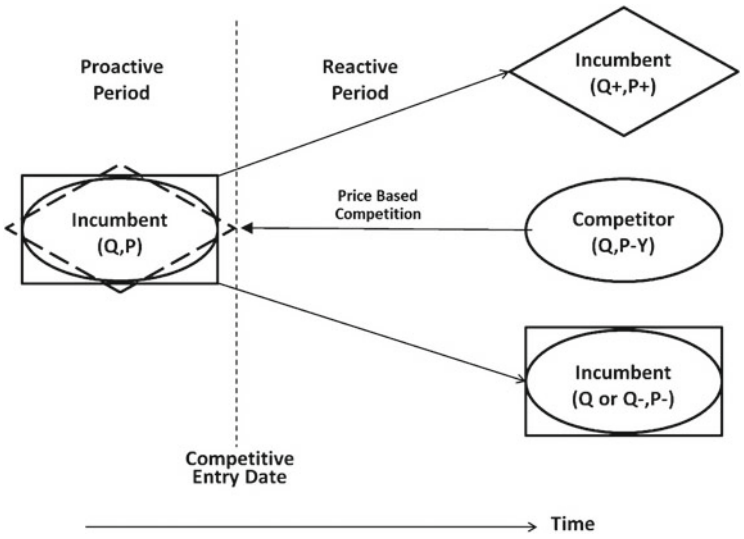


Fig. 9.2 Quality, price, time, and branding dimensions of a proactive or reactive sandwich pricing strategy

In the pharmaceutical context execution of the sandwich approach benefits from proprietary knowledge of the quality dimensions that incumbents may develop pre-expiry. Brand equity that may be developed through DTC advertising is an important attribute of the quality variable. If brand equity can be split (q+, q−) in a manner that avoids consumer confusion and cannibalization then it is conceivable that the sandwich so applied could help to minimize the negative revenue impact of price-based competition.

The Place variable and or the distribution channels for prescription drugs are regulated (physicians, pharmacists, apothecary etc.) in most countries. While there has been an increase in online and mail order prescriptions delivery and cross border prescription drug purchasing behavior in the recent past, we will limit our discussion of Place to patent expiry-related moves by the incumbents into new channels such as going over the counter (Berndt et al. 2003). These researchers explored the "sunset" portion of the H_2 receptor antagonist market with brands such as Tagamet, Zantac, Pepsid, and others, all of which went over the counter post expiry. In short, they observed that the switch to OTC failed to save the incumbent drugs from dramatic overall sales decline or the more damaging effects of creative destruction from a new class of drugs that address similar disease indications (proton pump inhibitors).[8]

From the Product perspective, research into the economic returns on R&D for 118 new chemical entity (NCE) drugs introduced during the 1990s indicates that

[8]Going over the counter in those markets where it is possible is not in and of itself a strategy for avoiding the sales decreases associated with patent expiry (Berndt et al. 2003).

more than half of the overall market returns as measured by the present value of net revenues was captured by the top decile of earning drugs in the sample (Grabowski et al. 2002). Similar patterns of highly skewed earnings distributions are observed with other groupings of NCE introductions of earlier time cohorts. More than 60 % of the drugs in the sample failed to earn enough to cover the average cost of development. This research further suggests that the search for top decile earning drugs or blockbusters is what drives the R&D process in the pharmaceutical context.

These blockbusters are also viewed as a target market where the "size of the prize" for the first ANDA approved is ultimate. With multiple generic drug firms pursuing ANDA's simultaneously and poised to enter these lucrative markets post patent expiry, there will be substantial price-based competition and hence the sales decline effect of Fig. 9.1. Our interest in the later sections of this paper will be exploring methods used by large pharmaceutical innovators to delay generic entry and extend the advantages of the original innovation beyond patent expiry.

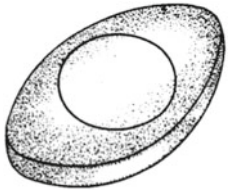
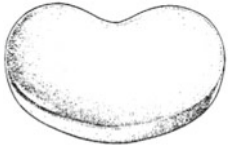
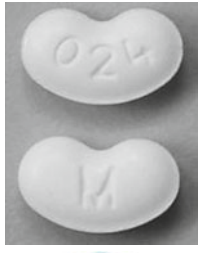
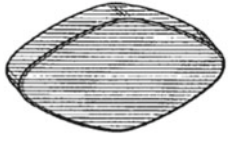
An emerging area of product-based competition in the prescription drug arena is in shape and or coloring of the pill or tablet. The shape or color of a medication may be the central component of an advertising message. An advertising focus on such attributes through direct to consumer (DTC) advertising become help to grow an important cognitive touch point of the user experience (Conley et al. 2008). Table 9.2 is a collection of pill shape and color-related trade mark registration data as found in the USPTO online Trademark Data Records.[9] Note that these are all "live" marks which mean that they are in use in the marketplace as of summer 2011.

The shapes of tablets listed in Table 9.2 are suggestive of their intended use such as the eye shape of Ocuvite Preservision for ophthalmic indications or the kidney shape of the Thalitone tablet for kidney-related indications. Similarly, pill color can be a distinguishing product feature that can secure source identity through registered marks. In the Paxil example, pill shape, brand name (Paxil) as printed on the pill and tablet color in combination become product design variables secured through unique mark registrations. In this context, color marks are used to distinguish between pill dosages. In the proton pump inhibitor category, two gold stripes on the purple pill means a 20 mg dose while three gold stripes corresponds to the 40 mg dose of the Nexium medication.

While the use and ownership of exemplary color or shape marks listed in Table 9.2 may not slow down generic entry in theory, they can be an important repetitive dimension of direct to consumer advertising both pre and post expiry. As expiry approaches, the color or shape used as a mark that may be further secured as a registered mark is banned for use by other market entrants such as the generic firms. So secured the colors or shapes can be used to migrate a brand loyal population from one generation of a patented medication to a second generation drug with a new patent. Hence the term *value transference* (Conley and Szobocsan 2001).

[9]Records of pill shape and color US trademark prosecutions and registrations are searchable through the Trademark Electronic Search System and Document Retrieval available at http://www.uspto.gov.

Table 9.2 Exemplary pharmaceutical tablet/shape mark registrations at USPTO as of 2009

USPTO	Image pill	Type	Drug name	Indication	Owner
		Shape	Ocuvite preservision	Eye	Bausch & Lomb Inc.
		Shape	Thalitone	Diurectic/kidney	Monarch Pharma. Inc.
		Shape	Viagra	Sexual dysfuntion	Pfizer Inc.

(continued)

Table 9.2 (continued)

USPTO	Image pill	Type	Drug name	Indication	Owner
		Name/color	Paxil	Disease/disorder of central nervous system	GSK
		Color	Prilosec	PPI Gastrointestinal diseases	AstraZeneca
		Color	Nexium	PPI Gastrointestinal diseases	AstraZeneca
		Color	Nexium	PPI Gastrointestinal diseases	AstraZeneca

Such product design features and or visual dimensions of the product can thus be the common visual cue to move the brand loyal population from one patented drug to another there by extending the brand equity advantages of the original patented invention (Conley et al. 2008).

The literature on the effects of the promotion marketing mix variable on sales through the expiry event is diverse and considered. We limit our discussion to direct to consumer (DTC) advertising and sales rep/doctor visits also known as detailing, the content of which is regulated in the United States by the FDA.[10] Iizuka (2004) finds that direct-to-consumer advertising (DTCA) of prescription drugs has skyrocketed in the United States, creating a controversy over the role of DTCA. Little is known however regarding what affects firms' advertising decisions and which drugs have been advertised to consumers. Using brand-level advertising data, the determinants of DTCA for prescription drugs are examined. It is found that drugs that are new, of high quality, and for undertreated diseases are more frequently advertised. Furthermore, advertising outlays decrease with competition. These results complement the demand-side evidence that DTCA has a market-expanding effect but little business-stealing effect (Iizuka 2004). DTCA increases are also correlated with more doctor visits per patient. Hence, to the extent that this can be segmented to the appropriate target patient group, DTCA can be used to grow the market for prescription drugs pre-expiry. This effect is found to wane in the face of price-based competition. A more recent review by Atherly (2009) points to the demand increasing effect of DTCA that is class wide and not limited to the specific advertised drug.

However the DTCA is undertaken, Scott-Morton (2000) has found that brand advertising in general is not a barrier to entry for generics. A strong determinant of the number of generics that will enter or attempt to enter post expiry is the size of pre-expiry revenues of any given drug.

9.2.4 Arbitraging the Rules

In considering how pharmaceutical firms may navigate the ground rules described above, it is helpful to clarify that the patent grant with attendant rights to exclude all others from making using or selling the claimed invention is issued by the local patent authority. In the United States this entity is the United States Patent and Trademark Office (USPTO) that operates under the Department of Commerce (Conley and Orozco 2007). Marketing exclusivities like those discussed above are granted by the US Food and Drug Administration (FDA) an arm of the US Department of Health and Human Services (Schacht and Thomas 2002). The FDA is not involved

[10]It is important to note here that the 1997 changes in US FDA governed direct to consumer marketing regulations resulted in a dramatic, fivefold increase in spending in DTC advertising. This change has brought about a new era of informed consumer behavior that should be accounted for in any comprehensive, academic review of the literature examining the effect of DTC promotional advertising on the market success of pharmaceutical products.

in patent or trademark prosecution/enforcement matters and likewise the USPTO is not involved in drug market entry approval or marketing exclusivity decisions. The Hatch Watchman extension for NDA review delays is the only exception. These decisions are patent term-related and are made at the USPTO. Hence there are two regulating agencies between which a particular firm can arbitrage a range of exclusivities and or patent grants/term extension to fend off price-based competition for the greatest period of time (Yoshitani 2007).

Note also that marketing exclusivity terms awarded by the FDA govern what can be advertised about a drug to consumers or healthcare professionals. When issued, the owner of a FDA marketing exclusivity is the only firm that can advertise the approved drug to the market for the approved category/disease indication. All ANDA's or approvals of generics of the drug in the category in question are delayed until the exclusivity term expires.

Note that neither patent monopolies nor marketing exclusivities keep physicians from prescribing drugs "off label" or for a disease indication that is not approved by the FDA (Salbu 1999). While this may be risky for the doctor "why did you prescribe a drug that was not approved?" it is not illegal. Off label prescriptions are not something that can be directly influenced by direct to consumer advertising, detailing to doctors or controlled through patent enforcement litigation. Note that some authors suggest that expedited orphan drug review can be used to get approval for a drug whose real market potential is for non-orphan disease indications that are as yet underserved in the broader market. Hence the Orphan Drug process may be used as a Trojan horse of sorts to get the drug into the market place and subsequently supported by off label prescription sales (Fugh-Berman and Melnick 2008).

9.3 Empirical Evidence

As described above there are a number of policy options and marketing mix variables that can be managed over the life cycle of a drug to minimize the revenue impact of patent expiry illustrated in Fig. 9.1. In what follows, we present empirical evidence of how two firms attempted to proactively manage the patent expiry event.

9.3.1 AstraZeneca, Prilosec, and Nexium

An interesting example of comprehensive pharmaceutical marketing planning and execution can be found in Astrazeneca's management of offerings in the gastro-esophageal reflux disease (GERD) drug category over the past 23 years (Conley et al. 2006a, b). In the late 1980s the target population of acid reflux[11] patients was

[11] Gastrointestinal track acid reflux or "Heartburn" is a symptom of GERD.

large, globally dispersed, and growing in size. The GERD drug category in the United States at that time was dominated by H2 receptor antagonist prescription medicines such as Tagamet (cimetidine) or Zantac (ranitidine). These solutions attempted to minimize the damage that might be done by the reflux of acid that was already in the digestive track.

With the US introduction of Prilosec (omeprazole) in the fall of 1989,[12] Astrazeneca (AZ) offered a new breed of medicines known as proton pump inhibitors (ppi). The treatment consisted of a daily dose regimen that slowed down the production of the stomach acids. Subsequent refluxing with more neutral stomach content is less irritating to the patient and minimizes the damage that leads to advanced GERD disease states such as erosive esophagitis. Prilosec[13] was the first proton pump inhibitor to enter the GERD category in the US. Proton pump inhibitors raised the performance of GERD medications and created a new expected standard of patient outcome or quality. Multiple other pharmaceutical firms eventually entered the ppi market with similar patented prescription drugs such as Protonix, Prevacid, and Aciphex but these did not have the same level of efficacy for GERD as Prilosec. Prilosec maintained a premium price during the pre-expiry period of $4/pill.[14]

By 1993 AZ had become a "blockbuster" with annual global sales of more than US$ 1 billion. Formal planning for sustaining the AZ revenue in the category beyond patent expiry began in 1995 by an interdisciplinary group of AZ marketers, scientists, and lawyers known as the "Shark Fin" project (Harris 2002). This group considered a host of marketing and intellectual property-based options including many described in Table 9.1.

The GERD category sales and marketing maneuvers of Astrazeneca over the period 1993 through 2011 are illustrated in Fig. 9.3. The figure is a compilation of management activities related to the product and its improvements, AZ marketing spending on various ppi offerings, intellectual property maneuvers, and AZ category revenue.[15] Note that the AZ revenue line in the figure is superimposed on an adjusted curve of "top decile" average sales dynamics for all pharmaceuticals (Fig. 9.1).

Comparing the two revenue lines in the figure, the AZ Prilosec revenue closely mirrors the sales growth activity of other blockbusters rising to an industry best and peak of US$6.2 billion/year by 2001.[16] After patent expiry, the top decile of sales drugs typically experiences a dramatic fall off in sales revenue as shown in Figs. 9.1 and 9.3 due to aggressive price-based competition from generics. *But the*

[12] AZ received US FDA approval for Prilosec on September 14, 1989.

[13] Outside the United States, Prilosec was marketed as Losec. AZ was not allowed to use the name Losec in the United States since it was believed that this might be confused with a blood thinner called Lasix.

[14] All prices discussed in this paper are full retail price in the US market and denominated in US$.

[15] Figure 9.3 revenue reflects global sales and come from public sources including US SEC 10 K filings.

[16] Sixty-eight percent or all AZ ppi sales in 2000 were in the US market. Hence focus of analysis is US market.

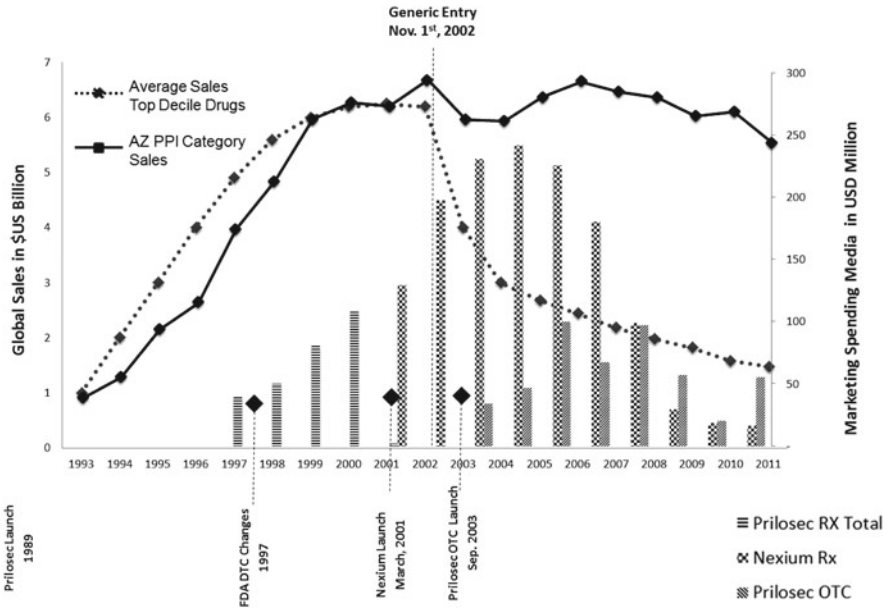


Fig. 9.3 AZ global sales, media expenses, and market launch events in GERD category (1993–2011). Global sales figures from Astra and AstraZeneca Annual Reports and 10 K Filings. Media Spending Data from Public Domain Sources

Astrazeneca ppi revenue does not drop off… as shown in Fig. 9.3. It stays constant at or about the US6$billion/year level for the next 10 years leading to an additional US$50+ billion in gross revenue over the 10 year period. How did this happen?

9.3.2 Priming the Promotion Pump

As shown in Fig. 9.3, the US rules for direct to consumer advertising changed in 1997 (Iizuka 2004) in a manner that increased the efficacy of media promotion for prescription and OTC medications. From 1997 through the end of 2000, AZ spent between $50 and $100 million/year[17] promoting Prilosec as the "Purple Pill" and the daily solution for sufferers of GERD. This campaign successfully built the brand equity of the color purple on the pill and other equities[18] as the source identifiers or cognitive touch points of heartburn relief for GERD patients who needed consistent,

[17]All media advertising expenditures in Fig. 9.3 from Kantar Media, *Ad$pender*, http://products.kantarmediana.com/security/. Accessed 1 Dec 2011.

[18]Registered US marks eventually included the use of the color purple on the pill, purple pills with two and or three gold stripes, purplepill.com, Prilosec, Nexium, and Prilosec OTC.

daily treatment (Conley et al. 2008). For chronic sufferers the connection to the purple pill became emotional (Harris 2002).

Anticipating the eventual entry of generics, AZ launched their second generation ppi known as esomeprazole magnesium and branded as Nexium in March of 2001. From March of 2001 through 2007 AZ spent between US$100 and US$240 million/year advertising Nexium as "today's purple pill." These Nexium media messages were targeting educated professionals with GERD that could afford the treatment. The Nexium pill itself was purple in color and included two or three gold stripes suggestive of the additional efficacy and denoting 20 and 40 mg dosages, respectively. It was positioned as an improved medication because on average it took shorter time (5 days vs. 7 days) for the GERD patient to experience relief relative to omeprazole.

The Nexium launch sales activities included aggressive detailing to doctors with a week of free samples for all qualified patients. Nexium was initially priced at a slight (4 %) discount relative to Prilosec in an effort to encourage patients, doctors, insurance companies, and health benefit managers to place Nexium on their formulary of covered compounds and approve the purchase of the new purple pill. As soon as the generic entered, Nexium's retail price was increased to US$5/pill. At that point, AZ had ceased all Prilosec promotional activities and was phasing out distribution of omeprazole as a purple pill.

9.3.3 Generics Maneuver for Entry

In order to be the first bioequivalent generic product approved for market entry post patent expiry[19] in October of 2001 generic companies including Genpharm, Andryx, Dr. Reddy's Cheminor and Kremmers Urban Development Co. (KUDCO) filed ANDA's[20] in 1998 and 1999. The FDA grants a 6 month marketing exclusivity to the first generic company to realize ANDA approval.

To counter this action, AZ quickly sued all of the above firms based on orange book patents[21] for coatings and manufacturing techniques that did not expire until 2007 and beyond. Such legal actions lead to a subsequent 30 month FDA delay of those ANDA approvals for omeprazole.

[19]The AZ molecule patent for omeprazole was in force when AZ entered the US market with Prilosec as a purple colored pill in October of 1989. A Hatch Waxman extension based on NDA approval delays at the US FDA was filed and led to a patent term extension until April 2001. A further 6 month marketing exclusivity was realized through pediatric studies that extended the expiry date to October 2001. Additional US patents on manufacturing related inventions and the enteric coatings used in popular Prilosec embodiments would expire a number of years after 2001 and were all listed on the FDA Orange book.

[20]Some of these ANDA's had paragraph IV certifications asserting that the AZ patents were invalid.

[21]AZ orange book patents in litigation w/generics included US Patents 4,786,505 and 4,853,230.

In October of 2002, a US Federal trial court found that all of the above ANDA applicants except KUDCO were guilty of infringing the AZ orange book patents for omeprazole and hence could not enter the market. The court further found that the two AZ orange book patents at issue were valid and hence enforceable.

With the litigation concluded, the FDA awarded the 6 months generic market exclusivity to the first applicants Genpharm and Andryx at 10 and 20 mg dose levels. Unfortunately, neither could enter the market because of the aforementioned infringement of orange book patents. Hence AZ could continue monopolizing the omeprazole market.

In the last 2 weeks of October 2002, KUDCO representatives met with Genpharm and Andryx and negotiated a deal. In exchange for revoking their respective ANDA exclusivities, these firms would partner w/KUDCO, the only ANDA applicant found not guilty of patent infringement in the litigation w AZ, to enter the generic omeprazole market.

On October 31st, 2002 the FDA received from Andryx and Genpharm requests for relinquishing the 6 month marketing exclusivity associated with their ANDA approvals. On the following day, November 1st, 2002, the FDA approved the next ANDA application (KUDCO) to enter the US generic market. In the subsequent months KUDCO and their silent partners Genpharm and Andryx became duopolists with AZ in the market for omeprazole. They priced their offering at a relative discount (approx. US$3/pill) to the pre-expiry Prilosec price. In 2003, KUDCO reported generic omeprazole sales in excess of US$1 billion. Other generics entered the omeprazole market in subsequent years eventually realizing a 30 % share of the ppi market.

9.3.4 Astrazeneca Strikes Back with "Sandwich" Approach

Fighting fire with fire, the AZ project team decided to pursue an OTC distribution option for a 20 mg omeprazole tablet. The required SNDA was approved in September of 2003. Following a plan dating back to 1995, AZ partnered with consumer packaged goods firm Proctor & Gamble to launch, distribute, and market what is now called Prilosec OTC. As shown in the Fig. 9.3, the annual media spending for this launch varied from US$40 million in 2003 to more than US$100 million in subsequent years. The messages targeted blue collar workers, laborers, and busy mothers who could neither afford Nexium nor see a doctor for their condition. As such, they avoided messaging conflicts that might cannibalize Nexium sales.

As the low cost producer of omeprazole with 15+ years of volume production experience, AZ's pricing and branding of the OTC offering became the lower portion of the sandwich approach illustrated in Fig. 9.2. AZ launched Prilosec OTC as a 20 mg dose of omeprazole (same quality level as prescription Prilosec) and in a

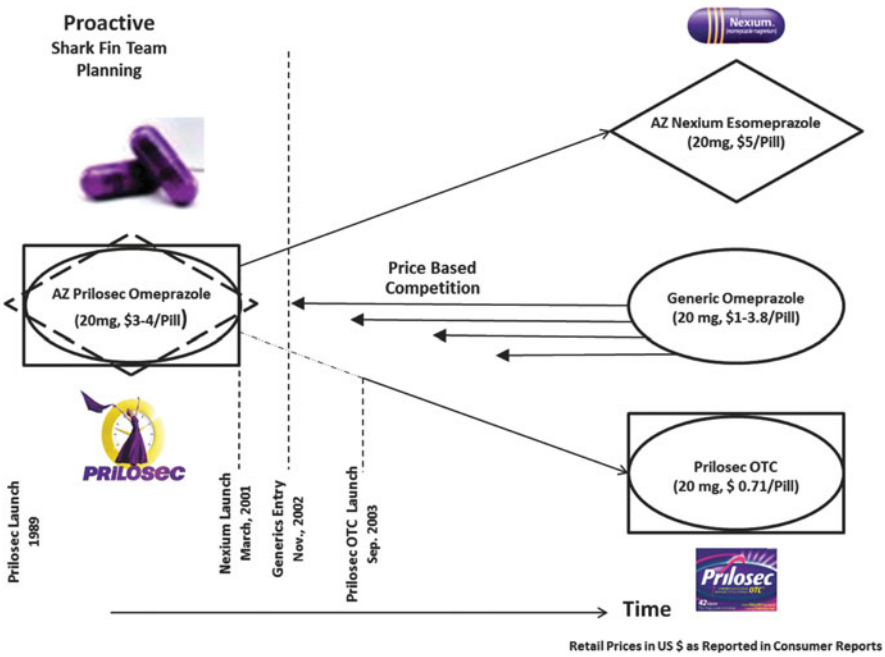


Fig. 9.4 AZ and sandwich pricing strategy applied to US PPI drug market

purple package suggestive of the association with the original Prilosec purple pill.[22] The launch pricing for Prilosec OTC was as low as US$0.71/pill. This was at a price point sufficiently low that the generics could not immediately compete. A further advantage of Prilosec OTC over the generics was that it did not require a prescription.

The dynamics of the sandwich approach as executed by AZ both pre and post generic entry are illustrated in Fig. 9.4. Pre-expiry, the 20 mg dose of the prescription Prilosec purple pill was retail priced approx. US$ 4/pill (q, p). During the period before and after generic entry Nexium was launched and positioned as "today's purple pill" with improved efficacy (q+) and eventually priced at a premium (p+). Prilosec OTC was launched with an active ingredient dosage equivalent to the generics (q) but at a substantial discount relative to the generics (p−). In the aggregate the approach surrounded the price competitive offerings of multiple generics effectively locking them into the middle of the market. AZ reported in 2004 that the effect of this effort lead to a 30 % drop in the generics share of the omeprazole market during the fall of 2003. Additionally AZ sales of ppi drugs eventually increased to over US$6.6 billion/year in 2006 and continued at approximately

[22]The Prilosec OTC medication was a pink tablet and not a purple pill. The only purple pill on the market would remain as Nexium. AZ eventually realized formal trademark registration for the exclusive use of the color purple on a pill in the "preparations for gastrointestinal diseases" category in 2004, US TM registration #2806099.

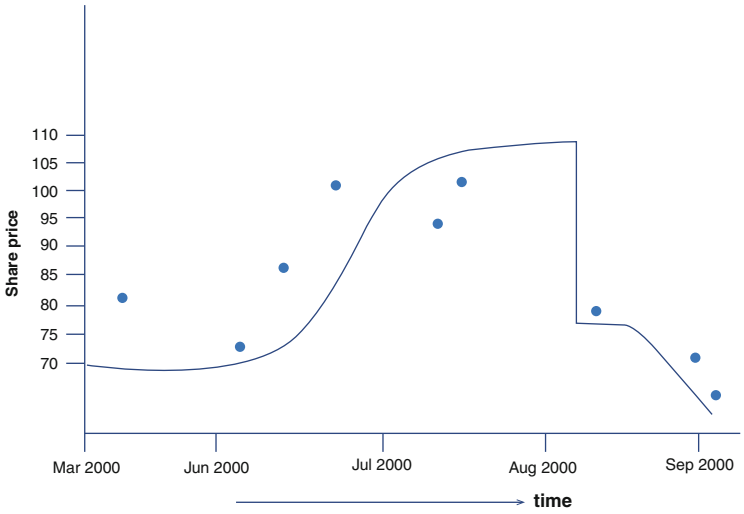


Fig. 9.5 Eli Lilly share price March to September 2000

this level through 2010. Hence AZ has avoided and continues to avoid the patent cliff sales decline that so many others experienced in the industry (Grabowski et al. 2002). A somewhat different management approach to a potential patent cliff is described below in the context of neurological medications.

9.3.5 Eli Lilly, Prozac, and Zyprexa

The most glaring example of a patent cliff occurred in August of 2000 when Eli Lilly unexpectedly lost a patent extension provision for Prozac, a blockbuster serotonin uptake inhibitor also known as fluoxetine. The unanticipated reversal handed down by the Court of Appeals of the Federal Circuit and the explicit lack of a plan to manage generic entry had a dramatic effect on the overall valuation of Eli Lilly as it lost 30+% of its share price in 1 day. The relevant stock price dynamics for Lilly in 2000 are illustrated in Fig. 9.5. The longitudinal revenue curve for Lilly for several medications in the same category is illustrated in Fig. 9.6.

While the shape of the Prozac sales curve both pre and post expiry[23] is consistent with other blockbusters in the industry as illustrated in Figs. 9.1 and 9.6, the apparent lack of a proactive plan to manage this event when it occurred caused a catastrophic cliff in shareholder confidence as illustrated in Fig. 9.5. Lilly eventually

[23]The CAFC appeals court ruled on August 9, 2000 that Lilly's claim 7 of US patent 4,626,549 as invalid.

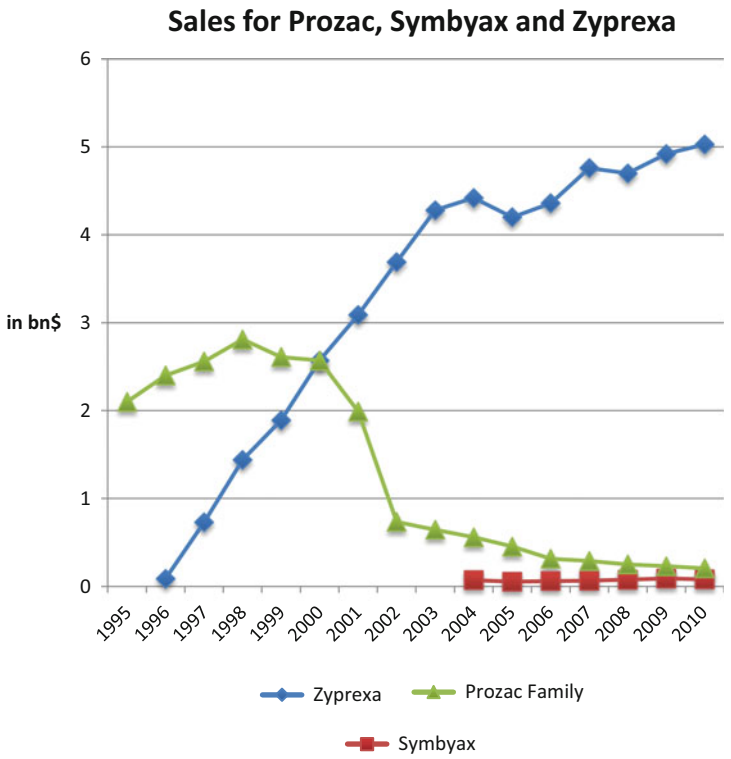


Fig. 9.6 Sales of Eli Lilly blockbuster neurological medicines as reported in 10 K filings

recovered share price and sustained market share in the category with the marketing and acceptance of new compound branded as Zyprexa (olanzapine). Like Nexium in the GERD category, Zyprexa was launched before the incumbent Prozac's patent cliff and eventually grew to twice the volume in sales. Zyprexa is a significant revenue earner for Lilly (Fig. 9.6) but is facing a patent cliff in 2011. Additional combination therapy drugs such as olanzapine containing fluoxetine in the same pill have been marketed by Lilly since 2004 as Symbyax but have not contributed significantly to Lilly's category sales.

While this class of drugs will not likely be an OTC product, they could pre-empt generic entry with a low cost generic of their own (Jain 2010; Kamien and Zang 1999). This was not done in the case of Prozac and it is not apparent that this was contemplated proactively before or reactively after the Zyprexa patent cliff was traversed in 2011. Preliminary data on Zyprexa sales in 2012 suggest that Lilly has already lost 70 % of sales for this drug.[24]

[24]Data from http://www.drugs.com/stats/zyprexa. Accessed 5 July 2012.

9.3.5.1 Summary

In this article, the authors have characterized and organized the relevant literature addressing pharmaceutical marketing models and policy options that can be managed to minimize the impact of patent expiry or patent cliffs. The various FDA regulatory regimes and intellectual property exclusivity options that can be tactically used to build and sustain competitive advantage in the pharmaceutical context are surveyed. Literature on marketing mix variables such as product, promotion, and pricing is reviewed. Novel models of dynamic pricing and methods for securing product identity through pill shape and or color are discussed. Uniquely, this article integrates related works from the law and economics literature that address comprehensive intellectual property regime management for building and sustaining the market advantages of an innovation. Empirical analysis of pharmaceutical product life cycles that include revenue, promotional expenditures, intellectual property maneuvers, and branding can help illustrate the complementarity of options and how they may interact to sustain the value of pharmaceutical innovations.

Analysis of pharmaceutical product life cycles that include revenue, promotional expenditures, intellectual property maneuvers, and branding can help illustrate the complementarity of options and how they may interact to sustain the value of pharmaceutical innovations. Empirical evidence for how pharmaceutical firms Astrazeneca and Eli Lilly attempt to navigate the patent cliff is presented.

9.3.6 Observations and Guidance for Managers

Based on the above analysis and discussion, just what can be done to manage the effects of patent cliffs? Some important observations and guidance for managers include:

1. The regulated market environment that is pharmaceuticals in the United States is complicated. Proactive or Reactive management of patent cliffs benefits from consideration of all the possible regulatory or marketing mix options available to firms. Table 9.1 is a preliminary listing of potential options. Successful traversing of the patent cliff benefits from advanced, anticipatory consideration of all the options listed in the table together with any others that are reasonable in the given market context.
2. The consideration of all the options listed in Table 9.1 requires a cross functional team with sufficient domain knowledge in regulatory exclusivity, intellectual property management, product development, legal, life cycle engineering, and marketing functions.
3. Dynamic pricing methods such as the *sandwich approach* can be useful in the appropriate context such as AZ's navigation of the Prilosec patent cliff. Economic analysis of this approach suggests that this leads to improved welfare for both branded drug manufacturers and their customers. Using this approach benefits from a *proactive disposition* e.g., the dedicated AZ project team.

4. Whether or not a company is proactive (AZ and Prilosec) or put into a position to react (Lilly and Prozac), product planning in a valuable category should create both up market (q+, p+) and cost competitive (q−, p−) options to be introduced at an appropriate time to sandwich the competition.
5. If an over the counter version of a drug is possible to introduce, this avenue can be used to fight against generic entrants. Note that OTC SNDA approval in the United States typically comes with a limited period of OTC market exclusivity that can be used to build the OTC brand. The nonprescription convenience is a positive and unique product attribute during the period of limited OTC marketing exclusivity.
6. Of the various marketing mix variables discussed, *price is the variable that firms have most control over in the US pharmaceutical context*. As such, it should be used carefully and with adequate consideration for its interaction with other variables.
7. Brand equity and how it is developed and used is becoming an important component of life cycle management. In the pharmaceutical context, product attributes that may be trademarked such as name or pill color and shape can be used to secure product uniqueness. This was eloquently demonstrated by AZ as they placed the incumbent brand name Prilosec on the price competitive product (q−, p−) and the incumbent brand color purple on the premium offering (q+, p+) with the new name of Nexium.

9.3.7 Suggestions for Future Research

The above literature review and case studies point to a number of avenues for future theoretical and empirical research. This research will be interdisciplinary and may best be undertaken by faculty from multiple schools of the academy. More specifically:

1. The patent expiry event in pharmaceuticals markets is a sufficiently data rich environment to support longitudinal marketing mix variable studies of product efficacy, price, promotion, and place. This research has offered the kernel of one such research context (see Fig. 9.3). Similar analysis of the large number of patent expiry events since 1984 (Hatch Waxman implementation) would facilitate a data rich study of marketing mix variable interactions. This research is best undertaken my marketing faculty guided by those who know how to interpret the FDA and USPTO databases.
2. Regulatory agency specific Intellectual property data bases such as the FDA Orange Book are another data rich, longitudinal record of an innovators (incumbent NDA owner) subsequent product inventions usually post launch. As such, they can be a window on what kind of product or manufacturing process improvements follow the NDA launch of a new chemical entity. This publicly available data set is amenable to both bibliometric and scientometric analysis.

3. The extant Marketing literature on pharmaceutical pricing both pre and post expiry would benefit from a comprehensive meta-analysis that integrates the theoretical with the more practical approaches. Some aspects of the sandwich pricing phenomenon for example have been contemplated by marketing scholars and economists. These bodies of thoughts would benefit from a comprehensive critical review that brings in the bodies of evidence as, for example, presented in Fig. 9.4 in this paper.
4. A focus on the product and price marketing mix variables as described in this paper would benefit from large scale empirical analysis. When have pharmaceutical companies applied the pricing sandwich if at all? What were the market conditions that led to the use of that pricing strategy? Does its use lead to decreased price and margin erosion over time relative to that exhibited in Fig. 9.1? While pricing models like the sandwich are appealing and useful as described, their success in a particular category might be contingent for example on access to the OTC market. A comprehensive empirical analysis is needed to address these questions in a significant manner.
5. Table 9.2 in this paper raises many interesting questions about visual brand equities such as color and or shape. Are visual equities such as color and shape being used to aggregate customer good will to the brand beyond patent expiry? Is there a way to measure how these attributes can be used to achieve value transference? Can the value of the associated source identity monopolies be measured both pre and post patent expiry? Questions of this type are low hanging fruit. What is needed again is an integrated team of those familiar with the pharmaceutical brand promotion literature and methods for mining and interpreting the publicly available trademark databases.

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Chapter 10
Risk Assessment: The Consumer as an Intuitive Statistician

Priya Raghubir and Robert Latimer

Abstract The authors present an overview of academic research on risk assessment. Consumers assess risk as though they were intuitive statisticians, combining two distinct processes to arrive at their perceptions of risk. With the bottom-up process, consumers rely on specific, individual-level risk factors. With the top-down process, consumers rely on the overall prevalence or "base rate" of a risk. Both processes may lead to over- or underestimation of actual risk, but the biases in each process stem from different sources. These sources of bias may be reduced or eliminated by implementing matching de-biasing techniques. Properly applied, de-biasing techniques may mitigate the negative consequences of over- or underestimation of risk.

10.1 Introduction

How do consumers assess their own and others' risk? Are their risk estimates biased upwards or downwards, merely inaccurate, or normative? How do biases in underestimating or overestimating risk affect consumers' behavior, and what are the implications of under- or overestimation of risk on pharmaceutical companies, medical establishments, the economy, and society in general? And why does knowing *how* consumers assess risk affect the manner in which companies, public policy officials, and consumer welfare groups can improve the accuracy of risk estimation and de-bias under- or overestimates of risk. That is, we suggest that *what* pharmaceutical companies and other parties do to help consumers assess risk will be differentially effective depending on their knowledge of whether risk was appropriately estimated, what was the direction of the bias in estimation, if any, and what the process used to arrive at the risk estimate was.

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10.2 Overview of Managerial Practices

In the last decade, since the Food and Drug Administration relaxed its rules in 1997, direct to consumer (DTC) advertising for prescription drugs has grown exponentially in the United States (Thomaselli 2006). Lexchin et al. (2012) estimate that in 2012 approximately $5 billion will be spent on DTC advertising. Spending appears to have leveled out as in 2005 DTC spending was estimated at $4.6 billion, representing 17 % of total industry promotional spending of $27.2 billion (Manning 2006). Pharmaceutical companies are estimated to have spent $4.7 billion in magazine and television advertising in 2008, a 10.7 % drop from 2007, with 15 % of these sales for drugs that were less than a year old (Swallen 2012). Less than a decade ago, in 2003, the estimated DTC spending of over $3 billion represented over 1/8th of the overall marketing budget of pharmaceutical companies that year, a compound increase of more than 30 % per annum since 1997 (Humphreys and Boersig 2004). Longley (2012) reports that the data from the Department of Health and Human Services suggests that half of the American population takes a prescription drug, with one in six taking three or more! Diabetes, cholesterol for heart disease, and depression are the three biggest health domains.

Advertisements are directed at consumers to help them assess whether they, or someone they know, are at risk and to encourage them to speak to their doctor about treatment. The advertisements appear to achieve this goal: In a statement before the Federal State Commission, Findlay (2002) reported that more than one in four of those who had seen a DTC ad talked to their doctor about it, with half of these specifically asking for a prescription. In the same report, he also states that whereas prescription for non-advertised drugs rose 4.3 % from 1999 to 2000, those of heavily advertised drugs increased by 24.6 %, a finding consistent with the fact that 78 % of primary care physicians reported that their patients asked them for drugs that they had seen advertised on television, with as many as two-thirds of them being prescribed the drug they had enquired about. This explosion of DTC drug advertising has led government organizations, both in the United States (US General Accounting Office) and overseas (e.g., Health Action International-Europe), to question its wisdom, while pharmaceutical companies have enjoyed record sales and profits. Claritin, the antihistamine, spent $137 million in 1999 on DTC advertising, and its sales increased by 21 % to $2.6 billion the following year (Charatan 2000).

Self-diagnoses are increasingly being relied upon by pharmaceutical companies (e.g., Bristol-Myers-Squibb uses two full page advertisements in national magazines to help consumers recognize whether they have bipolar disorder and informing them about the drug, Abilify[1]), health insurance providers (e.g., HealthNet), diagnostic web sites (e.g., www.WebMD.com), drug stores (e.g., Longs Drugs advertises the symptoms of depression), consumer welfare groups (e.g., 1-800-Gambler), and public policy providers to attempt to get people at risk to seek treatment. The surge in DTC advertising for a range of physical conditions including allergies, premenstrual

[1] Pages 15–16 in Newsweek, April 24, 2006.

disorder, anxiety, depression, obesity, diabetes, and erectile dysfunction demonstrates a range of symptoms that consumers are asked to identify in an attempt to self-diagnose. The conventional wisdom behind this strategy is that the more people know about the symptoms of a condition, the more they will self-diagnose.

However, many of those who need care still do not seek it. Gidengi (2012) reports that even though people's perceptions of risk for H1N1 appeared to increase with its actual incidence through the first year of the pandemic, among those who remained unvaccinated, intentions to be vaccinated dropped from 50 to 16 %. In a defense for DTC advertising, Manning (2006) reports high rates of nonacceptance (i.e., filling in a prescription) of high cholesterol (10 %), high blood pressure (15 %), and diabetes (11 %), with a large drop off in the percentage of patients continuing with prescriptions (e.g., non-persistence for diabetes was as high as 37 % after 1 year of having filled a prescription and rose to 51 % at 18 months). Diabetes is estimated to affect 16 million Americans, a number expected to grow by 42 % by 2025; with as many as 8 % of these cases undiagnosed (Franse et al. 2001). Cancer is also underdiagnosed: between 1998 and 2005, 27 % of men in the United States met the criteria for underdiagnosis of prostate cancer (Graifa et al. 2007), with the number as high as 30.3 % in a sample from Austria and Italy (Pelzer et al. 2007).

Compounding the issue of noncompliance and discontinuance of treatment, as advertising in the DTC space becomes crowded, consumers may begin to tune out these advertisements in the manner that they tune out the number of other ads directed toward them. This would reduce the efficacy and efficiency of drug-related advertising. From a consumer welfare and public policy point of view as well as from the point of view of the pharmaceutical industry, this suggests that DTC advertising may need to be made more effective. Central to its efficacy is a better understanding of how consumers assess risk.

One of the routes that pharmaceutical (and other) companies use to help consumers assess whether or not they are at risk is to provide a set of symptoms and ask people to identify which of the symptoms they or someone they know possess (Menon et al. 2002). On the other hand, other persuasion messages use base rates as a route to get consumers to accept their risk level and seek treatment. For example, an advertisement in a New York City subway car with a beach visual highlighted the odds of a shark attack (less than 1 in 10 million) against the odds of cancer, which is 1 in 5 people.[2] A poster in the Department of Motor Vehicles office in California in June 2011 highlights the dangers of texting while driving by listing the number of deaths per year from cobras ($n=5$), Uzis ($n=2{,}076$), cancer ($n=1{,}655$), floods ($n=30$), and texting (4,829). The poster goes on to say that traffic accidents are the leading killer of teens ages 16–19, ending more than 5,200 lives each year. They are careful to separate out the fact that more than two-thirds of these deaths had nothing to do with drugs or alcohol, implying that as many as 3,000 deaths were due to everyday driving behaviors and distractions. Therefore, it is important to examine how asking people to identify symptoms or presenting people with base rates will help them assess their overall levels of risk. This is the purpose of this chapter.

[2] http://www.cancer.org/Cancer/CancerBasics/lifetime-probability-of-developing-or-dying-from-cancer.

10.3 Chapter Outline and Goals

This chapter provides a broad and comprehensive overview of academic research on risk assessment. There has been recent and growing academic interest in how consumers assess health risk in both marketing (for a review, see Menon et al. 2008) and healthcare (for a review, see Hansen and Droege 2005).

Based on the two most commonly used managerial strategies for getting people to accept risk (symptoms and base rates), we propose that consumers assess risk as though they were intuitive statisticians using top-down and/or bottom-up methods, but that these estimates of risk may be systematically biased, leading consumers to frequently underestimate and occasionally overestimate their level of risk, both associated with downstream costs to the individual, economy, and society. The overall model is presented in Fig. 10.1. The two methods, top-down and bottom-up, rely on a different set of inputs to make judgments. Top-down methods rely on base rates. Bottom-up methods rely on symptom identification and integration. Biases in risk estimation creep in due to use of inappropriate inputs (e.g., base rates being discounted or symptoms being ignored leading to underestimation of risk) and/or the inappropriate integration of inputs. De-biasing strategies, accordingly, need to

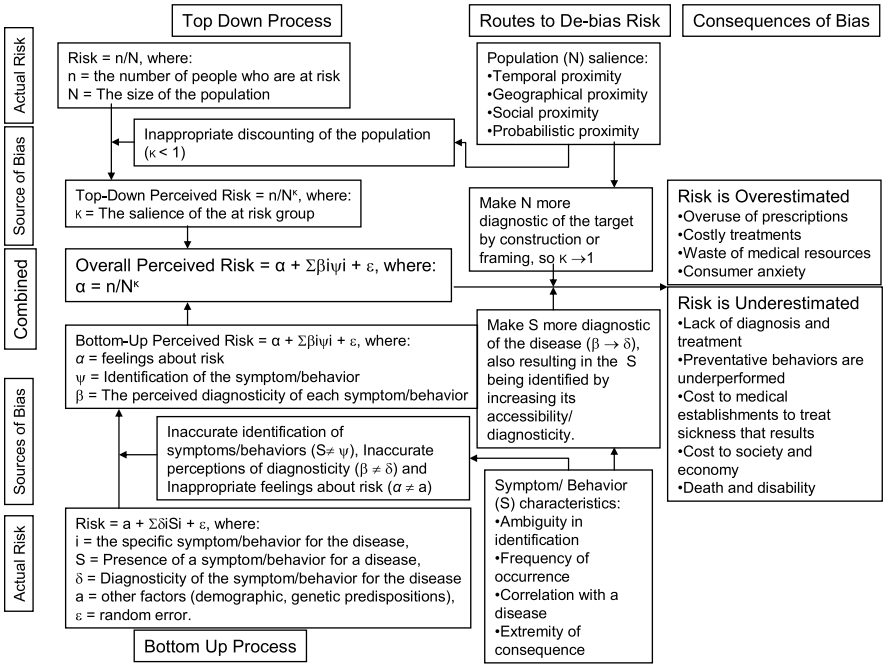

Fig. 10.1 Overall theoretical model and chapter structure

improve the likelihood that the correct inputs are used and those inputs are correctly integrated to form a judgment. For example, if consumers use a top-down strategy, then ways in which the base rate is constructed or framed will affect its likelihood of being appropriately used. On the other hand, if consumers used a bottom-up strategy, changing the construction or frame of the base rate would have limited effectiveness, and a more effective strategy would be to strength the link in the consumer's mind between a symptom and a disease. This would increase the symptom's likelihood of being identified and appropriately integrated into the risk judgment. Thus, the effectiveness of any de-biasing strategy will differ depending on the biasing input used. Accordingly, understanding whether top-down or bottom-up methods or a combination of both is used to construct risk is necessary to appropriately de-bias consumers and bring their risk estimates in line with reality.

But do errors in risk estimation really matter? Why is it important to bring risk estimates in line with reality? Underestimating one's risk brings with it the consequences of not seeking or taking treatment, or not engaging in preventative behaviors (for a review, see Brewer et al. 2007). This underestimate of risk has downstream consequences not only for the individual in terms of longevity and quality of life but also for their family and social circle, their work place as it can impede their efficiency and effectiveness and lower their overall productivity, lead to higher costs of treatment at a later stage, and be a cost to the medical infrastructure as well as the economy and society as a whole. On the other hand, overestimating risk could lead to consumers behaving like hypochondriacs, seeking and taking more treatment than they need, purchasing costlier treatments than are warranted, exploiting scarce medical professional time, being anxious and less productive at work, and concomitantly being a social and economic burden. Thus, the costs of over- and underestimating risk both have consequences that trickle down from the individual consumer level to society at large.

One of the most robust biases that have been documented in the risk perception literature is that people have a self-positivity or unrealistic optimism bias such that they believe negative things, like getting a disease, are less likely to happen to them than to others (Perloff and Fetzer 1986; Raghubir and Menon 1998; Weinstein 1980, 1987). However, there have also been documented cases when people overestimate risk and are pessimistic (Keller et al. 2002; Lin et al. 2003). Keller et al. (2002) showed self-negativity for depressed women's estimates of their relative chances of getting breast cancer: while depressives' absolute estimates of risk reflected pessimism (vs. the actual base rates), their relative estimates of self vs. another person reflected self-negativity. Lin et al. (2003) developed a framework to reconcile Perloff and Fetzer's (1986) finding of self-positivity with Keller et al.'s (2002) finding of self-negativity. They explored the connection between absolute levels of risk estimates (defining optimism and pessimism) and relative estimates of self–others' risk (that define self-positivity, self-negativity, or realism). They found that optimists (with low absolute levels of risk) demonstrated self-positivity (low relative levels of risk). The bias was robust and remained when base rates were provided: risk estimates were not updated for events that optimists believed were controllable, and were inadequately updated for events that were believed to be less controllable.

Thus, optimists' self-positivity bias remained significant, but was weaker for less controllable events, consistent with Perloff and Fetzer's (1986) results. Lin et al. (2003) suggest that this was because optimists use self-positivity (the effect that estimates of own risk are lower than estimates of the risk of other people), as a strategic device to maintain or enhance their self-esteem. Lin et al. (2003) also found that pessimists (with high absolute levels of risk) demonstrated self-negativity (high relative levels of risk) which is consistent with Keller et al.'s (2002) findings with respect to breast cancer. The primary difference between optimists and pessimists was in the extent to which they used contextually provided base rate information to update their estimates of risk. While optimists had shown no or inadequate levels of adjustment, pessimists readily updated their risk estimates using base rate information, leading to an attenuation or elimination of their self-negativity bias. Said differently, the diagnosticity of memory-based information (based on prior experience) was lower for optimists as compared to pessimists.

Lin et al.'s (2003) framework allows for a reconciliation of the effects of depressive realism with self-positivity. As depressives view their life and future in negative terms (Beck 1967, 1976), they have low levels of self-esteem (Gerrard et al. 2000), resulting in their being pessimistic at an absolute level and not prone to self-positivity at the relative level. The literature on self-positivity and self-negativity shows the importance that base rates play in people's assessment of risk as well as highlight the fact that risk estimates can be biased in either direction.

Given that both types of biases can lead to downstream consequences, the chapter will examine ways in which risk estimates can be increased or decreased as warranted, although as most work has found underestimation of risk, it will specifically address interventions aimed at increasing risk estimates based on both the top-down and the bottom-up processes.

We start with an overview of the two processes (bottom-up and top-down) of risk estimation as laid out in Fig. 10.1. For each process, we describe the basic inputs that are used, and the sources of bias that creep in as there is a departure of perceived risk from actual risk. It is within this context that prior literature that has examined specific factors affecting risk estimates is reviewed; we then go on to ask: how do consumers combine top-down base rate information about the likelihood of occurrence of a disease with bottom-up information about their own or others' risk factors to assess how much at risk they or others are, and whether they should seek treatment? The chapter concludes with some important and open research questions for risk perceptions.

10.4 The Effect of Risk Factors on Risk Assessment: The Bottom-up Process

The bottom-up process, frequently used in demand estimation, is characterized by working up the individual (or segment) likelihood of various consumers performing a series of probabilistic actions that then aggregate to a macro-assessment of market size.

In the current context, we use the term to signify the individual risk factors, behaviors, or symptoms that probabilistically contribute to overall risk for an individual. The theory of reasoned action (cf. Ajzen and Fishbein 1975; for applications to risk perception, see Fishbein and Middlestadt 1989; Fishbein et al. 1994; for a recent meta-analysis, see Albarracin et al. 2001) was the first theory applied to understand how consumers assess risk using what we term the "bottom-up" process. The risk factors that a consumer could typically use as inputs are their prior behaviors (e.g., having unsafe sex in the context of AIDS) and whether or not they have symptoms that characterize a disease. Of course, individual differences in demographics (e.g., age, gender, and race), family history (given that certain diseases like thyroid disorders may have a genetic aspect), and geographical location (e.g., incidence of skin cancer is greater in Australia and New Zealand than in India) would also factor into their risk estimates. The manner in which individuals use information about their behaviors or symptoms to construct their level of risk is covered in this section. (How individual differences in demographics, family history, and location among others affect risk perception is covered in the subsection of conditional base rates where top-down processes are combined with bottom-up processes to form an integrated perception of risk).

10.5 Inputs to the Model: Behaviors, Existing Symptoms, and Feelings

The theory of reasoned action suggests that people make judgments as if they are performing cognitive algebra, such that they identify a set of attributes, assign weights to them, and then aggregate across these weighted attributes. In the domain of risk perception, this suggests a process whereby people identify their risk factors and then integrate them by assigning weights to each identified behavior or symptom.

The bottom-up approach involves identifying and interpreting causal factors (e.g., symptoms, behaviors, and situational factors), and then aggregating them to assess the extent to which a person is at risk. The model follows a signal detection theory paradigm with the addition that the signal needs to be interpreted prior to being identified as present.

The model formulation is as follows:

$$\text{Risk} = a + \Sigma \delta_i S_i + \varepsilon$$

where

i = the specific symptom/behavior for the disease
S = presence of a symptom, risk behavior, or preventive behavior for a disease
δ = diagnosticity of the symptom/behavior for the disease
a = other factors such as demographic and genetic predispositions
ε = random error

However,

$$\text{Perceived Risk} = \alpha + \Sigma \beta_i \Psi_i + \varepsilon$$

where

ψ = identification of the presence/absence of a symptom, risk behavior, or preventive behavior
β = the perceived diagnosticity of each symptom/behavior
α = feelings about a risk

This formulation suggests the following sources of biased perceptions of risk:

1. The inaccurate identification of symptoms or behaviors (i.e., $S \neq \psi$)
2. The inaccurate perceptions of diagnosticity of the symptom or behavior ($\beta \neq \delta$)
3. Inaccurate feelings about a risk ($\alpha \neq a$)

So why do consumers inaccurately identify symptoms/behaviors or inappropriately estimate their diagnosticity? What are the sources of bias that lead to a divergence between S and ψ, between β and δ, and between a and α? Next, we examine the sources of bias in a bottom-up process as understanding the antecedents of the bias provides usable ways to de-bias risk.

One set of factors that is likely to affect perceptions of risk is the frequency and recency of having engaged in behaviors that increase or decrease risk of a disease, such as smoking for lung cancer, unsafe sex for sexually transmitted diseases (STDs), and or vaccinations for Hepatitis-B. Another set of factors are the symptoms that are associated with the disease itself.

Underestimation of risk would imply that if consumers were using a bottom-up process to estimate their risk, then they were not adequately taking into account their own risk behavior or symptoms while constructing their risk judgment, or exaggerating the impact of their preventive behaviors. Accordingly, manipulations that can increase the accessibility of their own risk behaviors or symptoms and reduce the accessibility of their preventive behaviors should be effective at helping consumers make less biased risk judgments.

An overestimation of risk, on the other hand, would imply that consumers were excessively weighting their risk behaviors or symptoms, or underweighting their preventive behaviors. Accordingly, to de-bias overestimates, manipulations should be aimed at helping consumers appropriately calibrate the diagnosticity of the behaviors or symptoms for a disease. Overestimation could also be due to consumers including behaviors or symptoms that are not actually associated with a disease into their cognitive algebra. The route to de-bias overestimates through this route is the same; helping consumers recognize that the behavior or symptom is not diagnostic of the disease and, accordingly, should not be included in their cognitive algebra.

Increasing the accuracy of a consumer's assessment of the presence and diagnosticity of a single symptom or behavior will not necessarily increase the accuracy of their risk estimate (Brewer et al. 2004). If a consumer already underestimating risk

became aware of a preventive behavior they are already performing, they are likely to underestimate their risk still further. Similarly, a consumer might overestimate their risk when they identify a risk behavior (e.g., visiting wooded areas for Lyme disease), if they fail to consider a preventive behavior that they already perform (e.g., using tick repellent).

To summarize, the routes to de-bias bottom-up estimates of risk center on increasing the accessibility and calibrating the diagnosticity of the individual behaviors and symptoms that relate to it. An integrative framework for behaviors and symptoms that need to be identified and aggregated as part of a bottom-up process is discussed next.

10.6 Sources of Bias in Identification and Integration of Risk Factors

Consumers use the presence or absence of various symptoms and behaviors to assess whether or not they are at risk. In fact, a large percentage of DTC advertising highlights symptoms hoping that the mere awareness that a state is a symptom of a disease will persuade consumers to assess their risk. However, symptoms vary along many dimensions. Some symptoms are common across many conditions (e.g., fatigue), whereas others are more specific to a certain malady (e.g., joint pain). Some appear extreme (e.g., thoughts of suicide or death in the context of depression), whereas others appear more "normal" (e.g., feeling unusually sad or irritable over a 2-week period). Some occur with a high frequency for one individual (e.g., daily drinking in the context of alcoholism), and others with a lower frequency for another individual who may be at equal risk (e.g., binge drinking).

Signal detection theory is a useful theoretical framework to think of how people use behaviors or symptoms to make risk judgments. It postulates that there are six characteristics of signals (in this case, symptoms or behaviors) that affect their use (Sperling and Dosher 1986): their degree of existence, their actual expected consistency, the frequency of occurrence of the signal, their causal clarity, measurement error associated with them, and the expected gain from the signal detection task. Signals that have a *higher threshold of detectability* (i.e., are less ambiguous), have low *measurement error* (i.e., are difficult to reinterpret due to their ambiguity), have lower *actual expected consistency* (i.e., are expected to occur only some of the time), are *infrequent*, have higher *causal clarity* (i.e., if every time a symptom occurs, the disease also occurs), and provide a high *expected gain from signal detection task* (i.e., have extreme consequences) are likely to be weighted to a greater extent in the information integration task (Raghubir and Menon 2005).

In many situations (such as depression, thyroid imbalance, lupus, diabetes, and heart disease), the symptoms vary in terms of many of the above characteristics. For example, in the case of depression the symptom of "thoughts of suicide/death" is different from the remaining eight symptoms (loss of interest or pleasure in activities, being sad or irritable, sleep disturbances, decreased ability to concentrate,

appetite changes, tiredness, feelings of guilt or worthlessness, and restlessness or slowed activity) along all six dimensions. It is a behavior that is present or absent vs. a feeling state that exists to some extent (increasing its threshold of detectability and actual expected consistency, and reducing its measurement error), has a high predictive ability for depression (increasing its causal clarity), with extreme consequences and a low frequency of occurrence in the population, leading to its being perceived to be more diagnostic of depression than the other symptoms (Raghubir and Menon 2005).

The six characteristics of signals suggest four underlying characteristics of symptoms that would affect their likelihood of being identified and integrated: their ambiguity, their frequency of occurrence, their correlation with a disease, and their extremity of consequence.

Given that the bottom-up framework implies that there are two aspects to the use of an input: its identification (or accessibility) and its perceived diagnosticity, it is possible that these four characteristics can affect both. Feldman and Lynch (1988) proposed the accessibility–diagnosticity model as a useful framework to think of how people construct judgments in general. Its basic tenets are that people use an input (in this case a specific behavior or symptom) to the extent it is accessible (in this case identified or ψ) and diagnostic (β) of the judgment at hand and as an inverse function of the accessibility and diagnosticity of alternate inputs that can be used to make the same judgment. We now examine how each characteristic of a symptom or behavior can affect its likelihood of identification or perceived diagnosticity.

(a) *Ambiguity*: Symptoms that can be identified as occurring or not occurring (such as specific behaviors) have a higher threshold of detectability than those that can exist to some extent (such as states or feelings). Thus, in the domain of behaviors, the threshold of detectability may be a nonissue, but, in the domain of symptoms, identification errors may be due to symptom ambiguity. Ambiguous symptoms need to be interpreted prior to being identified (e.g., "feeling tired" in the context of depression, Raghubir and Menon 2005). In one of the earliest papers to examine how symptoms are used to constructs judgments, Raghubir and Menon (2005) suggested that consumers differentially interpret ambiguous symptoms in the context of depression as a function of whether or not they believe they are at risk. Specifically, if respondents were asked to estimate their level of risk prior to identifying whether or not they had the nine symptoms associated with depression, they were less likely to identify that they had any of the symptoms that were ambiguous. In fact, seven of the nine symptoms (with the exception of the "thoughts of suicide and death" and "feelings of guilt") were less likely to be identified as symptoms that a person possessed if that person was asked to identify the symptoms after completing their estimate of risk vs. before completing their estimate of risk. The extent to which a behavior or symptom can be reinterpreted increases its associated measurement error. The more extreme and less ambiguous a behavior or state, the less likely it can be reinterpreted as being something else. Unambiguous symptoms and most behaviors (e.g., "thought of suicide or death" in the context

of depression and tattoo piercings in the context of Hepatitis-C), on the other hand, require less interpretation prior to being identified. This implies that communication aimed at de-biasing risk estimates based on behaviors needs to increase their accessibility, whereas communication aimed at de-biasing risk estimates based on symptoms needs to first disambiguate them, that is, define what the symptom is in terms of specific, concrete examples.

(b) *Frequency of occurrence*: If a symptom is expected to occur only some of the time (e.g., an infrequent behavior), rather than all of the time (such as a state or feeling or a very frequent behavior), then it is a stronger signal. This is because the symptom's occurrence in the individual is unexpected, and, therefore, it is more likely to be recalled, that is, accessible.

Behaviors that occur frequently in a population also have lower signal value than those that are rarer and less normal. Consumers may also simply be unaware of the symptoms associated with a disease (Feinberg 2012). The frequency with which a behavior or symptom occurs affects both the accessibility of the signal and the diagnosticity of the signal. This is because the greater the frequency of any behavior, the higher its accessibility (Higgins 1989), but the lower its diagnosticity as per signal detection theory. If the behavior or symptom has low frequency then its accessibility needs to be increased if it is likely to be identified, but once it is identified it is likely to be incorporated into a risk estimate due to its higher perceived diagnosticity. On the other hand, if the behavior or symptom has high frequency, then its diagnosticity for a disease needs to be established for it to be appropriately incorporated into a risk assessment.

There are multiple ways of increasing the accessibility of a (low frequency) behavior or a symptom. Merely asking people to recall a behavior associated with a disease can serve the purpose, although as the number of behaviors people are asked to recall becomes more difficult, this can backfire and lower risk perceptions as the lack of accessibility is used as information in and of itself (Raghubir and Menon 1998 in the context of AIDS). Providing a list of symptoms can also increase the accessibility of the symptoms in a context-based (vs. memory-based) task, as the list improves the overall awareness of the symptoms associated with a disease (Raghubir and Menon 2005 in the context of depression), though if the set of behaviors included are performed with a lower frequency and are unusual, then this too may backfire (Menon et al. 2002 in the context of Hepatitis-C).

Increasing the perceived diagnosticity of high frequency behaviors or symptoms, on the other hand, may require different tactics. A simple solution is to manipulate the availability of alternate inputs that are available to make the risk judgment. For example, Raghubir and Menon (2005) showed that depression symptoms of "loss of interest or pleasure in activities normally enjoyed" or "feeling unusually sad or irritable over a 2-week period" that are more diagnostic of depression as per DSM-IV guidelines than the less frequent symptom of "thoughts of suicide and death" were more likely to be used to construct a risk estimate when the depression inventory did not include the infrequent symptom.

Note that these symptoms differ in more than their frequency of occurrence in a population and their actual expected consistency. They are also differentially ambiguous, which could be another reason contributing to why the less ambiguous symptom of "thoughts of suicide/death" had an inappropriately high weight in people's judgments of risk of their own level of depression. However, fortunately for managers of pharmaceutical companies who manufacture depression drugs and public policy officials, this bias in consumers' risk assessments can be eliminated by providing them with information about the DSM-IV guidelines and highlighting the appropriate diagnosticity of each of the symptoms. When respondents saw the appropriate DSM-IV classification scheme, the presence of the unambiguous behavior was less likely to dilute the perceived diagnosticity of the other behaviors on the self-report inventory. To summarize, the perceived diagnosticity of a high frequency behavior or symptom can be increased by education and by reducing the accessibility of alternate cues that have higher perceived diagnosticity due to their lower ambiguity, lower frequency, higher correlation with a disease, or greater extremity of a consequence: factors covered next.

(c) *Correlation with a disease*: If every time a symptom occurs, the disease also occurs, it is defined as having high causal clarity. On the other hand, if there is a high rate of false alarms (whereby a symptom exists but is due to reasons other than the disease) the symptom has lower causal clarity.

(d) *Extremity of consequence*: The more serious the consequences associated with a symptom, the greater its signal strength.

This implies that symptoms and behaviors that are less ambiguous, less frequent, and more serious will be perceived to be more diagnostic and feed into perceptions of higher risk, even if they are not higher in their actual correlation with a disease than other behaviors or symptoms. It also implies that the mere presence of symptoms that are perceived to be diagnostic but are not identified will lead to perceptions of lower risk as they are alternate accessible sources of information with a higher perceived diagnosticity that can be used to make the same risk judgment. Risk perceptions are most easily shifted by changes in the perceived diagnosticity of already accessible symptoms and behaviors or changes in the accessibility of symptoms and behaviors already perceived as diagnostic.

Affect: In addition to the accessibility and diagnosticity of symptoms and behaviors, consumers may use their positive or negative feelings about a risk when making their estimate. Perceived risk may be closely associated with the feelings of dread that risk evokes (Fischoff et al. 1978) and consumers' judgments of whether a hazard is good or bad predict their estimates of its danger (Alkahami and Slovic 1994). When consumers like something, they estimate its risk as low and its benefits as high; when consumers dislike something, they estimate its risk as high and its benefits as low (Finucane et al. 2000; Slovic et al. 2007). Attempts to change the feelings associated with a risk often focus on the risk itself rather than its symptoms or associated behaviors. For example, government agencies buy advertising displaying

the graphic trauma that can result from automobile collisions to try to offset the consumers' fear-reducing familiarity with driving. Prior research has examined changing the affect associated with messages by manipulating the level of affective intensity or simply the frame of the message.

For example, Meyerowitz and Chaiken (1987) examined the effect of framing a behavior as a loss or a gain in the context of a breast self-examination. They found that messages framed using a negative frame of benefits lost (i.e., "Women who do not do BSE have a decreased chance of finding a tumor in the early, more treatable stage of the disease") were more persuasive than those that were framed positively in terms of benefits gained (i.e., "Women who do BSE have an increased chance of finding a tumor in the early, more treatable stage of the disease").

Block and Keller (1995) found that negative frames were more persuasive than positive ones in the context of skin cancer and STDs, but only when people processed the information in-depth; with in-depth processing more likely to occur when a recommendation only probabilistically led to a desired outcome (i.e., was less efficacious than a deterministic recommendation).

In related work, Keller and Block (1996) uncover that the underlying mechanism driving persuasion is fear arousal. Low arousal doesn't encourage adequate elaboration but high levels of arousal can lead to too much elaboration. Changing the reference of the person can change the level of elaboration: Self-reference leads to greater elaboration than referencing another person. Accordingly, self-referencing increases the effectiveness of low fear appeals and other-referencing increases the effectiveness of high fear appeals. This implies that if the accessibility or diagnosticity of a person's own behaviors or symptoms can be increased, they will be less likely to use their feelings as a source of information to make risk judgments.

10.7 De-biasing Bottom-up Strategies

To conclude, perceived risk may deviate from actual risk when consumers are using a bottom-up process due to the inaccurate identification of symptoms and behaviors, an inaccurate perception of their diagnosticity, and inappropriate use of feelings about risk. The routes to de-bias these risk estimates revolve around making symptoms and behaviors more accurately perceived as diagnostic of the disease. Making symptoms and behaviors more accurately diagnostic would bring β in line with δ given that they have been identified, and reduce the impact of α (feelings). The characteristics of the symptoms or behaviors provide usable methods to increase the diagnosticity of symptoms and behaviors: make ambiguous behaviors unambiguous to help in their identification and improve their diagnosticity, increase their accessibility when they are frequently performed, provide information that allows consumers to assess the correlation of the symptom/behavior with the disease, and highlight the extremity of their consequences. Examples of these routes to de-bias consumers who use the bottom-up process are provided in Table 10.1.

Table 10.1 How can practitioners de-bias consumers?

Process used	Source of bias	Required action	Possible solutions	Example
Top-down	Inappropriate discounting of population	Increase salience of population by reconstructing the base rate	↑ Temporal proximity ↑ Geographical proximity ↑ Social proximity ↑ Probabilistic proximity	Describe the incidence of STIs last year in a nearby college dorm when targeting students
		Increase salience of population by reframing the base rate	Semantically change the manner in which information is provided	People infer that "1 out of 5" is lower in magnitude than "20 %"
Bottom-up	Inaccurate Identification of symptom	Increase the likelihood that the symptom is accurately identified	Make ambiguous symptoms less ambiguous	Risk behavior framed as "drank more than six alcoholic beverages in the last week" rather than "drink alcohol frequently"
			Increase accessibility of infrequent symptoms	Recalling a *few* risk behaviors for AIDS increases risk estimates
			Present evidence regarding the consequences of ignoring the symptom	Describe a specific individual who ignored a particular symptom and the resulting consequences
	Inaccurate perceptions of the diagnosticity of the symptoms	Improve the diagnosticity of the symptom	Present evidence of correlation of symptom with a disease	Celebrity testimonial of the symptom they noticed that led to diagnosis

10.8 The Effect of Base Rates on Risk Assessment: The Top-down Process

While the individual presence of symptoms for an individual is one way to help people recognize their risk, providing them with the overall base rate of occurrence of any event or disease in the population is another. Many companies use absolute numbers ("Seventeen million Americans have diabetes, and … nearly six million of

them do not know it") or rates with or without a time period associated with the rate of incidence ("In 1999, roughly 1 out of every 13 U.S. high school students reported making a suicide attempt in the previous 12 months …." or "Mental Illness will hit one out of every two people in the U.S." and "… 4.7 % of adults reported alcohol abuse in 2001–2002, and 3.8 % reported alcoholism"). Research has shown that these may not be the most effective ways at communicating the overall likelihood of incidence, and could be reconstructed and/or reframed to be made more effective. It is possible that merely making consumers aware of the base rates can affect their risk perceptions, as there is a gap between people's perceptions of risk of death from different causes and the actual base rates. For example, Feinberg (2012) reported that only 21 % of women were aware that heart disease was a significant risk to them and 46 % of all women believe that breast cancer is their most serious health threat (vs. 4 % who accurately believe that it is heart disease).

The higher the base rate, presumably, the greater the likelihood that people will recognize the fact that they may be at risk and take preventative action or undergo screening. Therefore, many companies (for profit as well as not for profit) highlight the overall likelihood of a disease with a specific goal of getting consumers to speak to their doctors, get routinely tested (e.g., for skin or breast cancer), and stop engaging in risk-causing behaviors (e.g., smoking for lung cancer). The problem is that a large body of literature in judgment and decision-making and social psychology has documented that people do not appropriately use base rate information and sometimes ignore it entirely. Providing base rate information can lead to consumers to be optimistic (underestimating their risk), become realistic (i.e., unbiased), and, on occasion, become pessimistic (i.e., over estimating their risk; Lin et al. 2003).

10.9 Inputs to the Top-down Process: Base Rates

The top-down approach involves applying memory-based or contextually provided base rates of incidence to a personal situation. The overall base rate may be applied in differing degrees to one's own situation due to cognitive (translating the actual base rate into a perceived base rate that would be captured in terms of the perceived risk of the average person) and motivational factors (translating the perceived base rate into perceptions of own risk vs. risk of the average person). The model is based on the following formulation:

$$\text{Base Rate} = n / N$$

Psychophysical models of estimation have shown that people's estimates may be biased and follow a power law with an exponent that is less than 1. Raghubir (2008) proposed that the salience of the numerator (n) is biased as a function of the likelihood of being able to imagine oneself in the population, N. The larger the N, the less easy it is to identify with it, and, therefore, the less effective the numerator n. Thus, perceived base rates may be psychophysically represented as:

$$\text{Perceived Base Rate} = n / N^{\kappa} \quad \text{where} 0 < \kappa < 1$$

When $\kappa = 1$, perceptions of base rates are in line with reality, and as $\kappa \rightarrow 0$, there is a systematic bias in underestimating the base rate. The larger the population (denominator N), the more difficult it is to identify with those at risk (numerator n), and the smaller the κ ($\rightarrow 0$). The larger the overall number of people who are at risk (numerator n), the easier it is to imagine oneself being a part of this group, and the larger the κ ($\rightarrow 1$). The higher the actual incidence or as $n \rightarrow N$, $\kappa \rightarrow 1$ and perceptions of base rates are unbiased.

The question then is, what are the factors that determine the sources of bias in base rates estimation and application (i.e., that can explain the deviation of κ from 1)? These are explored next.

10.10 Sources of Bias in Base Rate Use

One of the most common alternatives to which base rate information has been compared has been individuating information—that is, information about a single person who performs a given action, or has a problem or disease. The social psychology literature has documented that providing individuating information is more effective than providing base rate information in a variety of judgment tasks (e.g., Bar-Hillel 1980). Objectively, base rate information is more reliable than individuating information as it is based on a larger sample, but information about an individual can be more persuasive as it is more vivid (Bar-Hillel 1980). Researchers interested in improving the accuracy of judgments have studied ways of increasing the utilization of base rate information. They have found that increasing the relevance of base rate information increases the likelihood of its use in general (Tversky and Kahneman 1982). In line with this, Ginossar and Trope (1980) argue that when subjects see base rate information as relevant to the judgment they are required to make, they do take it into account, with information used as a function of its perceived diagnosticity for the task at hand. Ginossar and Trope (1980) reversed the base rate effect by showing that subjects ignored individuating information in favor of base rate information when the former was less task-relevant.

In this section we propose that overall population base rates are less meaningful to a consumer than are base rates constructed from populations that they can relate to, that is, are close to the consumer for a range of reasons, including their genetic disposition, family history, and experience. This is because these populations are easier to bring to mind, allowing the respondents to be able to imagine that they personally will be harmed (Rothman and Kiviniemi 1999; Kahneman and Tversky 1982). Being able to imagine that the base rate does apply to them specifically should cognitively lead to perception of higher risk and translate into higher intentions to engage in preventive behaviors.

Kahneman and Varey (1990) originally demonstrated that proximity correlates positively with people's perceptions of the probability of an event occurring, and thus acts as a direct influence upon perceived risk. There are four different dimensions

of perceived closeness: time, space, social, and probability, that "affect mental construal and … in turn, guide prediction, evaluation, and behavior" (see Trope et al. 2007 for a review). As such, constructing base rates such that they are more proximate using one or more of the dimensions of proximity is likely to be more effective than base rates constructed for an overall population. The distinct ways in which each dimension of proximity affects risk perceptions is discussed next.

Temporal proximity. The closer an event is in time, the more temporally proximate it is. A proximal consequence is perceived to have a greater risk than a distant consequence (Paterson and Neufeld 1987). Consumers appear to not engage in preventive behaviors until they feel a risk is imminent (Luce and Kahn 1999; Weinstein 1993). Trope et al. (2007) argue that this is because the distant future is seen as more abstract while the immediate future is seen as more concrete and spurring action.

Chandran and Menon (2004) examined the effect of framing a risk for Mononucleosis using a per-day vs. a per-year frame. Estimates of incidence of a disease, perceptions of risk, and a greater concern for Mono were higher when the frame used a day (vs. year) frame. They argued that this was because a "day" frame makes a threat more concrete and proximal using construal level theory (Trope and Liberman 2003). These results are consistent with the idea that base rates constructed on a smaller and temporally closer population (the day frame) lead to a higher perceived risk than those based on a larger and temporally distant population (the year frame).

Geographical proximity. Geographical proximity is the actual or perceived physical distance between a consumer and the population for which a base rate is provided. Maderthaner et al. (1978) first showed that physical proximity (perceived closeness) to a danger increased perceptions of risk. Recently, Fischhoff et al. (2003) demonstrated that US citizens assessed higher risk of terrorism in the future, not only in general but also for themselves, the closer they were located to the World Trade Center. Raghubir (2008) also showed that base rates framed using smaller denominators were more effective when the denominators were geographically close.

Social proximity. Social proximity pertains to the perceived similarity that a person feels to a social group, irrespective of whether the group is cultural, family-based, friends, professional, or other (Teigen 2005). The perceived similarity between the individual and the group can affect people's risk judgments (Brown et al. 1992), with higher risk perceptions when people can relate to the population of the threat (Rothman et al. 1999).

Carvalho et al. (2008) showed that greater cultural similarity, an aspect of social proximity, with the origin of a food-contamination threat, increased risk perceptions and intentions to engage in preventative behaviors, especially when personal relevance for the risk was low. However, they also found that cultural proximity backfired (i.e., risk was assessed as higher the less culturally similar its origin) when personal relevance was high.

Social proximity relates to how similar another person is to oneself. Raghubir and Menon (1998) demonstrated that people believe that their best friend (most similar) is perceived to be less at risk that an average undergraduate (less similar) who, in turn, is perceived to be less at risk than the average person (least similar).

Knowing someone with a disease can also affect social proximity, but it has not reliably been shown to reduce self-positivity in estimates of risk. Blalock et al. (1990) found that individual whose close friend or sibling underwent cancer treatment was more realistic about the likelihood of contracting cancer. Experience may also lead to perceptions of higher risk for others if the self-positivity bias is due to people lacking sufficient information about others and failing to consider their circumstances (Regan et al. 1995). Consistent with this argument, Weinstein (1980) asked students to generate a list of factors that would increase or decrease their chances of obtaining specific positive and negative future outcomes. A second group of students who read these lists subsequently became significantly less optimistic about their own chances with respect to negative outcomes.

Weinstein (1980, 1987; see also Weinstein and Lachendro 1982) used a correlational approach to test the effects of experience on risk perceptions. He used a range of positive and negative life events (including having a drinking problem and heart attack) to assess the influence of past experience on self-positivity and found no correlation between them. Weinstein and Lachendro (1982) provided detailed, personalized information about the risk status of five other students and showed a lower level of the self-positivity bias than others who did not see such information. Another way in which the self-positivity bias was attenuated in their study was when the respondents were asked to imagine that they were the typical same-sex student. Note that in both these experimental conditions, the respondent has not been provided with an overall base rate, but can bring to mind a specific person or persons who they are similar to (individuating information), and presumably uses the information about the individual to visualize that the events happening to the individual could also occur to them.

Burger and Palmer (1992) asked undergraduate students who experienced the 1989 California earthquake to estimate their own and others' (average undergraduate at the same school and average person) likelihoods of being hurt in a natural disaster (e.g., earthquake, flood, and storm). Their results showed that the students did not show self-positivity when they were asked these estimates within 3 days after the earthquake, but when they were asked 3 months later, self-positivity returned. Thus, the effect of experience appears to be contingent on the temporal proximity of an event.

van der Velde et al. (1994) asked four different samples that differed in their a priori actual levels of HIV risk to estimate their risk of HIV infection: general population, heterosexual subjects with multiple private partners, gay men with multiple partners, and visitors to a STD clinic who had engaged in prostitution contact. Only the group of visitors to the STD clinic who reported having prior experience with an STD estimated themselves at higher risk than those who did not have such prior experience and were less prone to self-positivity, possibly reflecting their actual higher level of risk. All other groups displayed self-positivity.

Probabilistic proximity. Trope et al. (2007) reason that a low probable event is seen as more distant than a high probable event, and that increasing probability of an event lowers the "psychological distance" between oneself and that event. This implies that one can relate more to high rather than to low probability events.

Similarly, Kahneman and Varey (1990) posit that high probability events are perceived as more proximal than low probability events, and thus act as a direct influence upon perceived risk.

10.11 De-biasing Top-down Strategies

Based on the above literature, base rates that are constructed using socially and geographically proximate populations and framed in terms of being closer in time are more likely to be attended to than those based on more socially distant, far populations. Beyond reconstructing base rates, one can also reframe base rates to make them more likely to be attended to. In fact, when risks are low, and cannot be probabilistically made higher, this may be the only managerially actionable route to explore.

Reframing base rates: Halpern et al. (1989) assert that very few people understand the properties of numbers, and, therefore, it is important to understand whether consumers process this information accurately, whether its format and frame affect their judgments, and whether it is assimilated into their risk estimates. Specifically, Halpern et al. (1989) showed that respondents ignore the format in which numerical information is provided and make judgments based on the absolute magnitudes of the number provided. The frame "100 % greater" was perceived to mean "twice" as large, and "200 % greater" was perceived to mean "twice" as large as well! Halpern et al. (1989) also showed that the unit of measurement of magnitude information was ignored: "4.15 times greater" was perceived to be the same as "415 % times greater" rather than the appropriate "315 % times greater." In an incomprehensible twist attesting to people's difficulty in processing numbers, Halpern et al. (1989) went on to demonstrate that even though "4.15 times" and "415 %" are judged to be equivalent, 415 % is perceived to be a greater risk of death than 4.15 times because it has a higher magnitude! Consistent with these results, Raghubir and Menon (1996) show that counter-biasing base rate information is more effective when the frequency is worded as an actual number vs. a percent. Their results suggest that respondents are more likely to infer "1 out of 5" as being lower in magnitude, and, therefore, more effective at reducing the overreport of socially desirable behaviors than "20 %." Even simply reframing a risk as 1/100 is more effective at persuading people that they have a higher risk than framing the same risk as 10/1,000 (Raghubir 2008).

10.12 Overall Model of Risk

While there are multiple ways in which the two routes, bottom-up and top-down, can be combined, one route is to incorporate the base rate as the constant (α) of the bottom-up model. This is the proposed model set forth in Fig. 10.1.

10.13 Consequences of Risk Estimation

The question is how do estimates of risk translate into the consequences that pharmaceutical companies, public policy officials, and consumer welfare groups would like to see? These would include the decisions to engage in preventative actions to prevent a disease occurring, seek medical treatment, start a medical regimen, and continue with it. These behaviors could lead to faster diagnosis and treatment, consumers engaging in more preventative behaviors, more frequently, and reducing sickness and the costs associated with disease to medical establishments, society, and the economy, to say nothing of the individual and their social circle. These behaviors may also lead to the overuse of prescriptions, the greater likelihood of undergoing costly treatments, waste of medical resources, and consumer anxiety due to hypochondria. Some of the consequences of biased over- and underestimation of risk are laid forth in Fig. 10.1.

One preventative behavior that has been studied is consumers' proactive willingness to get screened: e.g., have a pap smear or mammogram. The Vagisil Women's Health Center conducted a study among women for who it is recommended to have an annual pap smear. They found that 28 % did not with the most common reason cited being that they did not think it was necessary as they did not have any health problems (Society for the Advancement of Education 2003).

It is widely accepted that high perceived risk leads people to engage in preventive or corrective behaviors that seek to reduce that risk (Luce and Kahn 1999; Morris et al. 1994; Raghubir and Menon 1998; Rogers 1975, 1983; Weinstein 1993) and that people's responses to precarious situations are dependent upon the perception of their own risk (Weinstein 2007). A meta-analysis found that people's risk judgments of a disease motivated their actions toward vaccination (Brewer et al. 2007). Kuttschreuter (2006) explored several psychological determinants that lead to people's behavioral intentions toward a risk and found that people's perceived risk strongly determined their risk avoidance.

However, perceptions of risk do not always follow through to behavior. Perceived control over the disease moderates the link. Perceived control relates to both the perceived controllability of the disease and preventive behaviors—events that are not within one's control are less likely to implicate one's self-esteem, and are, therefore, more robust to biases such as self-positivity (Lin et al. 2003). Further, unless a disease is perceived to be controllable, patients may not wish to see the doctor to have it cured. To investigate this possibility, Raghubir and Menon (2005) examined that while the mere presence of the symptom "thoughts of suicide or death" in a depression inventory led to perceptions of lower risk, it also led to perceptions of greater controllability over depression—for exactly the same reason—it was extreme and unambiguous. Thus, its presence was a double-edged sword that could only be leveraged with a relatively simple contextual manipulation: including "None of the above" as an option on the inventory. The mere presence of the "None of the above" option served as a signal in line with Gricean norms of conversation that the mere presence of any of the symptoms on the

inventory was a reason for respondents to update their perceptions of risk. This finding led to a simple and straightforward recommendation to those interested in getting consumers to accept higher risk: highlight that *any* of the symptoms mentioned could place them at risk.

10.14 Concluding Thoughts

The goal of this chapter was to present an overall model of how consumers assess risk and the biases that could creep into the process. The thesis was that understanding the process used to construct a risk estimate and identifying the source of the bias would present managerially actionable ways to de-bias risk estimates, irrespective of whether they were over- or underestimates of risk. Prior literature in the domain of risk perception was reviewed in the context of the presented model. However, in this section, we conclude with some thoughts on the open questions that remain unanswered in this field. Some of these are summarized below.

10.14.1 Symptom Typology

A typology of symptoms and how they could affect the manner in which symptoms are aggregated into a bottom-up risk estimate has only just begun (Raghubir and Menon 2005). There is a genre of physiological health problems that are diagnosed using self-reported psychological inventories. Besides depression, these include alcoholism and the attention-deficit syndrome (ADD). Alcoholism is defined by Alcoholics Anonymous as allergic physiological reaction to the consumption of alcohol with the consequence of an inability to stop drinking once the first drink has been consumed (Alcoholics Anonymous World Services, Inc., 1998). ADD is another psychological disease with a physiological basis, relying on self- and other-inventories. These inventories invariably rely on a set of behaviors characteristic of the malady. In the context of alcoholism, binge drinking would be a behavior with extreme consequences that is often used in a self-diagnostic inventory together with a behavior such as daily drinking which has less extreme consequences. Behaviors associated with alcoholism are unambiguous, but differ in terms of their extremity. On the other hand, behaviors associated with ADD differ in terms of their ambiguity, but are less extreme. Examining whether the effect of including/excluding different behaviors from self-diagnosis inventories replicates to these contexts would help disentangle whether it is the extremity of the consequences of a behavior, its lower likelihood of being engaged in, or its relatively lower ambiguity that affects perceptions of risk.

Other diseases also rely on self-diagnosis at an initial stage. For example, the symptoms of Type I diabetes include “increased thirst and urination, constant hunger, weight loss, blurred vision, and extreme tiredness.” Note that these

symptoms are not unlike the ambiguous symptoms of depression. Type II diabetes is characterized by "feeling tired or ill, frequent urination (especially at night), unusual thirst, weight loss, blurred vision, frequent infections, and slow healing of sores. The symptoms of type 2 diabetes develop gradually and are not as noticeable as in type 1 diabetes" (http://my.webmd.com/content/article). Notably, the list omits "tingling hands and feet," a symptom that is less ambiguous and shares many of the characteristics of the "thoughts of suicide/death" symptom in the depression inventory (i.e., it has high causal clarity, low frequency, is a present/absent event rather than a state, etc.). This example also highlights the intriguing possibility that the interpretation of the symptoms may itself be contingent on actual demographics (or feelings or base rates) that are the α of the bottom-up process.

Further, it is possible that the detection potential of a signal is contextually determined. It is a function of the other signals that surround it as well as its own innate ability to predict. The concept that signals vary as a function of their *degree of existence* is conceptually similar to STD's "threshold of detectability." The degree of existence of a symptom is an innate aspect of a signal, but the manner in which it is perceived to be informative is again contextually determined. The consistency between an event occurring and how frequently it is expected to occur affects the perceived strength of a signal. But, as the expectation of occurrence is itself a function of whether the event is a state of being or a specific event, specific events are perceived to be stronger signals than are states of being.

10.14.2 Interactive Effects of Proximity

The effect of personal relevance on risk perceptions is nuanced. Prior research on persuasion suggests that personal relevance of the risk might activate a variety of defense mechanisms to protect the self when the individual's safety and health are threatened (Brown and Smith 2007; Kiviniemi and Rothman 2006; Leffingwell et al. 2007; Liberman and Chaiken 1992). For example, Freeman et al. (2001) found that smokers exposed to antismoking videos responded with a significant amount of defensive processing, including information derogation. Therefore, greater proximity may not always lead to perceptions of higher risk and may in fact lead to the well documented inverse U-shaped function where risk perceptions increase as the level of proximity increases and then reduce as it becomes too close for comfort.

The effect of geographic proximity may be contingent on social proximity, and other dimensions of proximity may also interact. Specifically, when geographical proximity to the origin of the risk is high, consumers perceive a greater risk to themselves (Fischhoff et al. 2003). When the risk is close by, the closer its social origin, the higher should be perceptions of risk. However, when the risk is geographically distant, then unless the risk is high at an absolute level *and* socially proximate, it would be difficult for people to imagine themselves at risk.

10.14.3 Cost/Benefit of Seeking Treatment (Psychological, Social, Financial)

Future research is urged to examine the effects of the costs and benefits of seeking treatment as a function of individual differences and contextual characteristics of a disease. For example,

1. Hypochondriacs/treatment-averse: How does one reduce the cost to a health care system from the former and encourage the latter to seek help?
2. Socially fashionable/stigmatized conditions: How does one reposition a stigmatized disease as one that needs treatment. Good examples of such diseases include those that are psychological and considered a weakness, as well as those that invoke private behaviors, such as STDs.
3. Role of controllability/curability: What is the role of the controllability and curability of a condition in the judgment for a person to accept risk and make a decision to seek diagnosis and treatment?
4. Presence of treatment and effectiveness of it on risk assessment: How does the mere presence of alternate treatments and options as well as their perceived efficacy affect consumers' judgments to estimate their own risk and engage in preventative behaviors.

10.14.4 Using the Two Types of Risk Estimation Methods at Different Stages

Finally, an interesting avenue for future research would be to examine when and how the two processes of top-down and bottom-up risk estimation are combined. Do different people use different methods? Are different methods used for different diseases? Or is it possible that there is a two-stage process such that there is a non-compensatory selection (identification) of symptoms and risk factors followed by a compensatory integration of identified symptoms that are then combined with (conditional) base rates to estimate risk?

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Chapter 11
Efficacy Expectations and Adherence: Evidence of Consumer Biases and Heuristics in Pharmaceutical Marketing

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Abstract Pharmaceutical non-adherence is a major issue in both the United States and worldwide. In fact, lack of medication adherence has been called "America's other drug problem." It is estimated that globally only about 50 % of patients take their medicines as prescribed, and in the United States the annual cost of poor adherence has been estimated to be approximately $177 billion. In this chapter, we cull from the vast body of work in consumer behavior those theories of consumer processing that are directly relevant to this behavioral problem. Although many factors influence (non)adherence to medicines, we focus our chapter on *perceived efficacy* since a consumer's perception of poor product efficacy is one of the primary reasons for non-adherence with a particular medicine and a major cause of brand switching. We identify the biases, heuristics, and lay theories consumers use to infer and judge pharmaceutical product efficacy at two primary stages of the evaluation process: pre-consumption efficacy expectations that drive initial adherence and post-consumption efficacy judgments that drive continued adherence. For example, consumers employ a no-pain-no-gain rule of thumb when judging product efficacy such that products with stronger side effects or bad taste are judged more effective than those without. Given the detrimental consequences of non-adherence in terms of health risks to consumers and losses for the pharmaceutical industry in general, we suggest that efforts to enhance efficacy perceptions are key in creating value for all constituents in the pharmaceutical marketing chain—from manufacturers to end users.

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11.1 Introduction

Given the growing importance of health and well-being in consumers' lives, pharmaceutical companies are held to particularly high standards of performance—even higher than those in other industries (Turett 2005). Such expectations, though justifiably high, make customer acquisition and retention—two paramount goals of marketing strategists—especially challenging. This challenge is perhaps most obvious in the compelling evidence in both the United States and around the world that patients are not taking their medicines as prescribed. In fact, lack of medication adherence is called "America's other drug problem" (National Council on Patient Information and Education 2007) as it leads to significant and at times unnecessary health problems. The World Health Organization (WHO) estimates that globally only about 50 % of patients take their medicines as prescribed, and in the United States the annual cost of poor adherence has been estimated to be approximately $177 billion. Therefore, it is crucial for pharmaceutical companies to first understand the factors that lead to poor adherence and then devise strategies to alleviate this problem.

We define adherence in the current context as conformity to, or adoption of, marketers' recommendation about medication acquisition (purchase) and correct usage (Bowman et al. 2004). It is important to note that we use the word adherence to stress the importance of consumers' relationship with marketers. We borrow from the medical pharmacology literature in distinguishing the subtle meanings between patient adherence and patient compliance. The original concept of compliance connotes a one-way relationship whereby the provider chooses the therapy and specifies, directs, or exhorts the patient to proceed as directed (Tilson 2004). Decades of clinical pharmacy practice have given way to a new social contract of patient adherence, which acknowledges that the patient is a partner in the decision-making process. Similarly, we adopt the term "consumer adherence" in recognition that the consumer is active in the search and evaluation of pharmaceutical remedies, and a primary decision maker in their purchase and consumption. For these purposes, adherence can be thought of as a process whereby consumers accept influence in the hopes of gaining specific rewards (e.g., health benefits) or avoiding specific detrimental effects (e.g., suffering from an illness).

Many factors influence (non)adherence to medicines. These include medication-related, patient-related, prescriber-related, pharmacy-related, and condition-related factors (National Council on Patient Information and Education 2007; Briesacher et al. 2008; see Fig. 11.1).

As such, poor adherence is not only related to patients failing to take their medicines as directed, but also to a variety of factors related to social-, economic-, medical-, and policy-related issues that contribute to the problem of non-adherence. Figure 11.1 presents a selection of prevalent issues under each factor.

Although these issues are equally important in reducing medicinal non-adherence, we focus exclusively on patient-related factors in this chapter. A survey commissioned by the National Community Pharmacists Association (NCPA) found a major

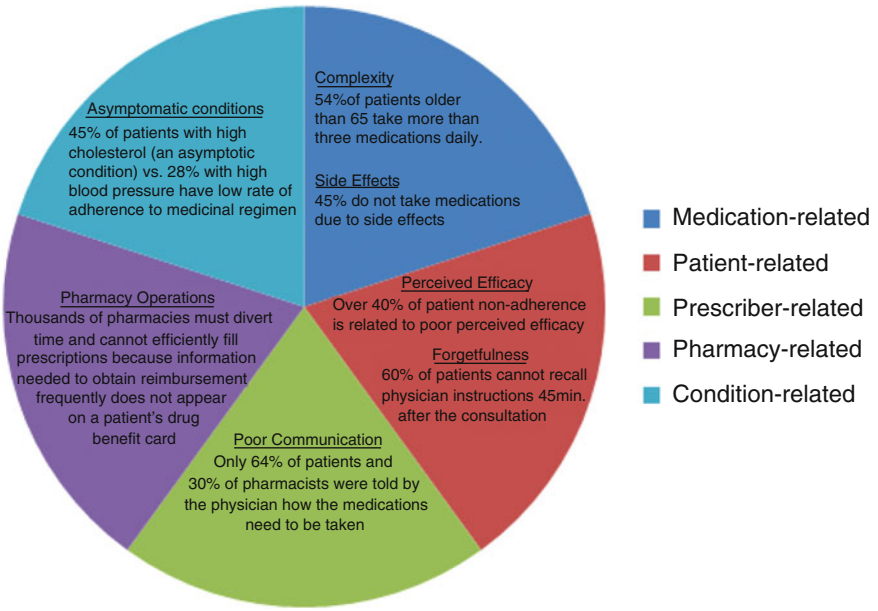

Fig. 11.1 Factors that lead to poor adherence

disconnect between consumers' beliefs and their actual adherence behaviors (National Council on Patient Education and Information 2007). For example, 3 out of 10 consumers had stopped taking a medicine before the dosed supply was finished and almost one-third of consumers had not even filled a prescription they were given. Industry studies like this one provide the first step by gathering statistics that demonstrate the discrepancy between patient beliefs and adherence behaviors. However, what is missing to date is an industry-specific systematic study of the underlying consumer processes that drive this discrepancy. Our goal with this chapter is to take the first step in this direction by culling from the vast body of work in consumer behavior those theories of consumer processing that are most directly relevant and applicable for this pharmaceutical-specific behavioral problem. Further, we focus our chapter not on all possible patient-related factors, but specifically on *perceived efficacy* for two fundamental reasons: (1) perceptions of poor product efficacy is one of the primary reasons for non-adherence with a particular medicine (Berg et al. 1993), and (2) over 40 % of patients switch brands and choose alternative medications for any specified condition due to perceptions of poor efficacy (Rees 2006). Thus, efficacy judgments are significant drivers of patient health and well-being and brand health and success.

Importantly, poor efficacy perceptions can influence consumers' medication choices not only after they begin a medicinal regimen and have direct experience with the medication, but also prior to use (when they consider the medication as a

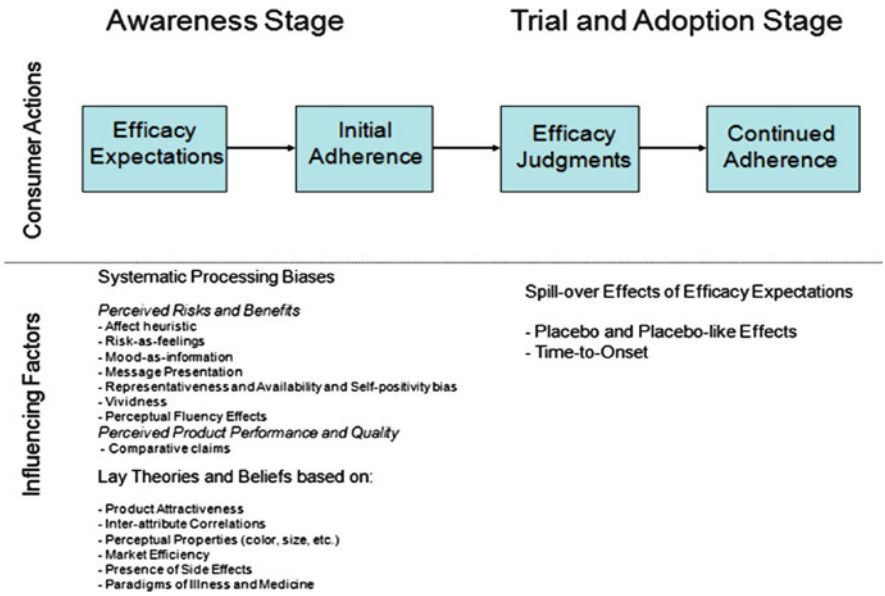

Fig. 11.2 Efficacy perceptions and adherence at two primary stages of the evaluation process

solution for their ailments in the first place). Thus, efficacy perceptions affect consumer behavior at two primary stages of the evaluation process: first, at the awareness stage, when consumers are exposed to information about the medication for the first time, estimate its effectiveness, and decide to initiate usage (i.e., initial adherence), and second, at the trial and adoption stage following initiation of the medicinal regimen, when they are able to judge its effectiveness (i.e., continued adherence). Adherence at the second stage entails proper utilization of medication, such as adherence to the recommended dosage and consumption duration (see Fig. 11.2).

11.1.1 Stage 1: Awareness

At the awareness (acquisition) stage, adherence is determined by the extent to which pharmaceutical marketers are able to persuade consumers to inquire about a specific medication or treatment (e.g., ask their physicians about the medication) and begin usage. Such adherence, however, is driven by medicinal *efficacy expectations* that, as we discuss later, are ultimately formed on the basis of heuristics and biases (depending on the way the product and information thereof is conveyed). Naturally, pharmaceutical marketers seek to increase the adherence rate by heightening consumers' efficacy perceptions via direct-to-consumer (DTC) advertising.

At this initial stage of medication assessment, consumers often attend to the risk and benefit information and make trade-offs between attributes. While traditional

expectancy models (e.g., expected utility theory; Ajzen and Fishbein's (1980) theory of reasoned action; Becker's (1974) health belief model) propose that people rationally weigh the risks and benefits inherent in a decision and act accordingly, evidence from both academia and practice suggests that oftentimes this is not the case. Specifically, rational decision-making models assume that consumers have the motivation, opportunity, and ability to exert sufficient cognitive effort to make optimal decisions. However, given the sheer number of decisions and evaluations made on a daily basis, consumers have inevitably formed an anecdotal toolbox of lay theories about their environment, meshed with a variety of heuristics and biases used to guide their decision-making (e.g., choosing a medication and judging its efficacy). Thus, rather than assessing the risk and benefit information in a systematic manner, many consumers utilize it in ways that lead to biased information processing, which results in inferences, both plausible and unmerited, about medication and treatments (Menon et al. 2003; Cox et al. 2006). Therefore, one of our objectives in this chapter is to discuss the different types of heuristics consumers utilize and show how they drive consumer efficacy expectations of pharmaceutical products at the awareness stage, resulting in initial (non)adherence. To achieve this goal, we illustrate how consumer expectations of medicinal efficacy are influenced by biases and heuristics that originate from (1) the manner in which risk and benefit information is perceived and (2) lay theories that consumers hold about their surroundings, such as beliefs about product attractiveness, inter-attribute correlations, market efficiency, and the like.

Before discussing the next stage, it is important to note that adherence during the awareness stage may vary with whether the medication is over-the-counter (OTC) or prescription (Rx). For OTC medications, consumers tend to make purchase decisions themselves, whereas for prescription medication, they also rely on physicians for guidance. Thus, in the latter case, marketers are presented with a dual task of raising efficacy expectations of physicians and consumers alike; indeed, a discrepancy between product efficacy expectations of a consumer and his/her physician may affect consumers' adherence to physician recommendations. As such, all else being equal, influencing consumers' expectations and stimulating initial adherence to OTC (vs. Rx) medication may be easier as there is no mediating individual between the marketer and consumer (Creyer et al. 2001; Hoy 1994). In this chapter, we focus on the factors that affect efficacy expectations and consequences such as non-adherence (e.g., in terms of foregoing a beneficial treatment) that apply to both OTC and Rx medications; readers should note, however, that other variables, such as physician–patient relationships and physicians' awareness of the medication remain outside the scope of this chapter but nonetheless may additionally affect adherence.

11.1.2 Stage 2: Trial and Adoption Stage

At the second stage—trial and adoption—efficacy perceptions influence whether consumers will adhere to their medicinal regimen as they *experience* the positive health effects of the medication; adherence at this stage is marked by proper usage

of the medication. Several factors may influence consumer adherence to medicinal regimen including salience/mindfulness, the cost and benefits associated with adherence behavior, cues from advertising and distribution, perceived negative effects of non-adherence, and perceptual properties of medications (Bowman et al. 2004; Coffield and Buckalew 1988). Importantly, when consumers misuse a medication as a result of suboptimal product inferences, they are unlikely to reap its full benefit and consequently, the medication itself becomes less effective. This experience negatively affects consumers' efficacy judgments that, in turn, lead to further non-adherence.

The aforementioned chain of events has significant consequences; after all, only about half of consumers who receive a prescription continue to take the medication as directed 1 year later, and the loss in sales due to un-refilled prescriptions is estimated to be between $15–20 billion in the United States annually (Loden and Schooler 2000). Considering that medicinal efficacy is actually a function of how well consumers follow the prescription (Sabate 2003; Wosinska 2005), the efficacy–adherence pairing constitutes a potential "vicious cycle." In order to facilitate adherence to the medicinal regimen, consumers must make positive efficacy *judgments* (and not only form positive efficacy expectations). Importantly, however, efficacy judgments are not fully independent of efficacy expectations. Rather, "spillover effects," or the biases on efficacy judgments resulting from one's prior expectation regarding how well a medicine should work, play an important role in medicinal adherence.

Next, we illustrate a series of biases, heuristics, and lay theories employed at the two aforementioned stages of the consumer evaluation process that ultimately determine (1) how consumers choose medications, (2) how efficacious they perceive the treatment to be, and (3) how product efficacy perceptions translate into adherence behavior.

11.2 The Awareness Stage: Factors That Affect Efficacy Expectations

Adherence at the awareness (acquisition) stage is marked by consumers inquiring about a specific medication or treatment and beginning to use the product. Such adherence is contingent on *efficacy expectations* that are often formed on the basis of (1) how product information, such as the risks and benefits, is perceived by consumers and (2) lay theories and prior knowledge. For example, a multitude of consumer judgment biases influences the way consumers perceive risk and benefit information. These biases as well as lay theories, in turn, affect efficacy expectations and adherence (see Fig.11.3). We begin with a discussion of systematic processing biases that influence efficacy expectations and then turn our attention to the role of lay theories and prior knowledge.

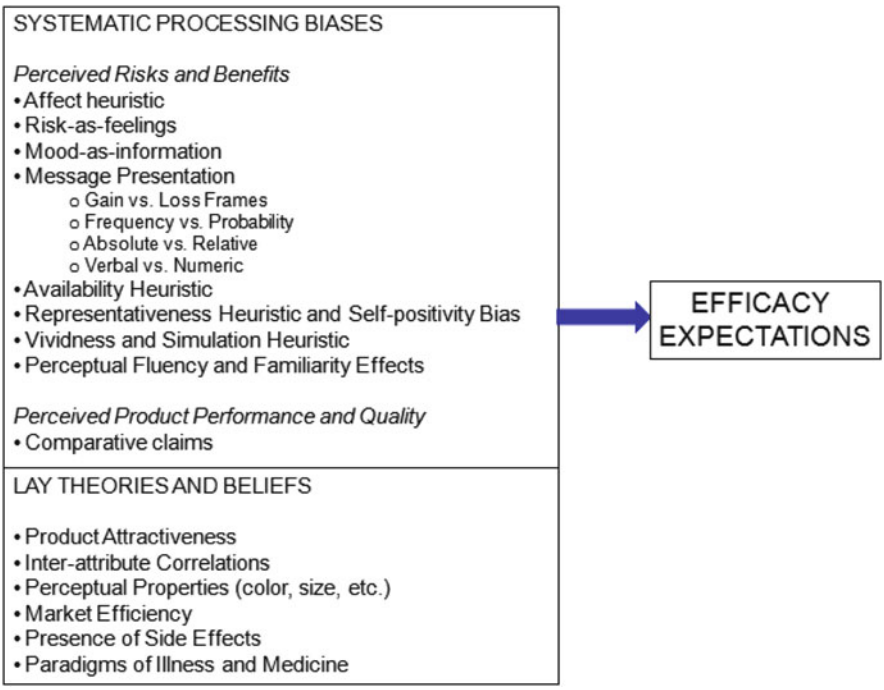

Fig. 11.3 Factors that affect efficacy expectations at the awareness stage

11.2.1 Systematic Processing Biases: Perceived Risks and Perceived Benefits

Consumers may intend to pay equal attention to benefits and risks and make an informed judgment; however, the way the information is presented may make certain information more salient, influencing perceptions by leading to usage of heuristics and causing biases in decision-making. Further, the incidental context in which the consumer makes judgments about a medication's efficacy (e.g., consumers' mood) may influence efficacy expectations.

11.2.1.1 Affect Heuristic

When consumers are exposed to information regarding risk and potential danger, they often make decisions based on their instinctive affective reactions (of which they may not be consciously aware). Since easily accessible affective (emotional) impressions are an efficient alternative to deliberate analysis in comprehending risk

information, affect has been proposed as a heuristic cue (Finucane et al. 2000; Slovic et al. 2002): a bit of information that may or may not be relevant input for the decision at hand. The *affect heuristic* suggests that if feelings toward a stimulus are favorable, people tend to judge risks to be low and benefits high (Slovic et al. 2005). In other words, if overall feelings toward a stimulus are unfavorable, people tend to judge risks to be high and benefits low, and the intensity of affective reactions determine the strength of such perceptions. As such, if a consumer's overall emotional response to a drug is favorable, he/she may tend to undervalue risks and overvalue product benefits, such as effective relief of symptoms.

11.2.1.2 Risk-as-Feelings

Similarly, according to the *risk-as-feelings* hypothesis, feelings may arise without any cognitive mediation and reactions based on feelings elicited by risk may depart substantially from reactions based on cognitive evaluations of it; whereas the vividness of imagined consequences coupled with personal experience with adverse outcomes determine people's emotional reactions to risk, these elements rarely affect cognitive assessments (Loewenstein et al. 2001). Other studies have found that in cases of intense affective responses, people may be unaffected by probability information altogether (Rottenstreich and Kivetz 2006; Rottenstreich and Hsee 2001; Kraus et al. 1992) because feelings of fear are more sensitive to the possibility rather than the probability of negative outcomes (Loewenstein et al. 2001). This would suggest that if a possible side effect of using a drug is loss of hearing, for example, and this information evokes extremely negative feelings among message recipients, evaluations of the product and perceptions of high risk will not substantially differ if the adverse reaction occurs in 1 or 10 % of users. In this case, consumers would undeniably opt against this medication.

11.2.1.3 Mood-as-Information

Even under circumstances when affect is the by-product of an event or stimuli other than the one under evaluation, people tend to misattribute their feelings to the product (mood-as-information; Schwarz 2002), and make judgments accordingly. For example, Johnson and Tversky (1983) found that when people read a sad article prior to making risk estimates for potential causes of death, they gave higher estimates than those who read an article that elicited positive affect. In the health domain, Agrawal et al. (2007) demonstrate that when people are in happy emotional states, self-referent health appeals are more effective than family-referent appeals, whereas when people are in peaceful emotional states family-referent (vs. self-referent) health appeals are more effective, suggesting that compatibility between message referent and the self-/other-relatedness dimension of the emotion affects message effectiveness.

Other research, however, provides evidence that speaks against these theories. For instance, Cox et al. (2010) found that positive mood (e.g., media-induced affect) actually elicits more nuanced processing of information. In their study, participants in the neutral-mood condition were only influenced by side effect severity information whereas those in the positive-mood condition used information about both frequency and severity in forming their behavioral intentions. When side effects were declared severe, participants did not prefer a product with more frequently occurring side effects and perceptions of risk, rather than product efficacy, drove behavioral intentions. However, when side effects were declared mild—which is often the case for many OTC and prescription medications—and participants were in a positive mood, higher side effect frequency actually led to greater perceptions (expectations) of product efficacy. Undeniably, such efficacy perceptions are likely to have downstream effects (e.g., asking a doctor about initiating a regimen, seeking additional information from other sources, and purchasing the product).

11.2.1.4 Message Presentation

Gain vs. loss frames. Investigating the effect of gain and loss frames on people's reaction to product risks, Cox et al. (2006) demonstrates that exposure to gain-framed (vs. loss-framed) messages (e.g., people who get [don't get] the hepatitis B shot are gaining [losing] a chance to protect themselves and the ones they love) increases consumers' tolerance for temporary product risks (e.g., temporary skin rash from using a lotion). Interestingly, however, regarding the possibility of more permanent, serious risks (e.g., contracting Hepatitis B) people exposed to gain-framed (vs. loss-framed) messages appear to exhibit considerable caution (e.g., more likely to get a shot of vaccination).

Frequency vs. probability. Research has shown an interesting connection between the affect heuristic and message framing. In a study on clinicians' responses to risk information, Slovic et al. (2000) demonstrated that when asked to evaluate the risk of a mental patient committing a crime within 6 months of release from a hospital, those presented with frequency information (e.g., "of every 100 patients similar to Mr. Jones, 10 are estimated to commit an act of violence") vs. those presented with percentage information (e.g., "Patients similar to Mr. Jones are estimated to have a 10 % chance of committing an act of violence") judged the patient to be more dangerous. Through subsequent studies, these results were attributed to the idea that frequency framed information elicited affect-laden imagery (e.g., envisioning many violent patients) whereas probability-framed information resulted in less emotional images (e.g., of one individual who is unlikely to commit a crime against others). In another study, participants rated a disease that kills 1,286 people out of 10,000 as being more dangerous than one that kills 24.14 % of people (Yamagishi 1997).

Siegrist (1997) used an alternative measure—willingness to pay—to study the effects of incidence rate format. Subjects were questioned about their willingness to pay for an improved medication (a safer alternative); and risks associated with the

old and new medicine (the chance of dying from the drug) were formulated as either a frequency or a probability (e.g., 0.0006). Results showed that those in the high-risk level/frequency format condition were willing to pay a much higher price, not only than those in the low-risk/frequency format condition but also than those in the high-risk level/probability format condition. Interestingly, there was no differential effect on willingness to pay between different risk levels for the probability format. The latter result can be attributed to misinterpretation of risk stated as a probability. After all, people of various educational backgrounds often have difficulty in evaluating numerical information in general (Schwartz et al. 1997; Lipkus et al. 2001; Sheridan and Pignone 2002), although natural frequencies are less likely to be misinterpreted (Gigerenzer and Hoffrage 1995; Hoffrage et al. 2000; Cosmides and Tooby 1996). The results can also be attributed to the fact that, as described by the affect literature, frequency information induced stronger emotional responses and triggered vivid images of death.

Considering that research on decision-making has shown that small probabilities tend to be underestimated (Kahneman and Tversky 1979), though they may be overestimated if they are affect-laden (Rottenstreich and Hsee 2001), people's (mis) interpretation of verbal risk information is of little surprise. Verbal risk presentation is generally conveyed in the form of "very common, common, uncommon, rare, or very rare" (Berry 2006). In the European Union, the European Commission has imposed guidelines to direct such claims, such that, for instance, "common" must refer to adverse side effects that occur in between 1 and 10 % of people who take the medicine (Berry 2006). Although in the United States there are no official FDA guidelines for the use of frequency descriptors, research shows that their use is comparable to that in the EU and that their numerical meaning is well understood among drug marketers (Cox et al. 2010).

While the frequency and severity of side effects may be well understood among pharmaceutical marketers, research suggests that this fluency is absent among the general consumer population. In both the United States and the European Union, lay people tend to overestimate risk (Cox et al. 2010; Knapp et al. 2004; Berry et al. 2002, 2003) and conventionally interpret adverse reactions categorized by "common" as occurring in 45–50 % of cases; physicians, interestingly, also misinterpret such language as around 25 % (Berry 2006). In contrast to comparable numerical descriptors, verbal descriptors have also been shown to correspond to more negative perceptions of the medicine (Knapp et al. 2004), greater perceptions of risk to health, lower satisfaction with the information, and lower intensions to comply (Berry et al. 2003).

Overestimation of the likelihood of side effects, a significant reason for consumers opting to refrain from initiating the use of a particular medicine, is more prevalent when risk information is presented verbally rather than numerically (Knapp et al. 2004). For example, in a study conducted by Berry et al. (2002), the estimated mean probability of experiencing an adverse reaction was over 3 times greater for those given a verbal descriptor of side effects than those given a numerical value (64 % vs. 20 %, respectively) and verbal descriptors also corresponded to perceptions of increased severity.

Moreover, positive and negative framing of information also have differential effects on interpretation and subsequent behavior (e.g., McNeil et al. 1982). Although results may or may not be attributed to ensuing positive affect, positively framed side effect information (99 % safe) vs. negatively framed effects (1 % chance of adverse health consequences), were found to result in greater consent to a treatment when the outcome was associated with a relief, such as loss of pain (Gurm and Litaker 2000).

Finally, Chandran and Menon (2004) showed that when health-related information is presented in a day (vs. a year) format (e.g., "every day [vs. every year] a significant number of people fall prey to Mono"), risks appear more proximal and concrete, resulting in increased self-risk perceptions, and enhancing effectiveness of risk communication.

Absolute vs. relative. Many studies have confirmed that information presented in relative terms and absolute terms elicits different responses (e.g., Halpern et al. 1989; Stone et al. 1994; Berry 2006; Malenka et al. 1993); with regard to risk reduction—a type of product benefit—for example, the relative format has greater effect on judgments, produces higher ratings of satisfaction and perceived effectiveness, and leads to the uptake of particular behaviors, to the extent that baseline information (e.g., it is predicted that 10 % of the population will be affected by the disease) is not provided (Natter and Berry 2005).

Malenka et al. (1993) found that when patients had the choice between two equally efficacious medications to treat a hypothetical illness (with an option to indicate indifference), 56.8 % opted for the medication whose benefits were stated in relative terms, whereas only 14.7 % chose the alternative whose benefits were presented in absolute terms irrespective of age, gender, education level, and experience with the medicinal treatment. Thus, it may be that consumers will opt for a new medication that is professed to relieve pain, for example, 50 % faster than the fastest pain reliever on the market, over one that is professed to relieve pain 5 min earlier the fastest pain reliever—assuming that the alternative brand relieves pain in 10 min.

Verbal vs. numeric. In addition to actual benefits, commonly stated information in pharmaceutical commercials, for example, is the number of people who have felt desired effects—quantification of success stories—such as 8 out of 10 people saw results in 1 month. Would consumers prefer a medication that has worked for 8 out of 10 people or for 10 out of 15? The latter, of course, has a much lower success rate (0.80 vs. 0.66), but would consumers' behavioral intentions reflect this information?

Denes-Raj and Epstein's (1994) study suggests that the answer may be "no." They find that when drawing a red jelly bean, individuals often chose to pick from a bowl containing a greater absolute number but a smaller proportion (e.g., 7 in 100) than from a bowl with fewer but greater probability of winning (e.g., 1 in 10). Participants reported having felt that they had a better chance of winning when there were more red beans. Researchers suggested that participants had imagined the numerator while disregarding the denominator, which elicited positive affect (e.g., the affect heuristic) that ultimately drove the decision (Slovic et al. 2005): the numerator effect. Accordingly, adherence at stage 1—namely the decision to acquire a medication and initiate use—depends on biases in message interpretation and the reliance on heuristic cues.

11.2.1.5 Availability Heuristic

Tversky and Kahneman (1974) identified the availability heuristic which is used in probability judgments, such as the estimation of the likelihood of an event's occurrence. The estimation is based on the ease with which one can recall examples of the event, such that when examples are readily recalled with little difficulty, the likelihood of the event is perceived to be high; accessibility experiences affect subsequent judgment (for a review, see Schwarz et al. 2009). For example, Wanke et al. (1997) found that perceived ease of recall has similar effects to actual ease of recall. When participants in a study were asked to list one pro or con argument for driving a BMW, participants generating the pro argument evaluated the brand more favorably since both the task and the actual accessibility of information was easy; those generating the con argument evaluated the brand less favorably. However, for participants who were instructed to list ten pro and con arguments, expected and actual ease of retrieval was low and the enumeration of reasons has little effect on subsequent evaluations.

In line with the literature that demonstrates the influence of the availability heuristic on judgment, Gana et al. (2010) found that women who are reminded of their family history of a certain disease (e.g., breast cancer) are more likely to perceive themselves as vulnerable to the disease compared to those who are not primed by family history. Similarly, Katapodi et al. (2005) found that people's risk assessments of breast cancer were disproportionately based on experiences with an abnormal breast symptom, experiences with affected family members and friends.

In DTC advertisements, pharmaceutical marketers must be aware of factors that may elicit use of the availability heuristic. For example, while common questions directed at consumers such as "why wouldn't you use [so-and-so drug]?" or "why not ask your doctor about…?" are intended to elicit intentions to seek product benefit information, they may have inadvertent consequences. That is, consumers may be readily able to generate one reason against trying the medication or asking the doctor for further details about risks of taking the medication, and the ease with which they generate such arguments may lead to greater confidence in opting against the medication (non-adherence at the awareness stage)—an impediment to moving on to the trial and adoption stage.

As another example of the effect of the availability heuristic, research shows evidence of bias in judgments depending on the order in which product risk and benefit information is provided (Bergus et al. 1998). Although for high-risk medical interventions (e.g., a bypass) people appear not be influenced by the order in which such information is presented, they are indeed influenced by the order in low-risk medical interventions (e.g., take a pill). In a study, Bergus et al. (2002) found that participants evaluating a low-risk therapy (e.g., Aspirin regimen) were affected by order effects, such that those receiving risks after the benefits formed more unfavorable impressions of the treatment and were less likely to consent. As information that is received recently is more available in memory (Deese and Kaufman 1957), risk information that is provided after the benefit information is likely to drive consumers' judgments.

11.2.1.6 Representativeness Heuristic and Self-Positivity Bias

The representativeness heuristic suggests that consumers make predictions about future outcomes based on the target's similarity to an exemplar, a schema, or a category (Tversky and Kahneman 1974). In the case of processing risk information (the latter type), people assess the similarity of the information to a mental representation, and the more similar the information is to the representation, the higher the perceived chance of an event's occurrence (e.g., contracting a disease). For instance, Menon et al. (2002) found that cues that make perceptions of contracting a disease more likely (e.g., when frequent, rather than infrequent, behaviors are presented) increased perceptions of personal risk, and actually reduced the self-positivity bias—in which people perceive themselves as less at risk than another. Notably, presentation of infrequent behavior, vs. no risk behavior, has worse effects in terms of risk estimates and behavioral intentions since the chances of contracting a disease seemed remote. Moreover, as the number of frequent risk behaviors presented increased, the self-positivity bias decreased (a longer list translates into more concern and intentions to get tested); however, as the number of infrequent risk behaviors presented increased, the self-positivity bias also increased. In the latter case, people reported higher intentions to get tested when they were presented with a short, vs. long, enumeration. Interestingly, they also found evidence of another bias—namely that people believe that infrequent behaviors cause a disease more than frequent ones do. Since both the type and the number of cues act as signals of representativeness, advertisement of vaccinations, for instance, must take account these factors in addition to order effects.

11.2.1.7 Vividness and the Simulation Heuristic

Research has found evidence of the simulation heuristic (Tversky and Kahneman 1974), where simulating (e.g., imagining/visualizing) an event translates into perceptions of greater likelihood that it will ensue. Johnson et al. (1993) demonstrated that people are willing to pay more for airplane travel insurance coverage against death from a terrorist attack than for coverage against death from "all possible causes"—which inherently includes terrorist acts—since the former is much more vivid and easily imagined. Other health-specific research has also suggested that vivid imagery is more effective in conveying warnings (Hendrickx et al. 1989; Hammond et al. 2004).

Although playing up risk, such as adverse side effects, in advertisements is hardly a goal of pharmaceutical marketers, presenting the risk of not consuming a pharmaceutical product (e.g., continuing insomnia, erectile dysfunction) is common. For example, consumers who are encouraged to imagine certain symptoms when receiving product information are more likely to feel susceptible to feeling them, and thus more likely to use the medication. Similarly, rather than merely enumerating product benefits, pharmaceutical marketers may benefit from encouraging message recipients to envision feeling the products' effects.

11.2.1.8 Perceptual Fluency and Familiarity Effects

Perceptions of fluency—the ease or difficulty with which information is perceived—determine perceptions of familiarity, such that fluently vs. disfluently processed stimuli/activities appear more familiar and elicit more positive affective responses (for a review, see Schwarz et al. 2009). As such, people infer familiarity from ease of processing—the latter depending on presentation variables such as exposure duration, high figure-ground contrast, and repetition. Moreover, familiar stimuli, such as information, are often accompanied by perceptions of popularity, liking, and truth. For instance, mere repetition of a product claim has shown to increase ratings of its validity (Hawkins and Hoch 1992; Hawkins et al. 2001; Skurnik et al. 2005). Thus, if consumers are continuously exposed to an advertisement stating how efficacious a medication is, they may eventually believe that it is indeed so.

Interestingly, Song and Schwarz (2009) found that difficult to pronounce stimuli (e.g., food additives) were judged to be more risky and harmful than easy to pronounce stimuli. Additionally, participants rated less vs. more easily pronounced names as more novel. Although the names of medicines are often imagined to contain rare consonants (e.g., "Z"), reliance on familiarity as a heuristic suggests that pharmaceutical medications could benefit from names that are more easily pronounced—to reduce perceptions of risk and perhaps increase intentions to buy. In general, marketers of pharmaceutical products can take advantage of processing fluency effects by presenting medication benefit information in easy-to-process formats (e.g., larger fonts), and risk information in hard-to-process formats (e.g., smaller fonts) to influence efficacy expectations at the awareness stage.

11.2.2 Systematic Processing Biases: Perceived Product Performance and Quality

11.2.2.1 Comparative Claims

Consumers also exhibit bias in evaluating message claims, for instance inferring that a product is superior to all competitors when incomplete comparatives are used (e.g., "Mennen E goes on warmer and drier"; Shimp 1978). In one study of the effects of alternative product claims, such as true statements (e.g., "Temporarily reduces headache pain"), expansions of true claims (e.g., "Complete relief from pain"), and qualified claims (e.g., "Complete relief from pain (pain associated with musculoskeletal inflammation)"), Burke et al. (1988) found that the latter two claims, vs. the former or no information condition, resulted in significantly higher levels of false beliefs about a medicine's effectiveness, lack of side effects, low price, and fast action. Interestingly, with regard to efficacy perceptions, although "true information" vs. no information increased perceptions of a product's performance on the latter three attributes, "true information" about a brand's effectiveness resulted in beliefs that the brand was *less* effective than in the no information

condition. Not surprisingly, expanded claims drove higher performance perceptions than true claims, qualified claims, and no information. However, although qualified claims reduced the potency of such perceptions (e.g., acted as a discounting cue), they still generated stronger beliefs about product performance than true information. Similar results were found with regard to purchase intentions—adherence during the awareness stage of the consumer evaluation process.

Consumers' initial product efficacy expectations often stem from partial comparative advertisements, such that one ad claim affects the interpretation of a subsequent ad claim: copy×copy interactions (Barone and Miniard 1999). For example, if DTC advertisement, Brand A may claim that it is more effective than Brand B, and then subsequently claim that Brand A offers long-lasting relief. Consumers may infer that Brand A offers longer-lasting relief than Brand B does, though such a claim was never made. In fact, if Brand B provides longer-lasting relief, consumers may hold inaccurate product beliefs.

Although various inference strategies may be used (evaluative consistency, schema-based, or probabilistic), Barone and Miniard (1999) propose that the aforementioned phenomenon is the by-product of priming, such that if a directly comparative claim is accepted by a consumer, he/she will hold the target brand's superiority in mind. Given the high accessibility of such thoughts when a noncomparative statement is made, the noncomparative statement will be interpreted accordingly (e.g., subsequent encoding in a prime-consistent manner). Even more so, such effects in partially comparative advertisements are present across numerous product attributes, regardless of whether the attribute in the noncomparative claim is typical or correlated with the attribute used in the direct comparative claim. However, target product users vs. comparison brand users were found to display such effects; the latter was "immune" to copy-by-copy interactions.

Notably, when asked to recall the noncomparative claims, Barone and Miniard (1999) found, in support for the priming effect and bias during claim encoding, that more of the participants incorrectly recalled the noncomparative claim as comparative in the partially comparative advertisement, vs. noncomparative, condition. Pharmaceutical marketers can take this into account, considering that product inferences stemming from DTC advertisement drive product expectations regarding efficacy (in comparison to viable alternatives) and adherence.

11.2.3 Effects of Intuitive Beliefs and Lay Theories on Efficacy Expectations and Adherence

Research suggests that consumers generate if–then linkages in a subjectively logical fashion (Kardes et al. 2004b; Kruglanski and Webster 1996) on the basis of various lay theories—beliefs and intuitions about one's surroundings (Wyer 2004). For example, people tend to deduce that durability is positively related to warranty even in the wake of discrepant information (Broniarczyk and Alba 1994) and that unhealthy foods taste

better than healthy options (Raghunathan et al. 2006), since the underlying intuitions are firmly held. With regard to pharmaceutical products, Roullet and Droulers (2005) found that drugs that were perceived to treat a benign illness were expected to have brief action, low risk, low price, limited side effects, OTC status, symptomatic treatment, and limited efficacy. In another study, consumers perceived effective pain relievers to be quick and more likely to cause aversive side effects (Burke et al. 1988). Thus, consumers rely on various lay theories when they infer the effectiveness of medications, which ultimately determines initial adherence: the decision to choose a particular medication. However, many of the intuitive beliefs have "spillover effects" into the trial and adoption stage; that is, efficacy expectations emanating from many of these lay theories may act as a reference point from which efficacy judgments are made. In this section, we present research findings that demonstrate the effects of the most commonly employed lay theories that would *primarily affect consumer expectations* about a medication's efficacy at the awareness stage. In the following section, we discuss such intuitive beliefs that have the aforementioned "spillover effects," marking the transition from the awareness stage to the trial and adoption stage, where adherence is characterized by proper medicinal usage with regard to dosage and duration.

11.2.3.1 Product Attractiveness

Pharmaceutical executives have noted that pharmaceuticals are lagging behind the consumer industry with regard to packaging (e.g., best practices and innovative solutions). In addition to serving an informational purpose, packaging is a major determinant of brand loyalty: a "tangible manifestation of an emotionally charged relationship to the brand" (Wade and Vrain 2005, p. 114). With the entrance of generics, pharmaceutical executives are now stressing the need for more eye-catching, memorable graphics and original design.

While the intuitive and seemingly indisputable claim that creating aesthetically appealing products is desirable in a competitive industry, research has found evidence of an *attractiveness bias* that suggests that highly attractive products may be, under certain circumstances, perceived less favorably (Batra 2009). When external product information is not available (e.g., brand reputation), consumers are skeptical of the efficacy of products with extremely high, vs. moderate, levels of visual attractiveness; this phenomenon is perhaps the result of a "*too beautiful to be good*" *lay belief* that results in an inverted U-shaped relationship between attractiveness and efficacy perceptions. However, when strong brand information is present, product attractiveness is shown to positively correlate with perceived efficacy. Inferring lower efficacy from attractiveness was also found to be a cognitive process, such that under high cognitive load, people use affect-based processing with more attractive products being perceived to yield better performance, even for weak brands (Batra 2009).

On the basis of the aforementioned findings, whereas lesser known brands would benefit from moderately attractive product packaging to induce perceptions of product efficacy, well known, reputable brands would benefit from attractive and

innovative package design. In fact, the *representativeness heuristic* (Tversky and Kahneman 1974) confirms this suggestion. Consumers may infer, for example, that a generic brands' performance is on par with that of a brand name exemplar if the packaging for the generic is similar to that of the branded good (Kardes et al. 2004b). For pharmaceutical marketers this heuristic has particularly significant consequences; the availability of generic drugs carrying a package design similar to its branded alternative may drive consumers to infer that the generic is equally efficacious, even when package design and efficacy are uncorrelated. Pharmaceutical executives have correctly noted that packaging is steadily becoming a tool to differentiate the product in the marketplace and build brand equity (Wade and Vrain 2005). The aforementioned lay theory is hence crucial for adherence, when consumers estimate the product's effectiveness for the first time and decide to initiate usage.

11.2.3.2 Inter-attribute Correlations

Aside from attractiveness, consumers also hold implicit theories of inter-attribute correlations, such as the positive warranty–quality relationship (Boulding and Kirmani 1993; Purohit and Srivastava 2001) or the price–quality relationship (Rao and Monroe 1989; Broniarczyk and Alba 1994; Dodds et al. 1991; Adaval and Monroe 2002). The latter is particularly pervasive, frequently yielding inferences about product quality on the basis of available price information (Huber and McCann 1982; Johnson 1987, 1989; Johnson and Levin 1985; Bettman et al. 1986; Broniarczyk and Alba 1994; Pechmann and Ratneshwar 1992; Rao and Monroe 1989). Not only do consumers tend to overestimate the price–quality relationship (Kardes et al. 2004b), but also tend to discount objective information that indicates otherwise (Broniarczyk and Alba 1994). Expectations drive consumers to focus selectively on cases that support the price–quality correlation and neglect or debunk nonsupportive evidence, yielding selective information processing, especially as the quantity of information increases (Kardes et al. 2004a).

In the pharmaceutical products domain, Western medicines (e.g., drugs), for instance, are perceived as fast-acting remedies whereas Eastern medicines (e.g., herbal medleys) are expected to have a slower action course (Wang et al. 2010) although this perception is more common among non- and infrequent consumers of herbal products (Carlisle and Shafir 2005). Moreover, Burke et al. (1988) found evidence of perceptions of inter-attribute correlations driven by medication claims. That is, claims about one medication attribute affected beliefs about another medication attribute. For example, claims about a medicine's pain relieving effectiveness resulted in beliefs that the medicine gives faster pain relief (or, on the other hand, quick relief claims resulted in stronger beliefs about its effectiveness in relieving pain). Thus, consumers may infer that a fast-acting medication (given that it is advertised as such) should be more efficacious than one that is perceived as having a slower time to onset. Such beliefs may have adverse consequences for consumers and pharmaceutical companies alike. If efficacy judgments *post use* do not match or exceed the reference point, nonadherence is probable. Consumers may prematurely abandon a prescription altogether

under the premise that it is inefficacious or adjust the regimen at their own discretion, leading not only to dissatisfaction with the product but also to possibly severe health risks. Therefore, expectations of efficacy that are built on one attribute not only determine adherence at the awareness stage but also continued adherence in the trial and adoption stage, as they may "spill over" to affect efficacy judgments post use, as discussed in the trial and adoption phase of this chapter.

11.2.3.3 Perceptual Properties

Besides attractiveness in general, medication's specific properties may influence efficacy expectations. Evidently, perceptions of product efficacy are driven by the physical properties of the product, including size, color, and form (Buckalew and Coffield 1982; Buckalew and Ross 1991; Coffield and Buckalew 1988; Jacobs and Nordan 1979; Sallis and Buckalew 1984). Studies have found, for instance, that capsules are perceived as being more powerful and efficacious than pills (Buckalew and Coffield 1982; Buckalew and Ross 1991) and that larger, vs. smaller, pills are perceived as more efficacious perhaps due to a "bigger is better" lay theory (Blackwell et al. 1972; Buckalew and Coffield 1982).

One stream of research focuses on the effect of color on perceived efficacy of medications to find that consumers' efficacy expectations are based on a drug's color, for both prescription and OTC medications. For instance, Sallis and Buckalew (1984) found that red drugs are perceived to be most efficacious and white drugs the least; in fact, the perceived efficacy of pills in decreasing order was as follows: red, black, orange, yellow, green, blue, and white. Moreover, in terms of therapeutic class, red pills were perceived to target cardiovascular and blood-related systems (Buckalew and Ross 1991) and were classified as stimulants, blue pills were classified as depressors or tranquilizers (Jacobs and Nordan 1979) and beige/orange pill were perceived to target skin conditions (Buckalew and Ross 1991).

The color of pharmaceutical product packaging was also found to have an effect on consumer perceptions. Roullet and Droulers (2005) showed that for pharmaceutical drugs, red, brown, and gray (vs. yellow and green) packages were perceived to be designed for serious illness; brown, red, and orange packages were perceived to require precaution of use (vs. blue, green, and yellow); and that brown and red packages were perceived to be more expensive than orange or yellow packages. In general, products in dark packages (red, blue, and brown) were perceived to act more rapidly, to be more expensive, involve greater side effects and be and more curative than light-hued packages (yellow, green orange, and gray).

In terms of potency perceptions, Roullet and Droulers (2005) found that brown and red packages corresponded to greatest potency scores (compared to green or yellow hues). With regard to perceptions of a drugs action area, dark packages were related to heart condition. Although their results did not reach statistical significance, light packages were related to antipyretics.

These findings have significant implications for pharmaceutical marketers. Oftentimes, in DTC advertising, pharmaceutical marketers specifically highlight

the color of their medication, arguably as a tool to differentiate themselves and enhance consumers' memory for the drug (e.g., "Nexium, the purple pill"). This strategy, however, can either aid or hinder the marketer, depending on the type of medication. When faced with a choice between medications to treat a given ailment, consumers may rely on color and choose the alternative which seems as though it would target the desired problem area, even despite that alternative being of lesser quality. Even more so, if consumers expect particular results based on physical properties of a medication and such effects are not subsequently felt (e.g., during the trial phase), they may be dissatisfied. As such, aligning consumer expectations with a medicine's actual capabilities is crucial, and may be done, at least in part, by addressing elements such as the color and size of the drug and the packaging.

11.2.3.4 Market Efficiency

Consumers also hold theories of the marketplace efficiency: forces of supply and demand (Scitovszky 1945) and the nature of competition (Chernev and Carpenter 2001). As mentioned previously, such beliefs are rooted in the notion that companies may command higher prices if they offer higher quality products (including, perhaps, more efficacious medicines). However, when there is parity among brands and markets are deemed efficient (e.g., overall quality is perceived as equal among alternatives), brands that appear superior on an observable attribute may subsequently be inferred to be inferior on an unobservable attribute (Chernev and Carpenter 2001). Thus, if several similarly priced alternative medicines can be used to treat a particular ailment, and one brand is evidently superior on the frequency of side effects (e.g., very rare), for example, consumers may infer that the brand is lacking on another attribute, such as response efficacy. Similarly, consumers are more likely to infer a pain killer with common side effects to be more effective than one with rare side effects, but only when it had been on the market for a relatively long period of time (Kramer et al. 2011), suggesting that consumers rely on a market efficiency hypothesis when evaluating medication effectiveness. Importantly, such inferences are more likely to be employed by consumers who are high in need for cognition as they require consumers to process information relatively systematically. Thus, these compensatory, negative correlation-based, inferences are not the "default" because they are more difficult to learn and comprehend (Johnson et al. 1989). When markets are perceived inefficient, people may use an evaluative consistency strategy. Undeniably, inferences made on the basis of marketplace beliefs determine whether consumers inquire, and subsequently purchase one alternative over another at the awareness stage.

11.2.3.5 Presence of Side Effects

Oftentimes consumers utilize lay theories that go beyond the correlations between the attributes of medications. Such lay theories rely on general knowledge and intuitions about how things work in life and, thus, manifest as a specific application of

a broader lay theory on judgments of medication efficacy. For example, the "no-pain, no-gain" theory is based on consumers' intuition that desirable results require undesirable associated by-products, such as in the finance sector (Pain 2009), politics (Corn 2008), education (Rendón et al. 1998), and business law (McMorrow 2002). In the pharmaceutical domain, this lay theory suggests that pharmaceutical products require detrimental attributes that impact consumers negatively in some way to be inferred to be effective. For example, Kramer et al. (2011) find that medicines that are associated with frequent side effects are likely to be perceived as more effective than those with rare or no side effects, given consumers' beliefs that more powerful medicines will be associated with more frequent or severe side effects. Similarly, medicines that taste bad are likely inferred to be relatively more effective. Conversely, medicines without associated detriments, such as those that taste good, are likely to be perceived as weak, as implied by the phrase "no-pain, no-gain."

11.2.3.6 Paradigms of Illness and Medicine

Wang et al. (2010) demonstrate that consumers hold lay theories about the nature of their illness and the nature of potential remedies (e.g., response efficacy beliefs) which ultimately drive preferences and consumption decisions. When attributing a particular cause to their symptoms is easy (e.g., diagnosis certainty is high), consumers tend to prefer a treatment that targets the specific cause directly (e.g., medication that focuses on particular parts of the body). Alternatively, when attributing a single cause to their symptoms is difficult, consumers face high diagnosis uncertainty and tend to prefer treatments that are attentive to the entire body. Consumers further hold beliefs about which medicines are optimal under the aforementioned conditions, such that Western medicine (e.g., prescription drugs) and Eastern medicine (e.g., herbal alternatives; Traditional Chinese Medicine and Ayurvedic) are presumed to be more efficacious in the former and latter cases, respectively. Furthermore, consumers hold beliefs about the nature of these alternatives and generally presume that Western medicine focuses on alleviating symptoms while Eastern alternatives focus on curing illness (since the entire body, and perhaps mind, is involved in the healing process).

In general, perceived effectiveness of herbal medication is lower than that of prescription drugs. In fact, research has found evidence of a *naturalness heuristic*, from which consumers perceive natural products to be less intrusive, mild, and less potent (Rozin et al. 2004). Ironically, the limited potential effects translate into positive evaluations of such remedies; in a survey of American adults, over 25 % were using herbals on a daily basis and over 80 % indicated an intention to take herbals in the future (Carlisle and Shafir 2005). In one study, participants were presented with three chemically identical options of water—either obtained from its source, filtered through bedrock, or filtered by humans—and asked to rate their attractiveness. Not only did people rate the first option as most attractive but also more willing to pay over a 50 % premium for it. In line with research on the naturalness heuristic, research has found the word natural elicits positive associations (Rozin et al. 2005).

Reasons for choosing herbal medicine over pharmaceuticals include perceived "naturalness" and lower perceived severity of side effects, in that order.

An interesting finding, however, is that when respondents are inquired about their willingness to take a particular medication, those presented with a "hybrid alternative" (e.g., a drug made by a pharmaceutical company from the leaves of a South American tree) reported greater willingness to take the product than those presented with an all-natural alternative (e.g., made from the leaves of a South American tree) and those presented with a manufactured alternative (Carlisle and Shafir 2005). As such, pharmaceutical marketers could benefit from incorporating natural ingredients into their products and emphasizing their presence.

11.3 The Trial Stage: Spillover Effects of Efficacy Expectations from the Awareness Stage

Our previous discussion centered on the factors that affect efficacy expectations that primarily determine adherence at the consumer awareness stage. However, such expectations undeniably affect efficacy judgments in the trial and adoption stage as well. Specifically, risk/benefit perceptions, lay theories of attractiveness, inferences based on color, intuitions about the marketplace, beliefs in market efficiency, and lay theories of medicine in general not only determine if consumers decide to purchase and initiate use, but also determine the reference point from which actual efficacy—after consuming the medicine—is judged. If initial expectations are set particularly high, for instance because of a detrimental product attribute which signals to the consumer that the medication should be efficacious (e.g., no-pain, no-gain), consumers judge experienced effects from this high reference point. Efficacy judgments that fall below this reference point (regardless of whether it is a valid base measure in the first place) can result in negative affect, poor efficacy judgments, and misuse (e.g., in terms of dosage or frequency). Non-adherence through improper usage, in turn, can result in the reduction of a medication's actual effectiveness, propelling judgments of inefficacy, and ongoing non-adherence. Therefore, in this section, we focus on the factors that influence consumers' efficacy judgments after they start taking the medications.

Pharmaceutical marketers need to understand the factors that affect *efficacy expectations* at the awareness stage and *efficacy judgments* at the trial/adoption stage because actual efficacy—which is rigorously tested prior to release—often considerably diverges from perceptions. Irrefutably, perceptions that a product is not providing expected results affect many constituents in the pharmaceutical value chain, including manufacturers, end users, and physicians (Bowmane et al. 2004). For the former, consumer dissatisfaction leads to negative word-of-mouth, lack of brand loyalty, and lost sales; for the latter, patients' inefficacy perceptions may lead to opinions of incompetence and induce switching service providers.

11.3.1 Placebo and Placebo-Like Effects

People are often unable to evaluate the quality of a treatment accurately even after starting the medicinal regimen (Pinto and Leonidas 1994; Pontes and Pontes 1997). In such situations, efficacy expectations, rather than the active ingredients of the medication, may become influential for achieving health outcomes via an expectancy-confirmation (or disconfirmation) route. An interesting phenomenon that unites the role of efficacy perceptions in the awareness and trial stages is the placebo effect: expectations that the medication will be (in)effective lead to actual (in)effectiveness of the medication (Stewart-Williams and Podd 2004). In fact, researchers argue that any response to a medication may be partly due to the active ingredients of the drug and partly due to the placebo effect (Stewart-Williams and Podd 2004). However, research also suggests that misconceptions and overly optimistic expectations about medication efficacy may lead to consumer disappointment, translating into non-adherence to the medicinal regimen (Sabate 2003). As such, while the two stages seem to be separate from one another, there may be conditions under which increasing expectations about efficacy at the first stage leads to self-fulfilling prophecies, which in turn influence consumer experiences (efficacy *judgments* and adherence) at the second stage.

Indeed, efficacy expectations that drive adherence at the awareness stage have spillover effects into the trial and adoption stage, such that they may act as a reference point from which efficacy judgments are made. Research on the placebo effect in marketing shows that expectations—which may be influenced by marketing actions and operate nonconsciously—can also alter experiences (Shiv et al. 2005). Shiv et al. (2005) found that participants who paid a discounted price for an energy drink thought to improve mental acuity subsequently solved fewer puzzles than did those who paid full price. These effects were magnified when expectations were reinforced. However, when the price–efficacy relationship was made salient (e.g., participants were asked to answer "Given the price I was charged…") the effect was eliminated; expectancy ratings were not different across those in the reduced-priced vs. regular-price condition. For pharmaceutical marketers and retailers of OTC medication, this phenomenon suggests that discounted medications may be perceived as, and subsequently be, less efficacious. These effects would presumably be less likely to arise when the medicine's effects are unambiguous (e.g., of erectile dysfunction medication), but present and persistent when the effects are more ambiguous (e.g., of relaxation drugs). Thus, while discounting pharmaceuticals may increase short-term sales, it may also lead to poorer efficacy perceptions. If consumers' experiences are in line with such expectations during the trial phase, they may discontinue the medicinal regimen or use the product at their own discretion. After satisfactory initial product use, research shows that consumers exhibit placebo-like effects in which they expect to experience the beneficial effects of medication more quickly on subsequent trials (Faro 2010); in the case where the effects lag onset expectations, poor efficacy judgments may be made, leading to subsequent non-adherence (Sabate 2003).

Motivation, or the desire to experience a product's benefits, is another underlying determinant of such placebo effects; it drives efficacy judgments at the trial and adoption stage. Irmak et al. (2005) found, for instance, that for those who reported a high desire to experience an energetic boost (highly motivated participants) a placebo drink (purportedly an energy booster) led to equivalent levels of physiological change as a non-placebo (caffeinated alternative). Indeed, consumers who inquire about medication and various treatments are motivated to feel some desired result. This suggests that consumers who are highly motivated to overcome a cold, for example, may feel the effects of Vitamin C in much the same way they would feel the effects of an OTC/Rx medication, especially if the former is reinforced with product claims regarding its effectiveness with preventing/alleviating various symptoms.

11.3.2 Time to Onset

Another placebo-like effect is evident in judgments of a products' time to onset. Faro (2010) proposes that people may begin feeling the effects of a product in an unrealistically short duration after consumption if they have used the product before. That is, if people believe there is a strong link between the product and subsequent performance—that a product did indeed have the intended effect on the person—they estimate the product as working sooner than if a stronger causal link is absent (e.g., that the product may or may not have been the direct cause of one's performance). Such efficacy beliefs translate into people opting to consume the product later in time (since time to onset is perceived to be quick) and begin the same tasks earlier. As such, duration estimates of a product's time to onset inevitably affect not only the timing of consumption but also perceived product efficacy in the trial and adoption stage. Furthermore, evidence implies that reliance on such beliefs to estimate time is a low-effort, automatic process (Faro 2010).

Ilyuk et al. (2012) extend this work by examining another temporal judgment: duration judgments of how long products remain efficacious (i.e., the length of time consumers believe products exhibit their beneficial effects). Consumers' estimates of how long products remain efficacious after consumption are a critical factor in determining product use and misuse. Ilyuk and colleagues show that these estimates depend on the nature of the task undertaken during consumption. Specifically, consumers' estimates of efficacy duration are shorter (longer) when the task is perceived to be difficult (easy). For example, consumers engaged in a difficult cognitive or physical task judged medicinal products to last a shorter amount of time than those engaged in corresponding, but easier tasks.

With regard to both prescription and OTC medication, estimates of a product's time to onset and duration judgments have important implications. DTC advertisements continuously reinforce that the target product is potent in providing benefits and often provide testimonials of people attesting to using the products and feeling their effects. Exposure to such ads might result in consumers underestimating the time to onset as well misjudging expected duration of efficacy.

Erroneous efficacy judgments of this nature can result in dosage non-adherence if consumers take the medication too soon (late) or too much (little). Consequences of dosage non-adherence range from consumer dissatisfaction to serious health effects. It is advisable to clearly state and reinforce, via advertisement and packaging, the medications' time to onset and duration of efficacy. Otherwise, subsequent trials may be marked by perceived poor efficacy judgments, disregard of the manufacturer's recommended use, and actual ineffectiveness of medication due to improper consumption.

11.4 Concluding Thoughts

We discussed different biases and heuristics that influence consumers' perceptions of medication efficacy. Efficacy expectations and judgments are critical factors in determining adherence. As we noted earlier in the chapter, use of the term "adherence" has become a discussion issue in the medical literature (National Council on Patient Information and Education 2007). Until the 1990s "compliance" was the term used for patients' adherence to a medicinal regimen. However, as "compliance" assigns a passive role to the patient and appears to discount patients' independent judgment, many stakeholders started using the term "adherence," which implies a more collaborative relationship between patients and clinicians. Notably, usage of the term adherence may have the power to change the stakeholders' behavior, making clinicians and pharmaceutical marketers more respectful of the role that patients can play in their own treatment decisions, enhancing the two-way communication, and leading to patient-centered treatment planning. Interestingly, the terms "persistence" and "concordance" have also entered the lexicon (National Council on Patient Information and Education 2007). Persistence refers to taking the medicine as directed beginning with the prescription being filled and continuing until the medicine is no longer recommended. Concordance is a term developed by the Royal Pharmaceutical Society of Great Britain to refer to a partnership between patient and clinician, reflected in shared health belief paradigms and use of shared beliefs to create successful medical outcomes; however this term is controversial as it may be more inspirational than realistic (National Council on Patient Information and Education 2007). Terminology is important, since the words that we use and the labels we apply directly influence our attitudes and corresponding behaviors. We think it is important that future scholarship be directed to a study and understanding of the effect of such terminology on consumer biases.

Research findings illustrated in this chapter demonstrate that consumers often use heuristics and fall prey to biases in making judgments about medicinal efficacy. It is important to keep in mind and be responsible to those consumers from vulnerable populations who are more inclined to fall prey to any potential nonadherence due to biased processing and judgments. For example, research shows that those consumers who have low health literacy or those who otherwise have a more limited ability to understand health messages (e.g., elderly people, or those with limited English

language proficiency) are particularly vulnerable to marketing communications. In fact, 45 % of the American adult population has literacy skills at or below the eighth grade reading level and more than 80 % of patients older than 60 cannot read or understand prescription labels (Institute of Medicine 2004). As a result, such consumers are less likely to adhere to pharmaceutical recommendations communicated through packaging, inserts or black box warnings; instead, they are likely to rely on lay theories such as those we discussed in this chapter. Research on vulnerable populations has investigated the reaction of consumers to experiences of vulnerability (e.g., homelessness, old age, immigration, etc.) in the consumption context (Baker et al. 2005; Hill 1995), but limited research has examined how such populations respond to health messages and the role of heuristics, biases, and lay theories on their judgments and decisions. Learning, for instance, what types of lay theories are more likely to be employed by these individuals may improve overall health and well-being in these populations.

Finally, there has been an increased popularity in alternative medicine in recent years in the United States. A 2007 survey by the federal government found that more than one-third of adult patients and nearly 12 % of children in the United States used alternative therapies such as acupuncture, reiki, and herbal supplements (Aratani 2009). As our discussion of the trial and adoption stage illustrates, one reason alternative medicine may be popular is that efficacy expectations influence actual efficacy. As such, adherence to such regimen is likely to also be a function of perceived efficacy and, thus, susceptible to the same heuristics and biases discussed in this chapter. One interesting question that may be answered by future research is that integrative medicine, through which patients are treated by both conventional and alternative medicine, may be more effective as it fosters an open dialogue between the physician and the patient, thereby enhancing adherence to medicinal regimen.

In this chapter, we have identified the factors that affect adherence at two stages of the consumer evaluation process: awareness and trial/adoption. Though not mutually exclusive, these factors were classified as driving efficacy expectations and efficacy judgments at the two stages, respectively. Given the detrimental consequences of non-adherence in either of these stages (in terms of health risks to the consumers and losses for the pharmaceutical industry in general), it is without doubt that efforts to enhance efficacy perceptions are key in creating value for all constituents in the pharmaceutical marketing chain—from manufacturers to end users.

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Chapter 12
Factors Affecting Adherence to Governmental Health Warnings and the Case of Over-the-Counter Cough and Cold Medications (OTC-CCM) in Children Under Two

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Abstract Governmental health agencies frequently issue warnings about new health hazards (e.g., smoking and excessive drinking). This chapter discusses factors affecting adherence to governmental warnings against the use of household products previously perceived safe. To be effective, a health warning must reach its intended audience and bring about behavior modification. This is challenging because, in order to modify behavior, the warning message must counteract and overpower the effect of habitual safe experience. Indeed the questions of how people perceive such warnings, whether they adhere to them, and what promotes or prevents adherence are central in marketing practice and research.

In this chapter, we review the psychological decision-making literature on trust of the source issuing the warning and safe experience with the risk-causing agent. Next we touch on basic requirements of awareness and understanding of the message. We then review the marketing literature on message design, focusing on factors practical for widespread implementation (i.e., vividness of message, one-sided vs. two-sided messages, regulatory fit). Next, based on behavioral decision research, we discuss how to counteract cognitive and emotional consumer biases that may reduce adherence. Finally, as a case in point, we evaluate adherence to the 2008 United States Food and Drug Administration (FDA) warning against administration of over-the-counter cough and cold medication (OTC-CCM) in children under age 2. We describe the results of three studies that examine whether parents had heard about OTC-CCM warnings and whether they intended to adhere to them. We conclude with recommendations for optimizing the design and dissemination of similar warnings.

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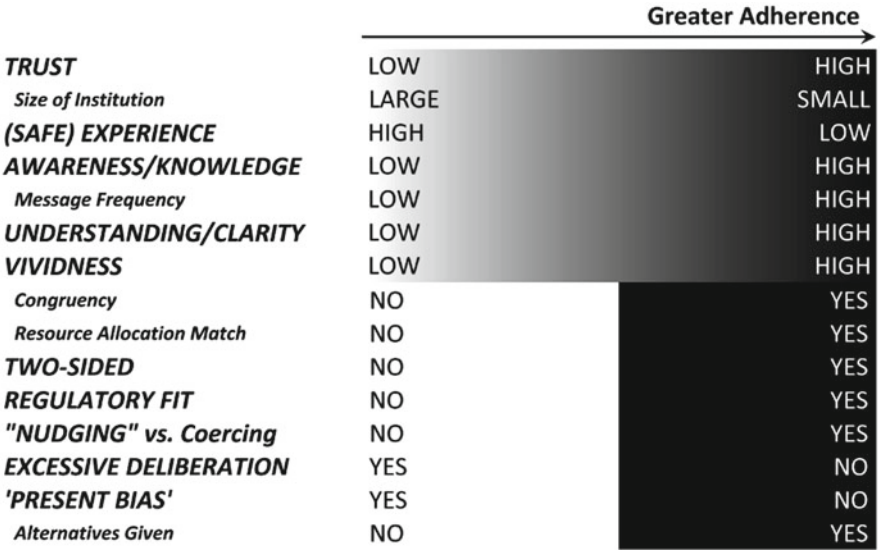

Fig. 12.1 Factors influencing adherence to health warnings

Governmental health agencies must frequently warn citizens about newly discovered health hazards (e.g., smoking and excessive drinking). This chapter discusses factors affecting adherence to governmental warnings against the use of household products previously perceived to be safe. To be effective a health warning must first reach its intended audience. In addition, the message must also successfully convince its intended audience to change its behavior. This is a challenging exercise in marketing, because in order to successfully convince consumers to modify behavior, the warning message must counteract and overpower the effect of habitual safe experience. Thus the questions of how people perceive such warnings, whether they adhere to them, and what promotes or prevents adherence are central factors to marketing practice and research.

This chapter is structured as follows: we begin by examining the psychological decision-making literature on such factors as trust of the source issuing the warning and safe experience with the risk-causing agent. Next we touch on basic requirements of awareness and understanding of the message. We proceed to review the marketing literature on message design (Keller and Lehmann 2008),[1] focusing on factors practical for widespread implementation, including vividness of message, one-sided vs. two-sided messages, and regulatory fit. Next, based on behavioral decision research (Ratner et al. 2008), we discuss natural cognitive and emotional consumer biases that may reduce adherence and how they may be counteracted. See Fig. 12.1 for an outline of the factors reviewed. To illustrate various factors, we

[1] For an exhaustive treatment of the topic, we refer the interested reader to the meta-analysis of 60 studies and 22,500 participants by Keller and Lehmann (2008), showing that message tactics have a significant impact upon intention to adhere to health-related recommendations.

include four sample warnings (Samples A through D). We go on to evaluate the specific case of the 2008 United States Food and Drug Administration (FDA) warning against administration of over-the-counter cough and cold medication (OTC-CCM) to children under age 2 (FDA 2008). The FDA warning serves as a prime illustrative case and nicely captures many of the issues relevant to health warning effectiveness identified by earlier literature. We describe the results of three studies, two conducted in the USA and one in the UK, that examine whether parents had heard about OTC-CCM warnings and whether they intended to adhere to them. Finally, we make recommendations for optimizing the design and dissemination of similar warnings in light of the literature reviewed.

12.1 Factors Influencing Adherence to Health Warnings

12.1.1 Trust of the Source Issuing the Warning

Trust of the individual or institution issuing a health warning has been shown a key aspect of health-related decision making (O'Neill 2002; Mechanic 2004; Hanoch et al. 2010). Even if a warning with the appropriate content reaches and is understood by its target audience, recipients may still not know what to believe if communicators are perceived to have a vested interest (Morgan et al. 2002; Jackson et al. 2004). Mechanic (2004) suggests trust in large organizations is equivalent to trust in government and business, which tends to be low. Walls et al. (2004) cite various studies indicating that trust falls as the level of abstraction of the institution goes up (e.g., "government scientists" or "local authorities" vs. "department of health"). Similarly, Brown and Calnan (2010) suggest that trust is low for broad systems/institutions, in part, because they are faceless to consumers. In contrast, patients seem to trust doctors over health care institutions, possibly due to their personal relationship (Mechanic 2004) and direct interaction (Brown 2009). In the UK, for example, parents' decisions not to vaccinate against measles, mumps, and rubella (MMR) despite assurances and campaigns to the contrary by the UK government stemmed largely from lack of trust in messages about the safety of these vaccines (Casiday 2007; Casiday et al. 2006; Hobson-West 2007). Similar issues have been studied in the context of genetic technology (Barnett et al. 2007), and there is a growing literature on trust as important to the link between risk perception and decision making (Williams and Noyes 2007).

12.1.2 (Safe) Experience with the Risk-Causing Agent

A growing body of literature has shown that people rarely incorporate information about negative rare events into their decision-making process (Barron and Erev 2003; Erev and Barron 2005; Fox and Hadar 2006; Hertwig et al. 2004; Kahneman

and Tversky 1979; Li et al. 2009). That is, given positive experience with a product, people tend to underestimate the likelihood that a negative rare event will occur (Brown and Calnan 2010). When information about a rare event comes externally from a description, as from a warning, people tend to overweigh the rare event in their decisions (Barron and Erev 2003; Li et al. 2009). In other words, people behave as if the rare event is more likely to occur than its objective probability. Conversely, when people learn from their own experiences, they tend to underweigh rare events, behaving as though the event is less likely to occur than its objective probability (Barron and Erev 2003; Erev and Barron 2005; Fox and Hadar 2006; Hertwig et al. 2004; Li et al. 2009).

In practice, people gain information from *both* external descriptions and personal experience. In deciding whether to adhere to a given warning, people who have previously used the risk-causing agent are subject to potentially conflicting influences from the warning and past experience. Others, possessing little or no experience with the risk-causing agent, are presumably more reliant upon the warning. Research has shown that inertia tends to guide the risk-taking behavior of people who have had safe experiences with the risk-causing agent, such that they continue their exposure to the agent despite new information about associated dangers (Barron et al. 2008).

Unlike trust in the source issuing the warning and experience with the risk-causing agent, the following factors pertain to the message itself rather than factors external to it.

12.1.3 Basic Requirements: Awareness and Understanding of the Warning

Though self-evident, for a warning to be effective, its target audience must be aware of the warning and receive sufficient warning-related information. To accomplish this, the target audience must be exposed to the message, preferably through multiple channels. Moreover, the target audience must have a clear understanding of the warning content. Related to message clarity is message vividness, one of the several message characteristics identified in the marketing literature as a promoter of adherence and suitable for widespread implementation.

12.1.4 Vividness of the Warning

Tailoring health messages to target a broad audience (e.g., all US parents of children under 2) is not trivial. Should warning messages be phrased in scientific terminology, or should regulators couch the warning in descriptive narrative underscoring the risks associated with the relevant product? Marketers have dealt with this

question in the context of vividness—the degree to which a message incorporates imagery that makes the message come to life. Block and Keller (1997) examined vividness in the context of health communications related to sexually transmitted diseases and skin cancer. They found a preference for vivid over non-vivid material, but only when participants believed they could follow the recommendations in the message (high self-efficacy). Another moderator of the effectiveness of vivid vs. pallid messages is congruence between the vivid elements and the theme of the message (Smith and Shaffer 2000). Vivid information led to greater recall, as long as the language was congruent with the message (e.g., describing a smoker as "gasping desperately for air," p. 777). Noncongruent vivid information, on the other hand, impaired recall of the message (e.g., "the nonsmoker's lung capacity is so powerful that the individual has the ability to inflate a balloon the size of a cow. The smoker, on the other hand, can only inflate a balloon the meager size of a golf ball," p. 778). In another study, Lemal and Van den Bulck (2010) compared narrative messages, deemed to be more vivid, and nonnarrative messages containing the same information with a control non-message condition. Four weeks later, participants exposed to the narrative message were 2–4 times more likely to have engaged in health promoting actions, compared to participants in the control group. In contrast, participants exposed to the nonnarrative condition only differed from that of the control group in that they sought out more information about skin cancer. Avis and colleagues (2004) found that more women who viewed a videotape promoting mammography had a mammogram in the preceding year as compared to a group who had received a pamphlet, but this effect was not significant after controlling for baseline screening rates in both groups (75 % reported a mammogram in previous year; 90 % in previous 2 years). Still, this increase was higher than for many other interventions. Further, the video group showed several longitudinal effects, whereby they became more likely to report feeling control over getting a mammogram (self-efficacy), and the percent of women who believed they had control increased over time. Also, the video group became more likely to report feeling that mammograms are beneficial and assuring. These longitudinal effects are particularly relevant in the context of the FDA warning, which was issued only once though parents are expected to adhere indefinitely. Finally, Keller and Block (1997) demonstrated the importance of resource allocation, indicating that irrespective of the vividness of the message, maximum persuasiveness will be achieved when there is a match between the resources allocated to the message (presumably high for OTC-CCM given the risk of life-threatening side effects) and those associated with the message. Thus, in addition to considering the vividness of the message, government agencies may need to determine how to achieve this resource match.

As they use large, vivid pictures to illustrate the benefits vs. harms of adherence vs. non-adherence, Sample Warnings A and B epitomize the use of vividness in communicating the intended health message. Sample Warning D also uses images, but they are less prominent and do not depict the consequences associated with adherence or non-adherence (i.e., quitting or continuing to smoke). Still, the images encourage the recipient to adopt the desired behavior of getting help.

12.1.5 One-Sided vs. Two-Sided Arguments

Should a message be one-sided, or, even when making a specific claim, should a message contain arguments to the contrary? Would such a two-sided approach be more persuasive, or would it dilute the effectiveness of the message? Rucker et al. (2008) suggest that two-sided messages are more persuasive than one-sided ones. Their account is based on attitude certainty. Rucker et al. (2008) propose that consumers value not only the content of their attitudes but also how they came to form them, so that if attitudes were formed using deliberation and weighing of evidence, rather than mere adoption of a message, consumers would have greater confidence in them. In other words, understanding how you came to have an attitude is a moderator of your certainty in it. Rucker et al. (2008) hypothesized further that making the presence of a two-sided frame salient to consumers (i.e., understanding the pros and cons and awareness that both were considered by others) may lead them to believe that their attitudes are based on greater knowledge and increase certainty. This is especially the case if the negatives are present but appear inconsequential as consumers may assume that there must be few remaining unknown negative attributes and can be confident in their positive evaluation of the message position. On the other hand if negatives are absent, consumers may feel they are missing information and will therefore be less certain of the attitude formed. The authors substantiated this premise in a series of experiments, showing that two-sided messages resulted in greater attitude certainty, although the effect was mitigated by knowledge, such that attitude certainty was increased by negative information only in participants of low self-reported knowledge. This finding is consistent with the idea introduced above that experience with a product may render consumers more immune to warning messages. Finally, Rucker et al. (2008) linked two-sided messages with behavior (Experiment 5), showing that individuals receiving the two-sided frame reported a greater willingness to purchase the product than those receiving the one-sided frame. Attitudes were also more predictive of behavioral intentions following a two-sided frame. As this study was run in the context of products associated with predominantly positive information, further research is needed to evaluate whether two-sided messages would also facilitate behavior and increase attitude certainty when the information on the product or service is mainly negative.

The messages conveyed by Sample Warnings A, C, and D are one-sided. However, Sample Warning B alludes to the positive consequences of non-adherence by referring to the "buzz" and playing on the phrase "takes your breath away" typically associated with a positive experience.

12.1.6 Achieving Regulatory Fit: Preventive or Promotional Focus

Described by researchers as a "loss" or "gain" frame, most health messages may be phrased as preventive and cautionary (e.g., "unless you eat carrots, you may lose your eyesight") or prophylactic and promotional (e.g., "eat carrots to preserve good eyesight").

This has been examined in the context of people's regulatory focus (whether preventive or promotional) and their appraisal of response efficacy (i.e., will the behavior result in the desired outcome) or self-efficacy (i.e., can I undertake the behavior). It has been shown that a preventive regulatory focus fits better with response efficacy and a promotion regulatory focus fits better with self-efficacy, and that regulatory focus may determine the weights for response and self-efficacy (Keller 2006). Critically, regulatory focus–efficacy fit has been shown to increase the desired behavior. Thus health messages phrased in the "loss" frame and appealing to response efficacy may lead to higher intentions to comply in individuals with a prevention regulatory focus, and those phrased in the "gain" frame and appealing to self-efficacy lead to better compliance individuals with a promotion regulatory focus (Keller 2006). In support, Zhao and Pechmann (2007) found that antismoking advertisements were most persuasive when the viewer's regulatory focus, the message's regulatory focus, and the message frame were compatible. As expected, for promotion-focused adolescents, a promotion-focused positively ("gain") framed message was most effective at persuading them not to smoke, but for prevention-focused adolescents a prevention-focused negatively ("loss") framed message was most effective. As previous research demonstrated that adolescents do not respond well to disease-related consequences (Hastings and MacFadyen 2002; Pechman et al. 2003), both prevention and promotion messages in the Zhao and Pechmann (2007) study focused exclusively on social consequences.

For examples of promotion-focused positively ("gain") framed messages, see Sample Warnings A and D. For examples of prevention-focused negatively ("loss") framed messages, see Sample Warnings B and C.

12.1.7 "Nudging" vs. Coercing

Thus far we have dealt with how warnings and alerts should be constructed to optimize receptiveness and efficacy. Ratner et al. (2008) raise the important issue of the legitimacy of limiting consumer freedom by disseminating messages that encourage specific actions (e.g., smoking cessation). They remind us that once health messages intended to increase personal and public welfare are released to the public, the consumer is free to choose adherence or non-adherence. Thus an intervention that guides consumers to be better off without restricting their choices may be necessary to assist them in making better, unbiased decisions (Thaler and Sunstein 2003). Indeed in their book entitled *Nudge: Improving decisions about health, wealth, and happiness*, Thaler and Sunstein (2009) elaborate on this "libertarian paternalistic" approach—creating a choice architecture that gently "nudges" citizens, patients, or consumers in the desired direction. This approach has been applied in a variety of contexts, including organ donation (Johnson and Goldstein 2003), where a default policy of organ donation (with an opt-out option) enhances personal and societal welfare by increasing prevalence of organ donation, relative to a default policy of no organ donation (with an opt-in option). Thus increased adherence to a health

warning may be obtained if the message is worded in a manner that "nudges" rather than coerces the recipient to adhere.

Sample Warning A exemplifies "nudging" rather than coercion in that it is worded to increase the recipient's awareness of the safer option and its consequences without explicitly instructing the recipient to choose it. Sample Warning B is a bit more coercive, but still makes it clear that the choice is ultimately up to the recipient (i.e., "think twice"). Sample Warnings C and D are more coercive, clearly instructing the recipient to adopt the desired healthier behaviors (e.g., avoid water contact and call Quitline).

12.1.8 Excessive Deliberation

Ratner et al. (2008) discuss several natural cognitive and emotional biases that may be counteracted to assist consumers in making better medical decisions. For example, consumers who deliberate excessively tend to focus too much on less relevant criteria (Wilson and Schooler 1991), become more emotionally attached to the options (Carmon et al. 2003), and experience lower post-decision satisfaction (Dijksterhuis et al. 2006).

All of the sample warnings included in the chapter involve some degree of deliberation represented by the textual portion of the warning poster. However, for highly vivid warnings like Sample Warnings A and B, deliberation is clearly secondary to the immediate impact of an emotionally charged image. Sample Warning C relies most upon deliberation, as it consists almost exclusively of text outlining the logical arguments in favor of adherence to the warning. Sample Warning D also relies upon deliberation in providing the recipient with a brief summary of the scientific evidence in favor of adherence; images are also included but (unlike Sample Warnings A and B) do not illustrate the risks of non-adherence or the benefits of adherence.

12.1.9 The "Present Bias"

Ratner et al. (2008) also review findings that people often weigh the here and now disproportionately (referred to as "the present bias") (O'Donoghue and Rabin 1999) and appear overconfident about how they will act differently in the future ("I can stop smoking later if I want to") (Soman 1998; Zauberman 2003; Zauberman and Lynch 2005). In the context of the FDA warning, "the present bias" may be evident as a tendency to administer the medication to the child, thereby achieving immediate improvement in the child's symptoms and discomfort despite the risk of potential harmful side effects. "The present bias" may be counteracted by suggesting alternative means of relieving children's cough and pain, and reducing their fever. Such alternative natural remedies may include honey and a humidifier to alleviate cough, and mild temperature baths to reduce fever.

12.2 An Illustrative Case: The FDA Warning Against Over-the-Counter Cough and Cold Medication in Children Under Age 2

12.2.1 The FDA Warning: Background

The FDA is responsible for ensuring public health and safety, and, like similar agencies around the world, it does so "by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, food supply, cosmetics, and products that emit radiation" (FDA 2010). While government organizations like the FDA are obligated to provide citizens with guidelines and warnings about possible health risks, citizens are often free to reject these recommendations. As part of its broad mission, the FDA often issues warnings about various consumer products (food, food supplements, makeup, and medications). On June 6, 2011, for example, it issued five recall, market withdrawal, and safety alerts on nonmedical products, including a Bratz makeup kit (FDA 2011a) and Kashi frozen pizzas (FDA 2011b). Given the wide range of products that may be recalled or pose a risk to consumers, FDA warnings are intended to reach a diverse range of audiences. This underscores the importance of creating messages that are persuasive and can convince citizens to modify behaviors previously considered risk-free.

Serious adverse events from OTC-CCM are relatively rare: while an estimated 95 million packages are sold each year (Brown 2008), approximately 1,500–1,600 children under 2 were admitted to emergency rooms for OTC-CCM-related issues between 2004 and 2005 (Centers for Disease Control and Prevention (CDC) 2007; Schaefer et al. 2008). In 2007, the FDA completed a review indicating that between 1969 and the fall of 2006 there were a total of 54 reported child deaths from decongestants and 69 from antihistamines, most involving children under 2 (Akhayan-Toysekani et al. 2007). Nonetheless, based on these safety data and the paucity of studies demonstrating efficacy in children under 2, the FDA strongly recommended "that OTC cough and cold products should not be used to treat infants and children less than 2 years of age because serious and potentially life-threatening side effects can occur from such use" (FDA 2008). In 2008, the Medicines and Healthcare Products Regulatory Agency (MHRA) of the UK issued similar guidelines discouraging use of OTC-CCM in children under 6. Given the ubiquity of OTC-CCM use (i.e., millions of bottles sold each year; Brown 2008), the FDA and MHRA recommendations attracted much media attention. Having generated substantial public interest and associated surveys and research, these warnings are prime candidates for examining issues related to adherence.

Were the FDA and MHRA warnings successful? For example, did they reach their intended audience (i.e., parents of children under 2), and did the recommendations actually precipitate a change in behavior? Having surveyed some recommendations from the marketing and behavioral decision-making literature on how to construct an effective warning, we now move on to describe the actual FDA warning. The original FDA press release (FDA 2008) was based on the FDA's review of data and discussion at a joint meeting of the Nonprescription Drugs and Pediatric

Advisory Committees on October 18 and 19, 2007. It addressed parents and caregivers, "recommending that OTC cough and cold products should not be used to treat infants and children less than 2 years of age because serious and potentially life-threatening side effects can occur from such use." It went on to specify what medications categories (e.g., decongestants) were subsumed under the recommendation. The stated reasoning of the FDA against use of the medication was twofold. First, the FDA described the perils of using the medication: "There are a wide variety of rare, serious adverse events reported with cough and cold products. They include death, convulsions, rapid heart rates, and decreased levels of consciousness." Then, the FDA quoted a statement by Charles Ganely, M.D., director of the FDA's Office of Nonprescription Products, as follows: "The FDA strongly recommends to parents and caregivers that OTC cough and cold medicines not be used for children younger than 2. These medicines, which treat symptoms and not the underlying condition, have not been shown to be safe or effective in children under 2." The release then went on to indicate that use of the medication in children ages 2–11 will be determined at a later stage and offered advice for safe usage; for example: "only use measuring spoons or cups that come with the medicine or those made specially for measuring drugs." Finally, the FDA recommended that "anyone with questions contact a physician, pharmacist or other health care professional to discuss how to treat a child with a cough or cold."

12.2.2 Did the Comply with Recommendations from the Marketing Literature?

The press release used to disseminate the FDA warning, as it appears on the agency's website, is not written in a vivid, narrative style (though its coverage in the popular press may have been more vivid). Further, the message is conveyed in a paternalistic tone, compelling, rather than nudging, parents to avoid administering OTC-CCM to their children under 2. Based on the marketing literature reviewed above, it may be more effective for the FDA to disseminate descriptions of vivid case studies illustrating the detrimental effects of OTC-CCM, thereby exploiting the affect heuristic (Slovic et al. 2002) and targeting the experiential rather than the rational system (Epstein 1994; Loewenstein et al. 2001; Slovic et al. 2004). We also note that the recommendation included two reasons for withholding administration of the medication—that it is neither safe nor effective. The implicit equal weighting of these consequences may actually have been suboptimal because parents appear to place more weight on safety (i.e., side effects) than efficacy (e.g., fever reduction) (see findings described below from participants in the Miron-Shatz et al. 2010 study). Further, Zhao and Pechmann's (2007) work also suggests that for a message to be effective, it must be pretested for attributes that resonate well with the target audience (e.g., social vs. health consequences for adolescents). Finally, the warning did not include suggestions for alternative means of relieving children's pain and cough, or for reducing fever, potentially important for minimizing "the present bias" (see above).

12.2.3 Were the FDA and MHRA Warnings Effective? Experimental Evidence

Shortly after the FDA warning become public, we (Hanoch et al. 2010) surveyed US parents' awareness of the new guidelines about OTC cough and cold medication use, their trust in the FDA, and their intention to stop or continue using the medication. We were also interested in parents' general knowledge, perception, and behavior with regard to OTC-CCM. Overall, 377 parents of children under 6 responded to our online survey, the majority of whom (280) were female.

Of all 330 respondents without missing data, our results showed, first, that 93 (or about 30 %) had not heard about the FDA warning. Next we examined whether parents with children less than 2 years old were more likely to have heard of the FDA warning compared to parents of children over 2 years of age. Among parents of children under 2, 142 of 189 (about 75 %) had heard of the FDA warning. In comparison, 95 of 141 (about 67 %) parents with children over the age of 2 had heard of the FDA warning. Although, as part of the target audience, parents of children under 2 were more likely to be aware of the new FDA guidelines, over 25 % of them had not heard of the FDA warning.

Our results were consistent with those of a National Public Radio/Kaiser Family Foundation/Harvard School of Public Health (2007, henceforth "NPR") study that surveyed a representative sample of US parents by telephone. In the NPR study, 32 % of parents indicated that they had heard either nothing at all or not much about the FDA warning. The NPR survey also inquired regarding whether parents understood the warning. They found that over a third (37 %) of parents indicated confusion about the warning. Thus not only was a substantial minority of parents unaware of the new recommendations, but among those who had heard of the warning, a similar percentage was unclear on how to interpret the recommendations.

Next, we examined parents' intentions regarding further use of OTC-CCM. Of the parents who had heard the warning, about a third (46, 32.4 %) indicated that they would continue using it and a similar number of parents (43, 30.3 %) were unsure what they would do. The remaining parents (53, 37.3 %) indicated that they would adhere to the warning.

Finally, we explored the relationship between parents' trust in the FDA and their intention to continue administrating OTC-CCM to their children. In our sample, close to 50 % of parents with children under 2 reported not trusting the FDA recommendations or were unsure whether to trust them. In accordance with our prediction and the literature cited above, we found that parents who expressed the least trust in the FDA recommendations were also more likely to continue using OTC-CCM. It should be noted that although the NPR (2007) study did not examine the relationship between adherence to the FDA recommendations and trust, it did find that as many as 71 % of parents reported trusting their child's doctors while only 29 % reported trusting the FDA.

Our results thus highlighted the need to effectively communicate health warnings to the general public by ensuring that they actually reach their intended audience.

In addition, our data highlight the role of trust in determining intention to adhere to governmental health warnings. Therefore, in keeping with the requirements outlined above for effective health communication, the FDA must both step up its efforts to reach target audiences and to do so convincingly. The challenges of creating effective health communications faced by the FDA may be unique to the USA and not representative of those relevant to similar health organizations in other countries. Indeed low trust of the FDA may be attributable to its recent approval and subsequent removal of another drug for chronic pain (Harris 2005) or low public satisfaction with healthcare reform (Taylor-Gooby 2006; Taylor-Gooby and Bromley 2003). Warnings about OTC-CCM usage are a prime case study for comparing similar warnings across countries.

The UK and USA differ with respect to their health care coverage (Laugesen and Rice 2002) and access to health care professionals, which may also affect trust in governmental health organizations. As such, in our second study (Himmelstein et al. 2011), we administered a similar survey to over 900 UK parents. This time we asked whether they had heard about the MHRA warning issued (following the FDA recommendations) in March 2008 (MHRA 2008). Similar to our US findings, over a third (343, 36.5 %) of UK parents reported that they had not heard about the MHRA warning. Of the parents who had heard of the warning and who had given OTC-CCM to their children (349), over half (54.4 %) indicated that they did not trust the MHRA or were unsure whether to trust them. Of the 382 parents who responded to our question about adherence to the MHRA warning, over 60 % (239) indicated that they would continue giving their children OTC-CCM. Furthermore, as with the US sample, we found a positive correlation between trust and adherence. Thus, UK parents exhibited similar tendencies to those expressed by their US counterparts. Not only did a sizeable minority not hear about the MHRA warning, but those who had heard the warning did not seem to place a great deal of trust in it, nor were they likely to stop giving OTC-CCM to their children.

On the basis of our two studies (Hanoch et al. 2010; Himmelstein et al. 2011) reviewed thus far, it appears that both the FDA and MHRA have had difficulty reaching their target audience and changing behavior. As above, one of the challenges facing the FDA and MHRA is the potential impact of varying levels of previous experience with OTC-CCM. Parents who have had extensive experience with OTC-CCM might therefore be more likely to ignore the FDA recommendation. Our third study (Miron-Shatz et al. 2010) examined the effect of parental experience on adherence to the FDA OTC-CCM warning.

By measuring adherence in parents with older children—who presumably have more experience with colds and use of OTC-CCM in children under 2—and those without older children, we were able to test the following hypothesis: behavioral inertia due to safe experience with OTC-CCM would reduce adherence to the FDA warning. In our study (Miron-Shatz et al. 2010), we surveyed 218 parents of children age 2 or younger who had heard of the FDA warning. Next, to examine the impact of experience, we divided participants into two groups: experienced parents (with older children in addition to a child age 2 or younger) and inexperienced parents (with only a child age 2 or younger).

In line with previous literature and our prediction that experienced parents' decisions would be based upon behavioral inertia (Brown 2008) motivated by a history of safe experiences with OTC-CCM, experienced parents (with older children in addition to a child age 2 or younger) were far less likely to adhere to the FDA warning relative to parents with only a child 2 or younger. That is, previous parental experience with OTC-CCM was a significant predictor of adherence, such that inexperienced (vs. experienced) parents were almost 3 times more likely to adhere to the FDA warning. In contrast, we found no significant differences on any of the other measures (i.e., amount of warning information received, prevalence of side effects, trust in the FDA, frequency of child's coughs and colds). Thus, the difference in adherence rate between experienced and inexperienced parents could not be attributed to any of these factors. However, amount of information did have a differential impact upon adherence within the experience groups. Among inexperienced parents, amount of information did not affect adherence rate. In contrast, among the experienced group, adherence to the FDA warning was higher in parents who had received more information. Thus only among experienced parents did amount of information received impact their decision regarding whether to continue administering OTC-CCM to their children. Taken together, these findings indicate that future FDA communication efforts should target households with many young children, as experienced parents are least adherent and yet most receptive to additional information.

As above, trust of the government agency issuing the warning and prior safe experience with the product appear to be key determinants of adherence. Indeed in both the USA and the UK, adherence to warnings against administering OTC-CCM to young children appears related to these variables. With regard to trust, it is startling that approximately half of parents in a US study (Hanoch et al. 2010) and a UK study (Himmelstein et al. 2011) did not trust the warning or were unsure what to believe. Regarding experience, as with other medications (Barron et al. 2008), previous safe experience with OTC-CCM in children over the age of 2 seems related to poorer adherence (Miron-Shatz et al. 2010). Based upon the marketing literature previously reviewed, we propose alternative phrasing and targeting of future warnings to help counter the barriers of low trust and safe past experience. We propose promising directions for further research in applying marketing principles to the design of pharmaceutical warnings and examining their impact on behavior and, subsequently, health outcomes.

12.2.4 Recommendations for Further Improving Warning Effectiveness

In this section we propose several directions for improving the effectiveness of public announcements of governmental warnings, such as the one against OTC-CCM in young children. These directions are based on our findings, as well as the marketing literature surveyed above.

First, we propose ways to increase awareness for the warning. Drug packages, especially in the case of OTC medication, are highly visible to the consumer. In addition to direct-to-physician dissemination of the warning, if the FDA were to mandate printing the warning on the packaging (similar to Sample Warning D), it would reach every potential consumer prior to the decision to purchase and possibly at home prior to the decision to administer the medication (if the medication is stored in its original packaging). This may be more practical than depending on a pediatrician, patients' most trusted source of information (Mechanic 2004; Brown 2009; Fig. 12.2), to convey the warning, especially in the context of over-the-counter products not necessitating a doctor's visit prior to purchase. We (Miron-Shatz et al. 2010) found that approximately half (55 %) of parents trust warnings on packaging at least somewhat, with experienced parents slightly more likely to trust the warnings. (Average trust ratings of participants in the Miron-Shatz et al. (2010) study for various sources of trust are shown in Fig. 12.2, separately for experienced and inexperienced parents.) Packaging has been used effectively for warnings in other contexts, including smoking (Kees et al. 2006; see Sample Warning D). Similarly, to warn smokers of the associated health risks, in 2003, the World Health Organization (WHO) adopted the Framework Convention on Tobacco Control requiring that health warning information cover at least 30 % of the principal display areas on tobacco packaging (WHO 2003, Article 11). Thus, warnings such as those of the FDA and MHRA may be more effective if printed on the medication package rather than by public announcement (but see Lokker et al. 2009).

Further, regarding awareness to the warning, the FDA warning was issued in 2008 and not repeated since (though the agency recently announced removal from the market of many unapproved prescription drugs with the same ingredients as OTC-CCM; FDA 2011c). Similarly, the MHRA did not repeat its 2008 warning (though the agency extended the warning to children under 6 in 2009; MHRA 2009). Parents who initially heard these warnings may have forgotten them, and new parents may be completely unaware of the warnings. Incorporating agency warnings into drug packaging may also serve to keep them prominent in consumers' minds. In fact, MHRA has indicated that it is working with industry to incorporate its warning into product labeling (MHRA 2009).

Second, in spite of Ratner et al.'s (2008) recommendation to minimize excessive deliberation in processing health and other public welfare messages, the FDA recommendation mentioned both safety and efficacy as reasons for discontinuing OTC-CCM use. We examined the importance of various factors in parents' deliberations regarding whether to administer OTC-CCM (for participants in the Miron-Shatz et al. 2010 study). Side effects were deemed "very important" by 53.6 % of the respondents. By comparison, a smaller proportion of respondents indicated that the following attributes were "very important": reduce child's fever, relieve child's pain, and relieve child's cough (40.5 %, 27.7 %, and 26.7 %, respectively). The greater parental emphasis on safety over efficiency is consistent with a more preventive regulatory focus and suggests that parents may have exhibited better adherence to the FDA and MHRA warnings had they been phrased in a "loss" or prevention frame appealing to response efficacy (Keller 2006), particularly prevalence of side

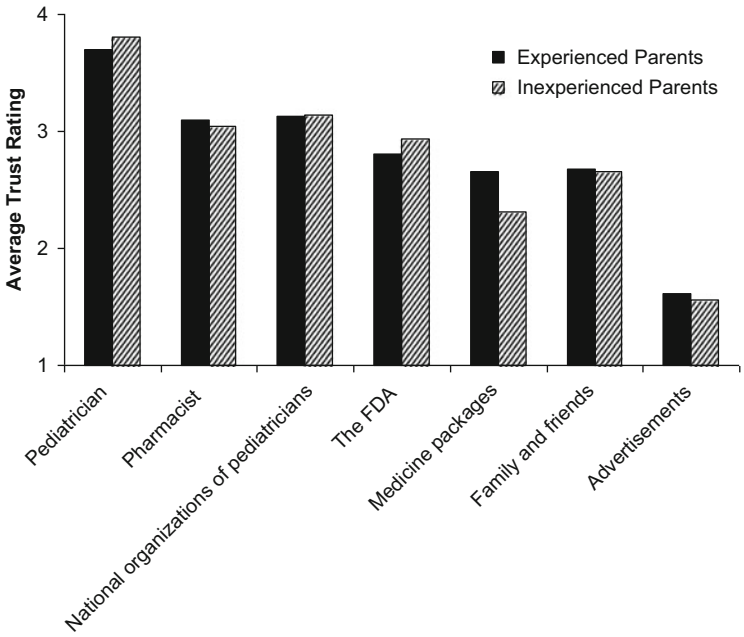

Fig. 12.2 Average parental trust of information sources by experience. "How much do you trust each of the following sources to provide you with accurate information about the safety and effectiveness of over-the-counter medicines for your children?" Experienced parents ($N=142$) had older children in addition to a child age 2 or younger. Inexperienced parents ($N=76$) had only a child age 2 or younger. Trust Scale: 1 = Not At All; 2 = A Little; 3 = Somewhat; 4 = A Lot. *Sample warnings*, Sample Warning A: A poster from the "Road Crew" organization of Wisconsin intended to reduce drunk driving by offering alternative transportation services between bars and homes in older luxury vehicles. "Road Crew" is funded by the National Highway Traffic Safety Administration, the Wisconsin Department of Transportation, and Miller Brewing. See: http://www.roadcrewonline.org/ and http://nudges.wordpress.com/how-do-you-keep-drunk-drivers-off-the-road-give-em-a-ride-home-in-a-limo/ (both accessed September 27, 2011). Sample Warning B: A poster from the FDA aimed at reducing misuse of prescription pain relievers among young people. Downloaded from: http://www.flickr.com/photos/fdaphotos/5323869799/in/set-72157625747043384 (accessed September 27, 2011). Sample Warning C: A warning sign from the North Coast Regional Water Quality Control Board in California about water safety issues due to toxic algae in the Klamath River. Downloaded from: http://www.klamathriver.org/images/Algae-warning-sign.jpg (accessed September 27, 2011). Sample Warning D: A cigarette package warning label from the Australian Department of Health and Ageing outlining the benefits of smoking cessation and promoting a help line for those who wish to quit. Downloaded from: http://www.docstoc.com/docs/32770535/Quitting-will-improve-your-health (accessed September 27, 2011)

effects. This way, excessive deliberation is minimized and there is a better fit with parents' focus on prevention of side effects relative to promotion of efficacy. Pretesting for the specific attributes that resonate best may be warranted.

Third, we suggest rephrasing the warning for greater vividness, ensuring congruence between the imagery and the message, and repeating the message over time (or incorporating in packaging). Our fourth recommendation is to construct a

two-sided warning, as such messages have been shown more persuasive, augmenting recipients' sense of choice and certainty. We also suggest incorporating alternative safe approaches (e.g., natural remedies) to counteract "the present bias." Finally, future studies should evaluate consumer resource allocation to a warning message so that resources associated with the message can be matched to it for enhanced effectiveness.

We believe that by implementing these suggestions gleaned from the marketing literature and our own research, governmental health agencies can increase the efficacy of their health warnings, resulting in significantly greater adherence and reducing the prevalence of adverse consequences in the general public associated with non-adherence.

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Chapter 13
Vaccine Marketing

Reinhard Angelmar and Pierre A. Morgon

Abstract Long perceived as an unattractive segment of the pharmaceutical industry, most of the leading firms have stepped up vaccine investments in recent years. Unlike mainstream pharmaceuticals, vaccines generally treat healthy individuals, most are administered only once or very infrequently during a life time, and they engender positive externalities, because vaccinated individuals reduce the risk of transmission to unvaccinated persons, leading authorities to mandate some vaccinations. Resistance to vaccination may lead to immunization failure and disease resurgence.

The public and private market each account for about one-half of the global vaccine market in value. Bringing new vaccines to market requires carefully orchestrated programs targeting the multiple types of customers. For example, in parallel with the clinical development program designed to obtain FDA approval for its HPV vaccine Gardasil, Merck developed health-economic evidence to obtain a positive recommendation for vaccination and public financing. Physician educational programs and unbranded DTC campaigns were started many months prior to launch. Following FDA approval and positive vaccination and public financing recommendations, Merck developed market access programs targeted at states and private insurers, and launched branded physician and DTC campaigns.

Successful global diffusion of a vaccine generally requires the development of a tiered pricing policy which takes country differences in per capita income into account.

A successful launch often creates new problems for vaccine marketers. They must maintain the motivation to engage in and pay for vaccination despite the quasi-disappearance of the disease. And they must combat anti-vaccination information claiming that the vaccine is the cause of serious side effects.

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13.1 Background on Vaccines

Vaccines are biological pharmaceuticals. Like other biologicals such as insulin, the active components of vaccines are extracted from living organisms and then isolated through separation technologies. What differentiates vaccines from other biologicals is their distinctive mechanism of action: they work by stimulating or restoring the immune system's ability to fight infections and disease.

Until recently, all vaccines were preventive or prophylactic vaccines,[1] that is, they were developed to prevent a future infection or attenuate its effects. In April 2010, the FDA approved Provenge, the first therapeutic vaccine, for use in male patients with metastatic prostate cancer.[2] Other therapeutic vaccines are under development, including vaccines against other types of cancers and Alzheimer's (Shirvill 2010; Andrews 2011). Figure 13.1 shows how vaccines are related to other types of pharmaceuticals.

Therapeutic vaccines, besides representing only a very small share of vaccine sales at this time, pose pricing and reimbursement issues (Provenge costs $93,000 for a course of treatment) and marketing challenges which are similar to those of other therapeutic biologics.[3] Preventive vaccines, however, face distinctive marketing challenges and a somewhat different market environment.

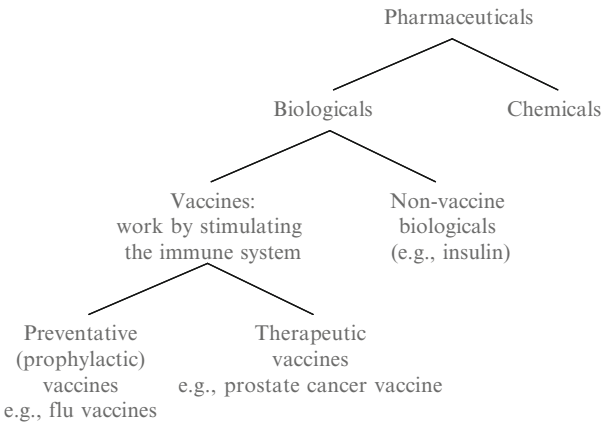

Fig. 13.1 Types of pharmaceutical products

[1] Some vaccines can be used both for prevention and treatment. For example, rabies vaccines can also be administered after an individual has been exposed to the virus (e.g., following a bite by a rabid dog).

[2] Provenge's sales have proven disappointing so far. http://blogs.wsj.com/health/2011/08/04/dendreon-shares-plummet-as-company-withdraws-provenge-sales-forecast/.

[3] Their slower onset of action compared with other therapeutic biologics represents a specific challenge for therapeutic vaccines.

Consumers are motivated to seek therapeutic treatment because they experience a current health problem, whereas preventive vaccination requires that consumers anticipate a future health problem. Marketers of preventive vaccines therefore must ensure consumer awareness of the risks of infectious disease and motivate them to take preventive action. This is particularly challenging when past vaccination campaigns have virtually eradicated a vaccine target. Beneficial outcomes from therapeutics are often easily observable because of the resulting improvement in health status (e.g., pain reduction), whereas a successful preventive vaccination does not improve the health status of the vaccinated person and can even sometimes deteriorate it due to adverse events. To perceive the benefits of prevention, individuals must engage in counterfactual thinking (Roese 1997), e.g., "If I had not gotten the flu shot, I would have caught the flu." While receiving less credit for benefits than therapeutics, preventive vaccines are easily blamed when previously healthy persons experience health problems which may be unrelated to the vaccination. Stories of healthy people presumably made sick by vaccines are very attractive for the media and may lead to an exaggerated perception of the risks of vaccination and skepticism about its value among the lay public. Ensuring an accurate perception of the benefit–risk balance therefore represents another distinctive challenge for marketers of preventive vaccines.

Many therapeutics are for chronic disease and involve daily or weekly use. Consumers therefore have an opportunity to learn from direct experience and develop intimacy with their treatment, which influences their decision to continue or switch. Except for seasonal flu vaccines, the vast majority of preventive vaccines are administered only once or very infrequently during a life time (e.g., every 10 years for tetanus booster shots). Personal use experience, therefore, plays no or a very small role in preventive vaccine treatment decisions, which are based on other sources of information such as health care professionals, advertisements, friends, information on the internet, and other media Cates et al. 2010; Kennedy et al. 2012 (Kennedy et al. 2011a; Freed et al. 2011a; Maurer et al. 2010a, b).

Both therapeutics and preventive vaccines have a direct effect on the health of treated individuals. Preventive vaccines in addition have an indirect "herd-protective" effect by reducing interindividual transmission and thereby lowering the risk of infection among unvaccinated persons (Smith 2010b). For example, it is estimated that a 50 % HPV vaccination rate of women will result in a 47 % reduction in cervical cancer incidence, with one in four cases prevented among non-vaccinated women (Bogaards et al. 2011). When individuals do not take these positive externalities into account, market failure may result, namely less vaccination than is efficient from a societal point of view (Fine and Clarkson 1986). The possibility of market failure provides a rationale for governmental interventions such as subsidies to consumers and mandatory vaccination. Mandatory vaccination, which is controversial because it restricts individual freedom in the interest of collective benefits, is another differentiating feature of preventive vaccine public markets.

Governments and supranational organizations play an even more central role in the preventive vaccine market than for therapeutics. They often subsidize R&D

and manufacturing investments in vaccines, may own vaccine manufacturers,[4] are important buyers and payers of vaccines, issue vaccination recommendations, and mandate vaccinations. Moreover, governments and supranational organizations may take responsibility for the distribution, administration, and marketing of preventive vaccines through public health campaigns.

Because of their distinctive characteristics compared to therapeutics, this chapter focuses on preventive vaccines.

13.2 The Vaccine Industry

Based on companies' annual reports, global 2010 sales of the leading vaccine manufacturers are estimated at $23.1 billion (Andrews 2011). Assuming that these companies account for 80 % of the total market (Kresse and Shah 2010), this values the global vaccine market at $28.8 billion, or 3.4 % of the total 2010 global pharmaceutical sales of $856 billion (IMS Health 2011).

Like for all pharmaceuticals, vaccine sales are generated mainly in high-income countries. For 2008, it was estimated that 77 % of global vaccine sales came from high-income markets comprising 14 % of the world's population and 8 % of the world's birth cohort (Morgon 2011). The United States represents the largest sales region (34.6 % of 2009 global vaccine sales), followed by the European Union (EU, 30.4 %), Japan (7.9 %), China (7.4 %), and India (6.4 %) (Sahoo 2010).

13.2.1 Vaccine Industry Structure

The five largest vaccine manufacturers (GlaxoSmithKline (GSK), Sanofi, Merck & Co., Pfizer, and Novartis) are also among the six largest pharmaceutical manufacturers overall, although not in the same order (see Table 13.1). They account for 80 % of global vaccine sales, which is considerably higher than the 27 % share of global pharmaceutical sales for the top five pharmaceutical companies. Except for Roche and Lilly, the top ten pharmaceutical companies have stepped up their investments in the vaccine sector in recent years, signaling the growing strategic role of vaccines in their corporate portfolio.

At 29 % (GSK) and 32 % (Sanofi Pasteur) the operating profit margins of the two leading vaccine companies are comparable to the average 30 % margin of originator pharmaceutical companies (Table 13.2). The significantly higher costs of goods sold of vaccines (38 % vs. 21 % of sales) are compensated mainly by lower marketing, sales, and administrative costs (17 % vs. 31 %). The higher vaccine costs of

[4] State-owned vaccine manufacturers include the China National Biotec Group (CNBG), the largest vaccine manufacturer in China, the Central Research Institute in India, Butantan and Fiocruz in Brazil, and PT Biofarma in Indonesia.

Table 13.1 Leading global vaccine and pharmaceutical corporations, 2010

Leading global vaccine corporations, 2010					Leading global pharmaceutical corporations, 2010				
Rank		Global sales[a] ($m)	Market share (%)	Cumulative market share (%)	Rank		Global sales[b] ($m)	Market share (%)	Cumulative market share (%)
1	GlaxoSmithKline	6,712	23	23	1	Pfizer	55,602	7.0	7
2	Sanofi[c]	5,663	20	43	2	Novartis	46,806	5.9	13
3	Merck & Co.[c]	4,117	14	57	3	Merck & Co.	38,468	4.9	18
4	Pfizer	3,667	13	70	4	Sanofi	35,875	4.5	22
5	Novartis	2,929	10	80	5	AstraZeneca	35,535	4.5	27
6	Others	5,743	20	20	6	GlaxoSmithKline	33,664	4.3	
	Global market	28,833		100		Global market	791,499		100.0

[a]*Source*: Sales of top five companies based on GSK broker presentation, sales for "others" assume the top five firms account for 80 % of the global vaccine market (Kresse and Shah 2010)

[b]*Source*: IMS Health, sales for audited markets only

[c]The sales of Sanofi Pasteur MSD are allocated 50/50 to Sanofi and Merck & Co.

Table 13.2 Revenue structure: vaccines and pharmaceuticals

	GlaxoSmithKline vaccines[a] (%)	Sanofi vaccines (Sanofi Pasteur)[b] (%)	Pharmaceuticals[c] (%)
Cost of goods sold	38	38	21
R&D	17	14	18
Marketing, sales, and administrative	17	17	31
Operating profit	29	32	30

[a]First quarter of 2011 (first time vaccine P&L was separately reported)
[b]Average of 2008–2010. Percentage of net sales
[c]Average of 32 originator companies. *Source*: European Commission (2009)

goods sold reflect the high capital intensity, the cost of highly qualified labor required by complex manufacturing processes, and the cost of meeting more stringent quality requirements. The lower marketing, sales, and administrative expenses result from the greater buyer concentration due to the high share of vaccines purchased by governments, and the smaller number of prescribers, who are mostly pediatricians plus, for flu vaccines, GPs and respiratory specialists.

In addition to the big five, three other large pharmaceutical companies, namely AstraZeneca, Abbott, and Johnson & Johnson, have recently increased their presence in the vaccine sector (Kresse and Shah 2010). Some 50 other manufacturers are located mostly in low- and mid-income countries. They generated 20 % of the global vaccine sales in value and 86 % in volume (World Health Organization (WHO), UNICEF, World Bank 2009). Most of these are local players who supply their domestic markets with low-cost high-volume old-technology vaccines. In recent years, a number of firms especially from India have upgraded their quality, obtained WHO prequalification, and become suppliers to public markets in other low- and middle-income countries. As vaccine manufacturers in China raise their manufacturing quality levels to meet WHO standards,[5] competition in low- and middle-income countries as well as in supranational tenders will further intensify, including competition for innovative vaccines. Some of the emerging market manufacturers have become suppliers of innovative products thanks to a combination of in-house R&D and strategic alliances, which have provided them with access to the required technologies (Milstien and Kaddar 2010).

The big five vaccine manufacturers dominate the markets of North America, Latin America, and Western Europe. Markets in most other regions are dominated by local manufacturers. For example, in 2009 local manufacturers captured 77 % of the market in China, 42 % in India, and 68 % in Russia (see Table 13.3). The Japanese vaccine market is also dominated by local manufacturers, with non-Japanese companies accounting for a mere 4 % of vaccine sales (Andrews 2011).[6] To increase their

[5] On March 1, 2011, WHO announced that the national regulatory authority of China met WHO indicators for a functional vaccine regulatory system, which meant that Chinese-made vaccines were henceforth eligible to apply for WHO pre-qualification.

[6] The 4 % share refers to volume. The value share of non-Japanese manufacturers is estimated at 20 % (private communication, industry executive from Japan).

Table 13.3 Competitor shares by selected regions and countries

	Western Europe (%)	Latin America (%)	China (%)	India (%)	Russia (%)
Sanofi Pasteur		29	10	36	20
Sanofi Pasteur MSD	36				
GlaxoSmithKline	30	23	10	12	8
Merck & Co.		6	Other multinational companies: 3	NA	2
Pfizer	16	27		NA	NA
Novartis	7	2		10	2
Subtotal	89	87	23	58	32
Others	11	13	77	42	68

Source: Sanofi Aventis, Vaccines IR Seminar, December 17th, 2009

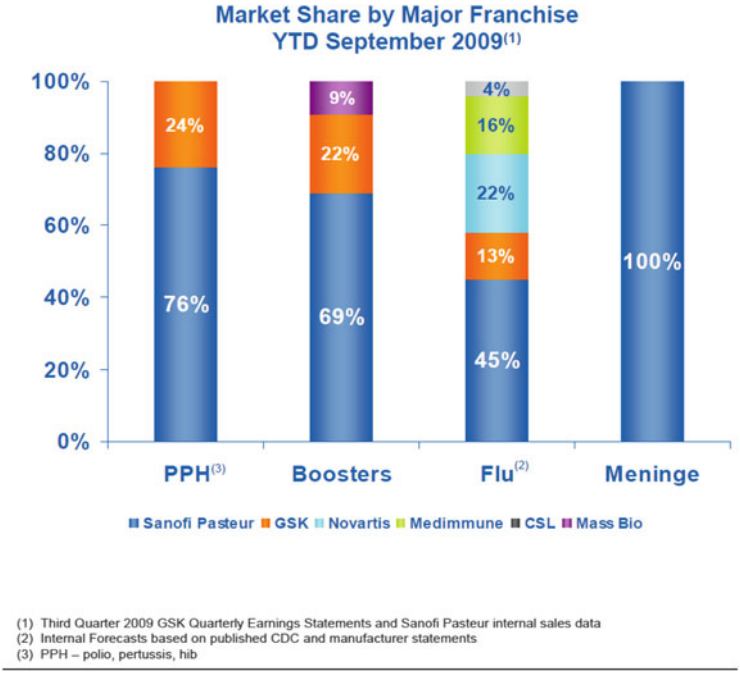

Fig. 13.2 Competitor share in selected franchises, North America. *Source*: Sanofi Aventis, Vaccines IR Seminar, December 17th, 2009

position in countries where their presence is still low, the big five have engaged in a multitude of deals and alliances with local manufacturers (Kresse and Shah 2010).

Concentration is very high in many franchises and indications. For example, Pasteur had a 100 % share of the Meningitis vaccine market in North America in 2009 (see Fig. 13.2). In the United States, 57 % of the 30 vaccine/age classes with Advisory Committee on Immunization Practices (ACIP)-recommended vaccines

Table 13.4 Number of vaccine manufacturers of ACIP-recommended vaccines posted on CDC vaccine price list, November 5, 2008

Number of manufacturers per vaccine/age class	Nr of vaccine/age classes	% of all vaccine/age classes
1	17	57
2	10	33
3	1	3
4	1	3
5	1	3
Total number of vaccine/age classes on CDC list	30	100

Source: Based on Table 3-1 in Berndt et al. (2009)

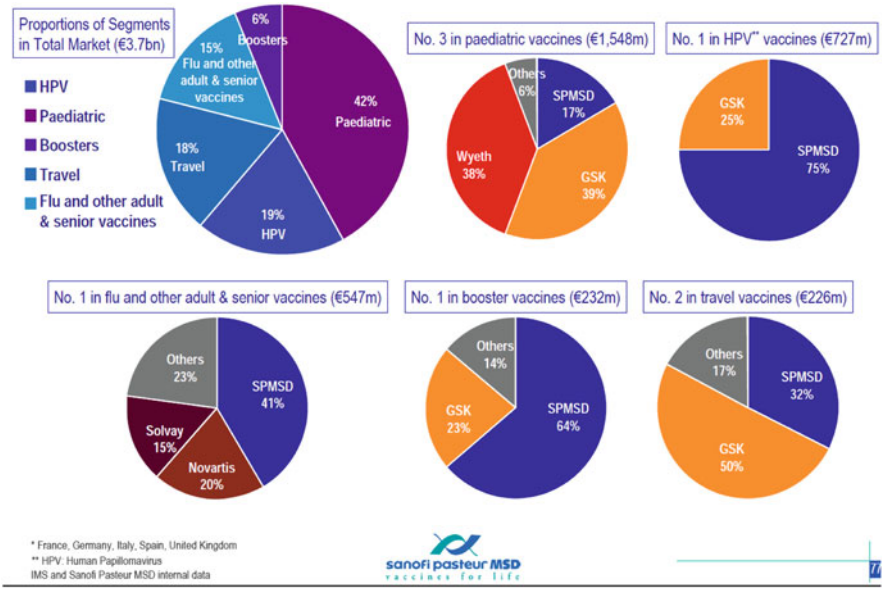

Fig. 13.3 Competitor share in selected franchises, Western Europe. *Source*: Sanofi Aventis, Vaccines IR Seminar, December 17th, 2009

had only one manufacturer, 33 % had two, and only 9 classes had between three and five manufacturers in 2008 (see Table 13.4). In Western Europe, two companies accounted for 100 % of the HPV vaccine market, and three companies for 94 % of the pediatric vaccine market in 2008 (see Fig. 13.3). Like for therapeutics, concentration is higher for novel types of vaccines than for older vaccines.

The high concentration in most high-income countries is the result of the exit of many manufacturers from the vaccine industry over the last 40 years combined with a low entry rate. For example, the number of companies manufacturing vaccines in the United States declined from 26 in 1967 to 17 in 1980 and to 3 in 2004 (Berndt et al. 2009). Countries, such as China which currently still have a large

number of vaccine manufacturers, are likely to experience future industry consolidation. Low-quality manufacturers will leave the industry as regulatory agencies raise quality standards, price competition fueled by overcapacities will reduce the number of flu vaccine manufacturers, and multinational companies will acquire emerging country players with low-cost high-volume manufacturing capabilities to compete in middle-income countries and multicountry public market tenders. Examples are Sanofi Pasteur's acquisition of the Indian company Shanta Biotechnics and the acquisition of the Chinese company Tianyuan by Novartis under 19 years.

13.2.2 Entry Barriers

Entry barriers are high in high-income countries for both innovative and follower vaccines.

Product patents play a lesser role in the vaccine industry compared to therapeutics, although they can play a role for specific antigens, adjuvants, manufacturing technologies (e.g., in hepatitis B vaccine production), and administration technologies (e.g., intradermal administration). Because of the complex production, clinical development, and regulatory approval processes, know-how in these domains represents a significant barrier to entry.

Manufacturing scale-up typically occurs in late phase II, and decisions to build expensive manufacturing capacity to scale must be made years before regulatory approval. Unlike the multipurpose manufacturing facilities for small-molecule pharmaceuticals, vaccine facilities for bulk antigen production are generally uniquely dedicated and therefore are sunk costs (Berndt et al. 2009).

High regulatory costs are another important barrier to entry. Clinical trials designed to show the efficacy of flu vaccines require large number of subjects because a low attack rate drives the need to power the clinical studies to demonstrate efficacy. Serious yet rare side effects detected for a vaccine raise the regulatory hurdles for similar vaccines. For example, subsequent to the market withdrawal of a previous rotavirus vaccine (RotaShield) due to rare but fatal adverse effects, Rotateq pre- and post-licensure safety studies ended up enrolling 70,000 children.

High fixed manufacturing and regulatory costs result in substantial scale economies. The size of a vaccine market relative to the minimum efficient scale therefore is an important determinant of entry (Scherer 2007; Danzon and Pereira 2011), which explains why there are more competitors in the large flu vaccine market than in most other, much smaller markets (see Fig. 13.2). Moreover, because vaccines are biological products, generics cannot use the low-cost abbreviated new drug application (ANDA) process that has resulted in rapid and deep market penetration by generic versions of small-molecule therapeutics in many countries. The resulting longer product life cycles of vaccines compared with small molecules are reflected in higher residual values in vaccine deal NPV calculations.

13.2.3 Threat of Substitutes and Supplier Power

Vaccines face two types of substitutes: alternative methods for preventing an infection and therapies for dealing with the consequences of being infected. For example, forthcoming malaria vaccines will compete with alternative prevention methods such as mosquito nets, insect repellents, and preventive drugs such as Lariam (mefloquine), as well as antimalarial medications such as artemisinin. Sexual abstinence to prevent HPV infection is one type of substitute for HPV vaccines, and therapies for genital warts, as well as pap testing and therapies for cervical cancer, are other kinds of substitutes for HPV vaccines. Antivirals such as Tamiflu and Relenza, which are administered to flu-stricken persons, are substitutes for flu vaccines. A price increase and/or performance decline of substitutes should increase the demand for vaccines and vice versa. Phelps (1978) and Nordquist and Wu (1976) have indeed shown that an increase in the price of curative medical care increases the demand for prevention, and demand for prevention may decline when health insurance lowers the price of curative care (Kenkel 2000).

As far as suppliers are concerned, some markets for critical vaccine manufacturing technologies and equipments (e.g., ultra centrifuges) are dominated by one or two suppliers, who command significant bargaining power. Small biotech and technology providers with valuable and rare technologies are also in a strong bargaining position vis-à-vis vaccine manufacturers.

13.3 Vaccine Customers

Like for therapeutics, the key customer roles of (1) consuming (receiving the vaccination), (2) buying (selecting the vaccine), and (3) paying (financing the purchase) are typically carried out by different persons or organizations. Table 13.5 provides examples of persons and organizations carrying out these roles in the vaccine market, and Fig. 13.4 shows a customer map.

We first describe the two main types of customer role configurations, namely private and public markets, and then discuss the following stakeholders: consumers, vaccine prescribers, organizations issuing vaccination recommendations, vaccine purchasers, and vaccination advocates and opponents.

13.3.1 Private and Public Markets

Vaccine markets are characterized as “private” or “public” markets, depending on who the buyers and payers are. In private markets, consumers and/or private insurers are the buyers and payers, whereas public players such as federal and regional governments buy and pay in public markets. Each specific vaccine generally competes in both private and public markets, with the sales mix depending on the

Table 13.5 Customer roles and examples of role holders in the vaccine market

Customer role	Role definition	Examples of persons and organizations carrying out the role
Consumer	Person who is vaccinated	Children, adolescents, adults
Buyer	Persons/organizations selecting the vaccine which is used	Consumers Prescribers National Immunization Technical Advisory Groups (NITAGs), e.g., Advisory Committee on Immunization Practices (ACIP) in the US Governments Supranational organizations, e.g., Strategic Advisory Group of Experts (SAGE) at the World Health Organization (WHO), UNICEF, Pan American Health Organization (PAHO)
Payer	Persons/organizations financing the purchase	Consumers Private insurances Federal and regional (state) governments in the vaccinating country NGOs, e.g., GAVI, and other international donors

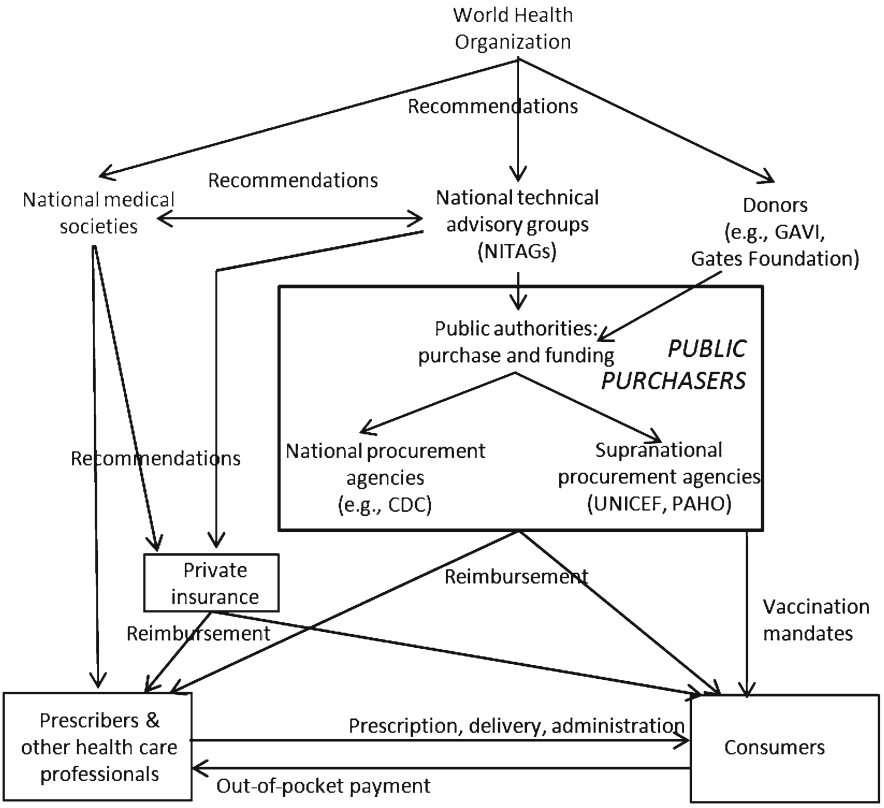

Fig. 13.4 Customers in the vaccine market

characteristics of the vaccine target group (e.g., age and risk status), the country or region, and the disease threat. In the United States, purchases through public sector programs account for slightly more than half of the market (in number of doses) for pediatric vaccines (for children 0–6 years of age), decline to one-third for adolescent vaccines (7–18 years of age) (Shen et al. 2009a, b), with public financing for adult vaccines lagging behind (Orenstein et al. 2007). When a vaccine is indicated for multiple age groups, who pays often depends on the age of the vaccinated person. For example, public programs pay for HPV vaccines for many adolescent women but not for uninsured adult women (KFF 2011). The importance of private vs. public buyers and payers also varies across countries and regions. In the Africa–Middle East–Eastern Europe region, the private/public shares are estimated at 26/74, compared to 55/45 for the Asia-Pacific region (Sanofi Pasteur 2009). Public players generally dominate when there are pandemic disease threats, as was the case for the 2009/2010 H1N1 influenza. Decisions made by public customers influence decisions in the private market. For example, private insurers in the United States tend to cover vaccines recommended for public purchase.

13.3.2 Consumers

Global vaccination rates for some vaccines and subgroups infants and children are high, e.g., 85 % for DTP, 86 % for polio, 85 % for measles, and 75 % for hepatitis B. But vaccination rates vary greatly across regions, countries (WHO 2011), and within countries. For example, the 2009 pandemic flu vaccination rate ranged between 4.8 and 92 % across 12 countries and different population subgroups (Brien et al. 2012). The 2010 US national vaccination rate of children aged 19–35 months with pneumococcal conjugate vaccine was 83.3 %, ranging from 70.8 % in Nevada to 91.1 % in Connecticut (Centers for Disease Control and Prevention 2011). Similar disparities in vaccination rates exist for other types of vaccines.

13.3.2.1 The Consumer Vaccination Decision Process

Why do some people get vaccinated and others not? To get vaccinated, an individual must engage in a number of behaviors including (1) accessing the health care system, (2) discussing vaccination with a health care professional, (3) deciding to get vaccinated, and (4) complying with vaccination.

Health care system access. Whereas children in high-income countries typically undergo a series of routine visits with health care professionals such as pediatricians, many children in low-income countries do not have access to the health care system. But even in high-income countries not everybody receives health care.

In the United States, 10.5 % of all children under 18 years had no health care visit to an office or clinic within the past 12 months, rising to 43 % among uninsured children (National Center for Health Statistics 2011).

Vaccination discussion. Every health care visit is an opportunity to discuss vaccination. But while most physicians routinely check immunization at wellness or health maintenance visits, far fewer discuss vaccination during illness or acute care visits, in which urgent concerns dominate (Schaffer et al. 2001; Szilagyi et al. 2005, 2008; Humiston et al. 2009). And wellness visits are less frequent than illness visits, especially among adolescents, for whom only 9 % of visits were for preventive care (Rand et al. 2007). The effectiveness of patient reminder and recall systems for improving vaccination rates in primary care is reviewed by Jacobson and Szilagyi (2005).

Vaccination decision. A vaccination discussion may or may not result in a decision to get vaccinated. Among adolescent girls (11–17 years) in the United States, 26 % were recommended to receive the HPV vaccine by their health care provider, but only 49 % of them actually received the HPV vaccine (Palli et al. 2010).

Vaccination can be voluntary or mandatory. Mandatory vaccination may be imposed by legislation and private organizations. All 50 US states require certain vaccinations for children entering public schools.[7] State mandates also exist for entry to colleges and universities,[8] long-term facilities, health care workers,[9] and other groups. However, many jurisdictions allow exemptions from vaccination requirements for medical or religious reasons, or when parents have philosophical or personal belief objections to vaccination.[10]

Compliance. Compliance is an issue whenever two or more doses and corresponding visits are required for effective vaccination. A study in the context of the three-dose HPV vaccination found that 72 % of US female adolescents (11–21 years) would need to make three visits in addition to their habitual physician visits if the vaccine were initiated at a preventive visit (Rand et al. 2007). Another study among young women (18–24 years) recruited by a university health clinic who were offered the three-dose HPV vaccine series for free found that just over half (50.7 %) received the first dose, 78.3 % of whom returned to receive the second dose, and 55.7 % of these returned for the third dose (Moore et al. 2010).

[7] Depending on the state, children must be vaccinated against some or all of the following diseases: mumps, measles, rubella, diphtheria, pertussis, tetanus, and polio.

[8] For example, state legislation in California requires that all students 19 years in state universities and the UC system provide proof of hepatitis B vaccination or a waiver. http://www.immunize.org/laws/hepbcollege.asp, accessed June 13, 2011.

[9] For example, New Hampshire requires that all hospital employees and inmates receive flu vaccination.

[10] http://www.vaccinesafety.edu/cc-exem.htm, accessed June 13, 2011.

13.3.2.2 Determinants of Consumers' Vaccination Behavior

Differences in consumers' vaccination behavior have been related to socio-demographic and social psychological variables.

Socio-demographic variables associated with vaccination include age, health status, gender, education, income, profession, race/ethnicity, and religion. For example, being aged 65 years and over or suffering from chronic illness or working in the medical field was the strongest predictor for having received the influenza vaccination across 11 European countries (Endrich et al. 2009). Increasing parental educational attainment was significantly associated with higher influenza vaccination uptake among US college dormitory students (Uddin et al. 2010). Combined seasonal or H1N1 influenza vaccination coverage among the US population aged ≥6 months was higher among non-Hispanic whites compared with non-Hispanic blacks and Hispanics (Setse et al. 2011). Religion was negatively associated with vaccination in the United States (Doyle et al. 2010a) and the Netherlands (Ruijs et al. 2011).

Many studies have investigated relationships between social psychological variables and vaccination intentions and behavior. The main conceptual frameworks underlying these studies are the health belief model (Becker 1974; Becker et al. 1974; Rosenstock 1974), Rogers' protection motivation theory (Rogers 1975, 1983), the theory of reasoned action (Fishbein and Ajzen 1975), and the theory of planned behavior (Ajzen 1988, 1991). The key constructs of these frameworks tend to overlap and include the following: (1) the perceived threat from a disease, (2) the attitude toward vaccination, (3) norms, and (4) behavioral control/self-efficacy beliefs. Additional factors investigated include anticipated regret and past vaccination behavior.

Perceived Threat/Risk from a Disease

The perceived threat or risk from a disease (e.g., Brewer et al. 2004; Chapman and Coups 2006; Weinstein et al. 2007) is a key construct in the health belief and protection motivation models. The perceived risk from influenza was significantly positively associated with medical students' vaccination intentions (Betsch and Wicker 2012). A low perceived risk of contracting pertussis was the main reason for not receiving tetanus diphtheria acellular pertussis (Tdap) vaccination (Miller et al. 2011). Perceived risk is based on the perceived likelihood of getting a disease (personal vulnerability/susceptibility) and the perceived seriousness or severity of the disease. Both can vary greatly across different ethnic groups (Timmermans et al. 2005).

The perceived likelihood of getting a disease is influenced by its prevalence, which economists see as an important driver of the demand for prevention: the higher (lower) the prevalence, the higher (lower) the demand for prevention (Philipson 2000). The prevalence-elasticity hypothesis predicts that the growth of infectious diseases is self-limiting because rising prevalence motivates preventive action such as vaccination, which reduces prevalence. It also predicts that vaccination success lays the ground for the return of an infectious disease because it reduces

the future motivation to vaccinate. Prevalence-elasticity can explain why in many high-income countries childhood diseases which were virtually eradicated, thanks to a very high pediatric vaccination rate, were followed by a decline in pediatric vaccination rates, which has led to a resurgence of childhood diseases. For example, measles is reemerging in Europe, with 85 % of the cases being unvaccinated.[11] In France, which accounts for more than half of the reported cases in 2011, the upsurge is attributed to a decline in the vaccination rate (Benkimoun 2011). Funk et al. (2010) review a number of models for explaining the dynamics of the disease prevalence–prevention behavior relationship.

Consumer beliefs about risk factors related to individual characteristics can also affect the perceived likelihood of getting a disease (personal vulnerability/susceptibility) and, therefore, the motivation for vaccination. For example, young women with a greater number of sexual partners had a high level of interest in receiving an HPV vaccine (Dekker 2006). Parents who believed that their child was not engaged in sexual activity and not at risk for HPV were less likely to endorse HPV vaccination or opposed to it (Brown et al. 2010). In Brewer et al.'s (2007) meta-analysis, perceived likelihood and susceptibility (e.g., "I get sick more easily than other people my age") were significant predictors of vaccination behavior.

The second factor contributing to the perceived threat from a disease is its perceived severity. In a meta-analysis, perceived severity significantly predicted vaccination behavior (Brewer et al. 2007a). In a conjoint analysis of vaccine decision-making among mid-adult women, the severity of disease was one of the two main drivers for vaccine acceptability (Stockwell et al. 2011). Poor parental knowledge about the harmfulness of measles infection seemed to be responsible for the low measles vaccination rates in Germany (Schönberger et al. 2009).

The perceived likelihood and severity of a disease are cognitive judgments. Rogers' protection motivation theory (Rogers 1975, 1983) also includes an affective component with its "threat appraisal" construct, namely fear. Consistent with this conceptualization, Chapman and Coups (2006) found that anticipated worry mediated the effect of perceived risk on influenza vaccination, and Weinstein et al. (2007) concluded that feeling at risk was a better predictor of vaccination behavior than purely cognitive risk judgments.

Attitude Toward Vaccination

The attitude toward vaccination is a key construct in all theoretical frameworks. The attitude object can be vaccination in general, types of vaccines (e.g., pediatric vaccines), or vaccines against a specific disease (e.g., flu vaccines).

Keane et al. (2005) clustered parents into four vaccination attitude and belief segments, which differed in vaccination rates: vaccine believers (33 %), cautious

[11] http://ecdc.europa.eu/en/publications/Publications/2011_June_measles_montly.pdf, accessed August 31.

(23 %), relaxed (34 %), and unconvinced (10 %). Gust et al. (2005) identified five parent segments: immunization advocates (33.0 %), go along to get alongs (26.4 %), health advocates (24.8 %), fence-sitters (13.2 %), and worrieds (2.6 %).

Most studies have been conducted about attitudes toward vaccination against specific diseases, and have generally found strong associations between attitudes, underlying beliefs, and vaccination intentions and behaviors. These associations hold both for persons who are not health care professionals (see, e.g., Dekker 2006; Flood et al. 2010; Galarce et al. 2011; Raude et al. 2010), and for decisions of health care professionals to get vaccinated (e.g., Maltezou et al. 2010; To et al. 2010; Betsch et al. 2011).

Attitudes toward vaccination are based on perceived positive (benefits) and negative (barriers) outcomes of vaccination, and their importance. Positive perceived outcomes include the efficacy of the vaccine to prevent the disease, avoid its spread to others, reduce its severity and school and work absenteeism. Negative perceived outcomes include the possibility that the vaccine itself may cause the disease which it should prevent, cause side effects such as transient swelling, redness, or fever, alleged but unfounded side effects such as autism or multiple sclerosis,[12] weaken the immune system, is painful, costly, and inconvenient (nonfinancial costs).

One generally finds that persons who perceive more positive and less negative outcomes show higher vaccination intentions and behaviors than persons with less positive and more negative beliefs. For example, parents who delayed and refused vaccines for their children were perceiving fewer vaccine benefits and were more likely to have vaccine safety concerns compared with parents who neither refused nor delayed vaccines (Smith et al. 2011b; see also Salmon et al. 2005). The belief that products may cause the very harm they are supposed to prevent violates consumers' trust and represents a "safety product betrayal." Safety product betrayals have been shown to cause negative emotions such as anger, resentment, anxiety, fear, sadness, disgust, and increase the tendency to choose options that provide less overall protection in order to eliminate a very small probability of harm due to safety product betrayal (Koehler and Gershoff 2003; Gershoff and Koehler 2011).

The perceived risk of a vaccine can vary across different ethnic groups (Timmermans et al. 2005). Different cultural values can generate divergent perceptions of the risks and benefits of a vaccine (Kahan et al. 2010), and disease prevalence may change the relative importance of efficacy and side effect beliefs. When prevalence is low (high), people worry more about the side effects (efficacy) than about efficacy (side effects) (Lantos et al. 2010).

The perceived financial costs of vaccination are directly influenced by a consumer's reimbursement regime. HPV vaccination initiation was higher for girls with more generous reimbursement regimes, and for girls that were informed personally about the reimbursement rules (Lefevere et al. 2011).

[12] A comprehensive review by the IOM (Institute of Medicine) (2011) concluded that the evidence favors rejection of a causal relationship between measles–mumps–rubella (MMR) vaccine and autism, and that there is inadequate evidence to accept or reject a causal relationship between hepatitis B vaccine and multiple sclerosis.

Beliefs about nonfinancial costs also represent a barrier to vaccination. In a US study, 17% of non-vaccinated nurses said they were too busy to get a flu vaccination (Clark et al. 2009).

Norms

Subjective norms refer to a person's perception of the degree to which important others (referents) think he or she should or should not perform the behavior (e.g., "people who are important to me would approve/disapprove of my having a swine flu vaccination"), and the person's motivation to comply with these referents (e.g., "people who are important to me influence my decision to have a swine flu vaccination," Myers and Goodwin 2011). Potential referents include governments, medical societies, physicians, family members, friends, and celebrities (e.g., "I heard a TV/movie personality suggest not getting the flu vaccine," Flood et al. 2010). Subjective norms, also called "injunctive norms," have been complemented by "descriptive norms," which refer to perceptions of what others are doing (Smith-McLallen and Fishbein 2008) (e.g., "most people I know vaccinate their children for the seasonal flu," Flood et al. 2010).

Making vaccination mandatory can raise vaccination rates substantially (Averhoff et al. 2004; Kharbanda et al. 2010; Salmon et al. 2006; Abrevaya and Mulligan 2011). However, Doyle et al. (2010b) found no correlation between meningitis vaccination rates and vaccination requirements across US states. Because most vaccination mandates and recommendations concern young children and selected groups of at-risk adults (diabetes, asthma, etc.), they may contribute to the higher vaccination rates observed among these groups compared to adolescents and adults not at risk. However, because mandatory vaccinations usually are subsidized, the impact of the mandate is confounded with the price impact. Mandatory vaccination may trigger reactance behavior (Brehm and Brehm 1981), by which people take measures to restore their perception of personal choice.

Whether or not a health care professional recommends vaccination, and the strength of the recommendation has a strong impact on a consumer's vaccination decision. Lack of provider recommendation was the most important factor explaining failure to receive the hepatitis vaccine A (Bardenheier et al. 2003). Among insured women aged 19–26 years, those who discussed the HPV vaccine with their physician and received a recommendation were overwhelmingly more likely to be vaccinated, and the likelihood of vaccination was 4 times as high when the recommendation was strong compared with when the recommendation was not strong (Rosenthal et al. 2011).

More generally, the belief that people's importance to self and support vaccination is positively associated with vaccination intention and behavior (e.g., Allen et al. 2010; Flood et al. 2010; Myers and Goodwin 2011). For example, young women who felt their mothers might not want them to be vaccinated were much less likely to complete the three-dose HPV vaccine series than those who felt their mothers would "definitely" want them to be vaccinated (Moore et al. 2010). One study found no direct influence of subjective norms on parents' vaccination intentions

(Tickner et al. 2010a, b), even though in interviews most parents said that they would attend for immunization because it was "the norm" (Tickner et al. 2007).

Descriptive norms (perceptions of how many friends already had or were considering the HPV vaccine) were the strongest predictor of HPV vaccination adoption stage among college women (Allen et al. 2009). In another study, a student became up to 8.3 % points more likely to get immunized if an additional 10 % of her friends received flu shots (Rao et al. 2007). The bandwagon effect was also evident in an experimental study of flu vaccination intentions (Hershey et al. 1994).

Other Factors

Additional factors associated with vaccination include anticipated regret, perceived and actual behavioral control, and past vaccination behavior.

Anticipated regret is a cognitively based negative emotion that arises when people imagine negative outcomes resulting from a decision. Two meta-analyses have shown that anticipated regret augments the predictive power of the theory of planned behavior (Sandberg and Conner 2008; Rivis et al. 2009), and several studies have shown that anticipated regret is a significant predictor of vaccination intention and behavior (Connolly and Reb 2003; Chapman and Coups 2006; Weinstein et al. 2007; Godin et al. 2010; Morison et al. 2010; Brewer et al. 2010). For example, HPV vaccination initiation was higher among parents who at baseline anticipated greater regret if their daughters got HPV-related disease because they were not vaccinated (Brewer et al. 2010). Anticipated regret was a stronger predictor than cognitively based risk perceptions in two studies (Chapman and Coups 2006; Weinstein et al. 2007).

People do not always control the performance of a behavior (Ajzen and Fishbein 2005). Behavioral control has been associated with vaccination intentions (Myers and Goodwin 2011; Tickner et al. 2010a, b; Petrovic et al. 2011) and vaccination behavior (Prislin et al. 1998; Payaprom et al. 2011).

Past vaccination behavior often predicts future vaccination behavior (e.g., Usher-Pines et al. 2010; Uddin et al. 2010; Flood et al. 2010). Vaccination against one infection is often associated with vaccination against others (e.g., Galarce et al. 2011; Vaux et al. 2011; Bish et al. 2011; Chor et al. 2011). For example, vaccination against HPV was associated with vaccination against hepatitis B (Jain et al. 2009), and receiving a recent influenza vaccination was associated with receiving an adult tetanus, diphtheria, and acellular pertussis booster (Tdap vaccination, Miller et al. 2011).

13.3.3 Vaccine Prescribers

Vaccine-related behaviors of health care professionals include patient vaccination status review and discussion initiation, vaccination recommendation, and delivery. Physicians differ in their vaccination behavior, and their behavior differs across

situations and vaccines. Ninety-five percent of US physicians reported that they review the immunization status of adolescent patients at health maintenance visits, whereas only 43 % reported routinely doing so at illness-related visits (Schaffer et al. 2001). Physicians in Asia initiated 56 % of conversations about HPV vaccination, but only 32 % of them were proactive initiators, defined as initiating more than 75 % of the conversations (Chow et al. 2010). Humiston et al. (2009) segmented physicians by their recommendation behavior into three groups: (1) vaccine advocates, who proactively encourage patients to receive recommended immunizations; (2) vaccine doers, who immunize as a part of their routine or do the service at the request of the patient; and (3) vaccine cautious, who may not offer immunization services or dissuade patients from receiving all recommended immunizations. Only 41 % of US primary care physicians strongly recommended a new herpes zoster vaccine, whereas almost all strongly recommended established vaccines, such as pneumococcal, tetanus, and influenza vaccines (Hurley et al. 2010). While 96 % of primary care physicians providing primary care to adults aged 19–64 years stocked at least one vaccine recommended for adults, only 27 % stocked all adult vaccines (Freed et al. 2011b).

13.3.3.1 Determinants of Physicians' Vaccination Behavior

Differences in physicians' vaccination behavior have been related to socio-demographic and social psychological variables.

Physician specialty is the socio-demographic variable most often studied. For example, physician specialty (pediatricians vs. family physicians) makes a difference for adolescent vaccination practices (Schaffer et al. 2001) and for HPV vaccination (Daley et al. 2010). Physicians who would not recommend HPV vaccination to all eligible patients were more likely to be generalists (Ishibashi et al. 2008). Internal medicine physicians were more likely to stock vaccines for adults aged 19–64 years than family physicians (Freed et al. 2011b). Other relevant socio-demographic variables include physician gender and practice characteristics. Female gender of provider was associated with a higher intention to recommend a cervical cancer vaccine (Riedesel et al. 2005). Infant combination vaccines were less likely to be used by smaller pediatric practices, by those with a lower proportion of publicly insured patients, and those with less inclusive state vaccine financing policies (Gidengil et al. 2010).

One study reported a relationship between general social psychological variables and recommendation behavior (Ishibashi et al. 2008). Physicians who would not recommend HPV vaccination to all eligible patients were more likely to have higher intrinsic religiosity and self-described themselves as being conservative. The study also found that pediatricians who recommended the recently launched HPV vaccine to all eligible patients reported earlier adoption of new drugs/vaccines.

The many other social psychological variables that have been used in studies of health care professionals' vaccination behavior can be grouped into three categories.

(1) *Medical concerns* reflect the goal to treat consumers in the medically most appropriate way. (2) *Consumer-related concerns* refer to health care professionals' beliefs about consumers' vaccination beliefs, attitudes, and behaviors, and how to deal with them. (3) *Financial concerns* represent health care professionals' beliefs about the financial outcomes resulting from their vaccination behavior.

Medical Concerns

Understanding the disease which is prevented by a vaccine makes pro-vaccination behavior more likely. Several studies have reported a positive association between physicians' perceived knowledge of and experience with a disease and their vaccination intentions and behavior (Chow et al. 2010; Kahn et al. 2005; Riedesel et al. 2005). The perception that the disease represents a significant health problem is also important. Physicians studied by Humiston et al. (2009) indicated that the prevalence, severity, and limited ability to screen for and treat a disease made vaccination more appealing. Physician perception of a high burden of rotavirus disease was associated with very likely adoption of the rotavirus vaccine (Kempe et al. 2007).

Not surprisingly, the most important vaccine characteristics to health care professionals are its efficacy (e.g., coverage of relevant strains and duration of immunity) and safety (Humiston et al. 2009; Riedesel et al. 2005; Zimmerman et al. 1997). A high level of confidence in prelicensure studies of safety was associated with very likely adoption of a newly licensed rotavirus vaccine (Kempe et al. 2007). Non-adopters of the pneumococcal conjugate vaccine were significantly more likely than adopters to report concerns about vaccine safety (Daley et al. 2005).

Health care professionals are very attentive to professional vaccination norms. The belief that the A(H1N1) vaccine would be well accepted by health professionals who administer vaccines was a main determinant of Canadian pediatricians' intention to recommend the vaccine to their patients (Dube et al. 2011). In the United States, recommendations by organizations such as the American Academy of Family Physicians, American Academy of Pediatrics, Centers for Disease Control and Prevention (CDC), and the ACIP significantly increase the likelihood that a vaccine is prescribed to eligible individuals (Riedesel et al. 2005; Kahn et al. 2005; Humiston et al. 2009; Millstein 1996; Askelson et al. 2010).

A health care professional's intended or actual vaccination of herself, a family member, or friend is associated with her vaccination behavior toward other consumers. In Ishibashi et al.'s (2008) study, pediatricians' answers to the question "would you give the HPV vaccine to your own child or the child of a close friend" was highly associated with whether or not they recommended the HPV vaccine to all eligible patients (vs. some or none). Parents often ask physicians: "What would you do if it were your child?" (Humiston et al. 2009).

Consumer-Related Concerns

One reason why physicians do not always recommend vaccination to all eligible consumers is that especially during illness visits urgent consumer concerns dominate (Szilagyi et al. 2005). Another reason may be that physicians segment consumers on the basis of their perceived vulnerability/susceptibility. Zimet et al. (2011) found that physicians gave higher priority for HPV vaccination to women who were single and dating or not dating than to women who were married or in a long-term monogamous relationship, with relationship status functioning as an indicator of the risk for HPV infection.

Some physicians see themselves as proactive advocates for vaccination and others as reactors to consumer requests. Seventy-two percent of high HPV vaccination discussion initiators in Asia agreed with the statement "It is my role to proactively provide advice on preventive health measures to my female patients" compared with 45 % of low initiators (Chow et al. 2010). Eighty percent of US pediatricians who recommended the HPV vaccine to all eligible patients agreed with the statement "I will recommend the vaccine and try to persuade those who are reluctant" compared with 38 % of physicians who recommended the vaccine to some/none of patients (Ishibashi et al. 2008). One barrier to advocating vaccination especially when it involves significant out-of-pocket payment is that physicians fear to be seen as "hard-selling an expensive vaccine" (Chow et al. 2010), or as "just trying to give my kid another shot" (Humiston et al. 2009).

Physicians' vaccination advocacy also depends on their perceived self-efficacy for engaging in vaccination discussions, and actually bringing about the desired consumer behavior. Among the physicians who were high HPV discussion initiators, 76 % felt "Quite comfortable/very comfortable initiating and conducting conversations with parents about HPV vaccinations," and 51 % felt that "a recommendation by their doctor will improve the likelihood of a mother getting her daughter vaccinated" compared with 53 % and 36 %, respectively, among the low discussion initiators (Chow et al. 2010). Daley et al. (2006, 2010) found that the perceived need to discuss sexuality prior to recommending HPV vaccine, and the belief that parents of 11- to 12-year-olds would be more likely to refuse than parents of 16- to 18-year-olds were associated with a lower likelihood and strength of recommending HPV vaccine to 11- to 12-year-old female patients.

Financial Concerns

Health care professionals are also concerned with the financial outcomes of their vaccination behaviors. The fee for vaccine administration may not adequately compensate them for the time spent (Humiston et al. 2009).

Additional financial concerns arise when physicians also dispense vaccines. In the United States, most physicians dispense both vaccines which are purchased by the government and private sector vaccines which are purchased by physicians in advance of patient demand. The latter involve costs for ordering and managing the stock, investment in refrigerators (or freezers for some vaccines), and financial risk (Shen et al. 2009b). These financial concerns can represent important barriers to physician

involvement in vaccination (Gidengil et al. 2009, 2010; Hurley et al. 2010; Freed et al. 2008a, 2011b; Campos-Outcalt et al. 2010; Coleman et al. 2009; Clark et al. 2011).

13.3.4 Organizations Issuing Vaccination Recommendations

The number of vaccine-treatable diseases and licensed vaccines has increased significantly over the last decades. Three types of organizations help consumers, physicians, governments, and private insurers define priorities: national technical advisory groups (NITAGs), national medical societies, and the WHO.

13.3.4.1 National Technical Advisory Groups

NITAGs are committees which develop recommendations on new vaccine introduction and vaccination schedules to national governments (Gessner et al. 2010).[13] The NITAG in the United States is the ACIP. Established in 1964, ACIP recommends licensed new vaccines to be incorporated into the routine immunization schedule and reviews older vaccines to consider revising its recommendations, among other tasks. ACIP guidance is sought routinely whenever a new vaccine is licensed or when there is a change in licensed specifications. In addition, ACIP designates those vaccines to be included in the federal Vaccines for Children (VFC) Program, which pays for vaccine administration to almost 50 % of American children under 6 years of age (Smith et al. 2009; Smith 2010a).

ACIP recommendations are made primarily on the basis of the burden of disease, vaccine effectiveness, and safety. Formal economic evaluation, e.g., through cost-effectiveness analysis, also plays a role in ACIP decision-making (Smith 2010a). ACIP recommendations are subject to approval of the Director of the CDC, which are part of the US Department of Health and Human Services (HSS). Except for the VFC designation, ACIP has no direct role in vaccine financing, purchasing, and administration. These decisions are made by other federal agencies, state health departments, and private insurers. However, ACIP recommendations are generally regarded as national policy, followed by public and private insurers, and set the standard of practice for physicians (Smith 2010a; Berndt et al. 2009).

Well established NITAGs can be found in all regions of the world.[14] In an international survey (Bryson et al. 2010), the presence of a NITAG was reported in 61 %

[13] Some NITAGs have broader mandates to work in other areas of communicable disease control (Gessner et al. 2010).

[14] For example, the NITAG in the UK is the Joint Committee on Vaccination and Immunisation (JCVI) (Hall 2010). Australia has the Australian Technical Advisory Group on Immunisation (ATAGI) (Nolan 2010), China the Experts Advisory Committee on Immunization Program (EACIP) (Zheng et al. 2010), and South Africa the National Advisory Group on Immunization (NAGI) (Schoub et al. 2010). More information on NITAGs can be found in *Vaccine* 28S (2010).

of 147 countries. But only 26 % of the NITAGs met all indicators of a well functioning NITAG.[15] The factors most widely considered by NITAGs when making recommendations are vaccine safety (100 % of countries), disease burden in the home country (99 %), public health/epidemiology (95 %), financial aspects such as cost-effectiveness (91 %), public perception of the disease (59 %), and recommendations from NITAGs in other countries (55 %). Vaccine effectiveness was the most widely used factor (98 %) in non-European countries (Bryson et al. 2010).

13.3.4.2 National Medical Societies

Many national medical societies issue vaccine recommendations. An internet search of recommendations on HPV vaccination identified four issuing organizations in the United States, five in Canada, and five in Spain, among others (Marquez-Calderon et al. 2009). Recommendations by medical societies have a significant impact on physicians' vaccination behavior (see section "Medical Concerns").

National medical societies can also influence recommendations issued by NITAGs. For example, the US ACIP includes liaison representatives from medical societies as nonvoting committee members.[16] They are required to bring the perspective of their organizations to the ACIP and to disseminate ACIP's recommendations back to their membership. ACIP recommendations may be developed and issued jointly with medical societies (Smith et al. 2009; Smith 2010a).

13.3.4.3 The World Health Organization

The WHO, an agency of the United Nations (UN), defines global immunization goals and plays an important role in all stages of the vaccine value chain. WHO supports vaccine and immunization R&D through partnerships (e.g., the Meningitis Vaccine Project (MVP), Butler 2010), issues recommendations to help countries decide which vaccines to introduce, sets technical specifications that form the basis of guidelines for vaccine production and prequalification, prequalifies vaccines, provides technical support to countries for the introduction of new vaccines, estimates the burden of vaccine-preventable diseases, monitors countries' immunization policies, and plays a key role in managing pandemics such as the 2009 H1N1 pandemic.

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[15] The SIVAC Initiative (Senouci et al. 2010) and PAHO's ProVac Initiative (Jauregui et al. 2011), both funded by the Bill & Melinda Gates Foundation, have as their main mission to help countries establish or strengthen their NITAG's capacity to make informed, evidence-based decisions on the introduction of new vaccines.

[16] As of 1 January 2010, ACIP liaison representatives include representatives from the American Academy of Family Physicians (AAFP), American Academy of Pediatrics (AAP; two representatives), American College of Obstetricians & Gynecologists (ACOG), American College of Physicians (ACP), and American Medical Association (AMA), among others (Smith 2010a).

For vaccine marketers targeting middle- to low-income countries, WHO vaccine recommendations and prequalifications are of particular importance.

WHO Vaccine Recommendations

WHO regularly produces and updates position papers on available licensed vaccines of public health interest, with recommendations on the optimal use of the vaccines, mainly for national public health officials and immunization program managers. The position papers are developed by the Strategic Group of Experts (SAGE), which consists of 15 international experts. SAGE takes into consideration issues such as disease epidemiology, clinical characteristics (e.g., clinical management of disease), vaccine and immunization characteristics (e.g., efficacy, population impact of vaccine; safety; vaccine availability and supply), economic considerations (e.g., cost-effectiveness and affordability of immunization), health system opportunities, and the existence of, and interaction with, other existing intervention and control strategies (Duclos et al. 2011; see also Milstien et al. 2010). SAGE global recommendations are reviewed and adapted at the regional level by WHO regional offices (Levine et al. 2011).

WHO recommendations are reported to be central to the vaccine policy process especially in developing countries and international funding agencies such the GAVI Alliance (Duclos et al. 2011). Seventy-eight (89 %) out of 88 NITAGs reported using WHO position papers when making recommendations (Bryson et al. 2010). However, an analysis of country adoption of Haemophilus influenzae Type b (Hib) vaccine found no influence of WHO position papers on country time to adoption (Shearer et al. 2010).

WHO Prequalification of Vaccines

The UN Agencies UNICEF and Pan American Health Organization (PAHO), which are important purchasers of vaccines, only purchase vaccines which have received WHO prequalification, the main goal of which is to assure that a specific vaccine meet international standards of quality, safety, and efficacy. A prerequisite for prequalification of a specific vaccine is that the national regulatory agency of the country of manufacture meets the WHO criteria for a "functional" regulatory authority. As of July 2012, 22 countries had such functional regulatory authorities, China being the most recent addition.[17]

[17] The list includes 4 agencies in the Americas (United States, Canada, Brazil, and Cuba), 11 agencies in Europe, 5 in Asia (China, India, Indonesia, Japan, and Korea), Senegal, and Australia. http://www.who.int/immunization_standards/national_regulatory_authorities%20/offices/en/index.html/, accessed August 15, 2011. The Chinese State Food and Drug Administration (SFDA) achieved joined the list in March 2011, http://www.who.int/immunization_standards/vaccine_regulation/nra_china_functional/en/, accessed August 15, 2011. http://www.who.int/immunization_standards/national_regulatory_authorities/offices/en/index.html, accessed July 4, 2013.

Vaccines which have been prequalified can compete for UNICEF and PAHO business. Because WHO prequalification is a quality signal, many individual countries use the list of WHO prequalified vaccines when purchasing directly from vaccine manufacturers (International AIDS Vaccine Initiative 2008a). WHO prequalified vaccines are subject to routine site audits and can be delisted in case the requirements for prequalification are not met.[18]

13.3.5 Vaccine Purchasers

13.3.5.1 Public Purchasers

In public markets, the decision to purchase a vaccine, its procurement, and its funding is often under the responsibility of different organizations.

The Decision to Purchase a Vaccine

The decision to purchase a vaccine can be made by national and regional authorities. For example, the US NITAG ACIP can add a vaccine to the federal VFC program, which funds vaccines for low-income children. At the same time, individual states can decide to purchase a vaccine for children not eligible for VFC, or to purchase a vaccine not funded at all by a federal program (Orenstein et al. 2007; Lindley et al. 2009; Freed and Cowan 2002).

A vaccine which has secured a recommendation from a country's NITAG has a much greater chance of being purchased by that country's public purchasers than one without. In most countries, NITAG recommendations are advisory, but sometimes they are mandatory, for example in the UK (Hall, 2010), and in the U.S. when ACIP designates a vaccine for VFC funding.[19] In Australia, a positive NITAG recommendation is a necessary condition for government funding of a new vaccine (the government cannot fund without a positive recommendation), but is not sufficient (the government is not obliged to fund when the recommendation is positive) (Nolan 2010).

Public opinion and political pressure can influence public vaccine purchasing. For example, the initial negative recommendation concerning the HPV vaccine Gardasil by the Australian NITAG immediately unleashed widespread opposition, prompting the Health Minister and the Prime Minister to express their

[18] An example of a recent delisting announcement can be found at the following address: http://www.who.int/immunization_standards/vaccine_quality/DTP_mono_hepb_aug2011/en/index.html, accessed August 23, 2011.

[19] To make a UK NITAG recommendation binding, the recommendation must be based on a question specifically referred by the Secretary of State, be based on an assessment which demonstrates cost-effectiveness, and not relate to travel or occupational health (Hall 2010).

support for funding. Less than 4 weeks later, the NITAG reversed its recommendation from negative to positive, and Gardasil obtained government funding (Roughead et al. 2008).

Affordability of a vaccine is another important factor in public vaccine purchasing. Budget limitations were the most common reason for lack of implementation of NITAG recommendations reported in a study of 15 NITAGs (Gessner et al. 2010). The decision by a public purchaser to purchase a new vaccine essentially implies a commitment to endless funding, since (save for smallpox) infectious diseases are never fully eradicated. To free up budgetary resources and create "fiscal space" for new vaccines, public purchasers put pressure on the prices of older vaccines. Thanks to their greater budgetary resources, high-income countries have historically adopted new vaccines rapidly, whereas in low-income countries vaccine uptake was delayed by 15–20 years despite their higher burden of disease (Levine et al. 2011).

A recent 147-country multivariate analysis of the time to adoption of the Hib vaccine showed that, compared to high-income OECD countries, time to adoption was longer for other countries. Other variables associated with a longer time to adoption were a higher vaccine price and higher GAVI cofinancing uncertainty. Variables associated with a shorter time to adoption were eligibility for GAVI financial support, having neighbor countries who already have adopted the vaccine, and a higher degree of democracy (Shearer et al. 2010).

Vaccine Procurement by Public Purchasers

Authorities may procure a vaccine directly from the manufacturer, through a public procurement agency which pools purchases to obtain more favorable conditions, or they may let health care professionals manage procurement. Public procurement agents may operate at the national level, pooling purchases from subnational authorities, or at a supranational level, pooling purchases from several countries.

In the United States, most vaccines for public immunization programs are procured by the CDC on behalf of subnational jurisdictions. The original "winner take all" contracts were later replaced by multiple-supplier contracts that guaranteed the largest market share to the lowest bidder, followed by the current approach, under which CDC negotiates each year federal contract prices for all public immunization programs receiving CDC funds.[20] The contract prices, published together with the manufacturers' list prices on the CDC website, range from 4 to 67 % below list prices (Centers of Disease Control and Prevention 2011). States and other jurisdictions purchase vaccines through the CDC at the federal contract price. Individual US states also purchase vaccines directly in some circumstances.[21] When the CDC has contracted

[20] CDC provides funds to states and other jurisdictions under the VFC program, which finances all ACIP-recommended childhood vaccines, and Section 317 funds, a program for which there are no eligibility requirements. The 317 funds must be appropriated each year by Congress.

[21] States purchase directly from a manufacturer when there is no federal contract for a specific vaccine, and when they are not allowed to rely on the federal contract for a vaccine, because they are using

different vaccines targeting the same disease, states are free to choose from among them (Institute of Medicine 2003). Some states select a subset among the competing brands to reduce system complexity and costs, while others leave the choice up to the health care professionals ("provider choice"), hoping this will raise the willingness of private practices to provide public vaccines (Freed and Cowan 2002).

The UK National Health System (NHS) has a dual system for procuring vaccines for its universal vaccination programs. Vaccines for the routine childhood program are procured centrally by the Department of Health and distributed directly to GPs. Vaccines for the seasonal flu vaccination program, however, are procured by GPs, who receive reimbursement for the cost of the vaccine plus a fee for procuring the vaccine. The NHS is currently considering central procurement of seasonal flu vaccine, a move which it estimates would reduce vaccine costs by 35 % and procurement administration costs by 76 % (Department of Health 2011).

The UN's UNICEF Supply Division and the Revolving Fund of the PAHO are the two most important supranational vaccine procurement agencies.[22] The UNICEF Supply Division is the major procurer of vaccines for low-income countries,[23] procuring immunization supplies on behalf of around 80–100 countries annually, reaching 58 % of the world's children. In 2010, UNICEF procured around 2.5 billion doses of vaccines, at a value of $750 million.[24] UNICEF procures only vaccines that have been WHO prequalified.[25] To promote vaccine security (the uninterrupted, sustainable supply of affordable vaccines of assured quality) UNICEF tries whenever possible to procure each vaccine from several manufacturers instead of pursuing a "winner takes all" policy (International AIDS Vaccine Initiative, 2008b). Countries or donors pay for vaccines upfront by depositing the needed funds with UNICEF, which provides manufacturers with demand forecast, and enters into multiyear supply arrangements (International AIDS Vaccine Initiative 2008b). A recent change in policy from posting only average prices to posting prices for individual vaccines[26] from manufacturers having given permission to do so revealed significant price differences. Some companies disclosed their prices, others refused, but all agreed not to disclose their cost structures. UNICEF hopes that the increased price

nonfederal funds, particularly funds from insurance companies (Benatar et al. 2010). Despite their smaller purchase volume, some states have reported instances in which they were able to negotiate a price below the federal contract price (Freed and Cowan 2002).

[22] The Gulf Cooperation Council (GCC), which procures vaccines for the UAE, Bahrain, Saudi Arabia, Oman, Qatar, and Kuwait, is another supranational vaccine procurement agency. See DeRoeck et al. (2006) for a review of the GCC.

[23] Excluding China, India, and Indonesia, 92 % of the 2007 birth cohort in low income and 47 % of the birth cohort in lower middle income countries were covered by UNICEF procurement. The percentage of UNICEF procurement in high income OECD countries was 0 %, 2 % in high income non-OECD countries, and 1 % in lower middle income countries (Rosenbom 2010).

[24] http://www.unicef.org/supply/index_vaccines.html, accessed August 22, 2011.

[25] UNICEF procures for governments, NGOs, UN agencies, international financial institutions, philanthropic organizations, and universities, but not for profit-making entities and individuals.

[26] http://www.unicef.org/supply/index_57476.html.

transparency will lead to a more competitive market and lower prices, especially for newer vaccines (McNeil 2011).

PAHO's Revolving Fund is a mechanism for the joint procurement of vaccines, syringes, and related supplies for PAHO's 35 member states.[27] In 2007, PAHO purchases amounted to about $225 million, with Brazil, Argentina, Colombia, and Venezuela being the top four purchasers by value (International AIDS Vaccine Initiative 2008b). PAHO procures only vaccines that have been WHO prequalified or approved in the United States, EU, Canada, Korea, or Australia. Manufacturers are selected based on the lowest price, the quantity offered, and the producer's quality and service record. To guarantee supply, PAHO contracts with at least two manufacturers. PAHO publishes weighted average vaccine prices per dose[28] and claims that a country that purchases through PAHO can save at least 14 % compared to purchasing directly from the producer (Pan American Health Organization 2010).

Funding of Public Vaccine Purchases

Public purchasers can finance vaccines with government funds (national and subnational fiscal resources) or with funds obtained from donors.

The share of government financing of vaccines used in routine immunization was estimated at 94 % in the Americas, 92 % in Europe, 84 % in the West Pacific, 79 % in the Eastern Mediterranean, 53 % in Africa, and 49 % in South East Asia. Having a specific line item for vaccines in the national health budget, as was the case for 86 % of countries in 2006, was associated with increased governmental budget allocations for vaccines and routine immunization financing (Lydon et al. 2008). Government-funding based on entitlement programs can accommodate the cost of new vaccines more easily than programs which depend on annual discretionary appropriations. For example, in the United States, vaccine funding under the VFC entitlement program increased by nearly 400 % from fiscal year 2000 to fiscal year 2008, compared with a mere 42 % increase for the discretionary Section 317 program (Lindley et al. 2009).

Donor financing of vaccines is particularly important in low-income countries, where total per capita government spending on health averaged about $15 in 2008 (Saxenian et al. 2011), while the cost of vaccinating a child fully through age 18 at the US federal contract price amounted to $1,105 for boys and $1,407 for girls (Lindley et al. 2009). Vaccine expenditures without donor contributions in low-income countries would have accounted for 4.2 % of government spending on health in 2010, rising to 6.3 % in 2015. By comparison, spending on vaccines in Latin American countries, which tend to be early adopters of new vaccines, amounts to slightly less than 1 % of government spending on health (Saxenian et al. 2011).

[27] As of August 2001, the 35 member states include Argentina, Brazil, Canada, Mexico, and the United States, among others.

[28] http://new.paho.org/hq/index.php?option=com_content&view=article&id=1864&Itemid=2234&lang=en%20, accessed July 4, 2013.

The GAVI Alliance, a public–private partnership between the Bill & Melinda Gates Foundation, WHO, UNICEF, and the World Bank, created in 2000 to promote immunization in the poorest countries, is the most important international nongovernmental vaccine funding source. GAVI pools donor contributions, and funds approved applications for the purchase of new and underused vaccines by eligible countries. Only countries with a per capita gross national income (GNI) equal to or less than US$ 1,500 are eligible. To ensure that GAVI funding comes in addition to and does not substitute or "crowd out" current funding, only vaccines that are not already introduced in the routine schedule and already financed are supported.[29] Procurement of GAVI-financed vaccines by UNICEF, the main procurement channel of GAVI,[30] reached about $360 million, representing 42 % of UNICEF's total vaccine procurement.[31] In countries which introduced vaccines with GAVI support, GAVI's share of the 2008–2010 immunization financing per infant was projected at 46 %, followed by governments (38 %), and multilateral and other donors (16 %) (Zuber et al. 2011).

Following the June 2011 pledging conference, GAVI's total available resources for the period 2011–2015 amount to $7.6 billion.[32] Through its various activities, GAVI has significantly raised the attractiveness of low-income markets by increasing the size and reliability of demand forecasts, which are key inputs for manufacturers' investment decisions. GAVI's challenge for the future is to help low-income countries increase national ownership and financing of immunization, while continuing to raise the funds necessary to support the countries which will still need external support (Saxenian et al. 2011).

13.3.5.2 Private Purchasers

In the United States and many other countries, physicians dispense vaccines, in addition to prescribing and administering them. In countries which do not allow physician-dispensing, as is the case in France, patients must make a first physician visit to obtain a prescription, get the vaccine from a pharmacy, take the vaccine

[29] The number of potentially supported vaccines expanded from the initial three (vaccines against Hib, hepatitis B, and yellow fever) to currently six (pneumococcal, rotavirus, and meningococcal A conjugate vaccines).

[30] For GAVI-eligible countries in Latin America, PAHO is GAVI's primary procurement partner (Anonymous 2011).

[31] http://www.unicef.org/supply/index_gavi.html, accessed August 23, 2011.

[32] http://www.gavialliance.org/library/news/press-releases/2011/donors-commit-vaccine-funding-to-achieve-historic-milestone-in-global-health/, accessed August 23, 2011. Donors (governments, foundations, private individuals, and companies) support GAVI through direct funding, long-term pledges to the International Finance Facility for Immunisation (IFFIm), an innovative financing mechanism which converts the commitments into immediately available cash resources by issuing bonds on the capital markets, and long-term pledges to the Advance Market Commitment (AMC) for pneumococcal disease (Kremer 2001a, b; Snyder et al. 2011).

home—hopefully not during a long trip on a hot day—stock it in their refrigerator, and then return with the vaccine to the physician for administration.[33]

Physicians are the main private market purchasers in countries which allow physician-dispensing. Other private market purchasers include pharmacies, hospitals, and—for influenza vaccines—employers.

The Decision to Purchase a Vaccine

Vaccine-dispensing physicians usually have both public and private vaccines in their refrigerator. Public vaccines are purchased by the authorities and made available to physicians at no cost. Private vaccines are purchased by physicians and involve the economics typical of pharmacies and other types of distributors. Key concerns include consumer demand, the profit margin, asset turnover, financial leverage (asset/equity ratio), and financial risk.

Drivers of the private consumer demand for a vaccine include the size of the population for which the vaccine is licensed, whether the vaccine is recommended by the country's NITAG and for which population, consumers' out-of-pocket costs, and the promotional effort for vaccination and the vaccine brand, in case there are competing brands. The speed, breadth (percent of the eligible population), and extent of insurance coverage (percent of the total retail price which is reimbursed) are important factors for the uptake of a new vaccine (Shen et al. 2009b).

Many US physicians complain about the profit margin from vaccines (see section "Financial Concerns"). In one study, one or more practices reported that the vaccine purchase price exceeded the most common payer reimbursement for 15 out of 21 vaccines (Freed et al. 2008b). In another study, the net profit margin (vaccine revenues minus vaccine expenses) was higher for patients with private insurance reimbursement than for Medicaid-enrolled patients, many of whom generated a negative net margin (Hunsaker et al. 2009).

Because asset turnover is reduced when physicians carry several brands of vaccines that target the same disease, physicians prefer to concentrate their purchasing on one of the brands.[34] Financial leverage is influenced by the payment terms of the vaccine supplier compared with the speed of insurance reimbursement. Financial risk derives mainly from demand and supply uncertainty. When the amount of vaccines purchased exceeds demand, physicians may experience high inventory, obsolescence, and expiration costs, the risk being especially high for seasonal vaccines such as influenza and for new vaccines. Purchasers attempt to shift the risks of over-stocking by requesting a returns policy. Such a policy requires monitoring by a manufacturer, to ensure that his vaccine is not the "first in but last out" at the purchaser.

[33] There is also an inofficial route in which pharmacists dispense a vaccine to regular clients, who subsequently return with the prescription obtained during the vaccine administration visit.

[34] Spreading purchases over several brands also reduces the profit margin because of higher purchase prices due to a lower purchase volume per brand.

Vaccine Procurement by Private Purchasers

Private purchasers can procure vaccines directly from vaccine manufacturers, purchasing cooperatives/buying groups, or distributors. A US study found a wide range of prices paid by physician practices for the same vaccine product, with the difference between the highest and lowest prices exceeding 100 % in several cases. More than half of the practices participated in a purchasing cooperative for at least some of the vaccines they purchased. Practices participating in purchasing cooperatives, medium and large practices, and those located in metropolitan statistical areas (MSAs) tended to purchase at lower prices. The average private-practice prices were higher than the federal contract price for 20 out of 21 vaccines studied (Freed et al. 2008b).

Vaccine Funding of Private Purchases

A vaccine which is not publicly purchased can be fully funded through private insurance, partially funded by private insurance with cost sharing by consumers, or funded entirely out-of-pocket by consumers.

In the US, ACIP recommendations are the main factor driving vaccine coverage decisions for children and adolescent vaccines by private insurers in the United States (Hunsaker et al. 2009). ACIP recommendations also influence private insurance coverage of vaccines recommended for adults. However, insurance plans require more cost sharing for adults than for children and adolescents (Orenstein et al. 2007; Shortridge et al. 2011).

Vaccine coverage decisions by private insurers may also result from legal mandates. For example, New York state requires that health plans cover recommended childhood vaccinations and that the coverage must be "first dollar," that is, deductibles, coinsurance, or copayments cannot apply (Benatar et al. 2010). A key provision of the US 201 Patient Protection and Affordable Care Act ("Affordable Care Act") which increases mandatory vaccine coverage is expected to reduce financial barriers to vaccinations for many consumers (Adult Immunization Working Group to the National Vaccine Advisory Committee 2011; Tan 2011).[35]

13.3.6 Vaccination Advocates and Opponents

Vaccination beliefs, attitudes, and behaviors are also influenced by individuals and organizations other than the preceding types of stakeholders. Their aim can be to promote vaccination or, on the contrary, oppose it.

HPV vaccination provides an example of pro- and anti-vaccination advocacy. Women in Government, a US organization for elected women in state governments

[35] All new health plans, and health plans that lose their grandfathered status, must provide all ACIP-recommended vaccines delivered by an in-network provider at no cost sharing.

focused on public policy issues, particularly those affecting women, played an important advocacy role for HPV vaccination (Baron 2008). In Europe, a number of civil society organizations actively supported the HPV vaccination agenda (Laurent-Ledru et al. 2011). Opponents in the United States were found mainly in conservative Christian groups who feared that HPV vaccines would spur promiscuity and undermine abstinence (Guyon 2005; Baron 2008).

Opposition to vaccination has a long history, starting in the eighteenth century with the first vaccine (Poland and Jacobson 2011; Spier 2001; Offit 2011). Concerns about vaccine safety are fueled by generally unsubstantiated anti-vaccination writings, which can lead to vaccination refusals and subsequent disease resurgence (Leask et al. 2010; Larson et al. 2011). A well-known case is a 1998 article in *The Lancet* claiming that the MMR vaccine causes autism. The article was formally retracted and recently shown to have been an elaborate fraud (Deer 2011; Godlee et al. 2011).

13.4 Vaccine Marketing Decisions

13.4.1 Deciding Where to Compete

The main dimensions for segmenting the vaccine market are disease targets, consumers, countries, and products (technologies).

The CDC website lists 26 different diseases which are preventable with currently existing vaccines.[36] Preventive vaccines against at least another 12 diseases are under development (Business Insights 2009).

The potential consumers for each vaccine are usually segmented by age (e.g., infants, children, adolescents, and adults) and/or other indicators of increased risk for the disease (e.g., injecting drug users for hepatitis B). Country/region is an additional important segmentation variable for consumers because of regional variations in disease risk, vaccine efficacy, and other country/region characteristics.

Differences in vaccine products, finally, are a fourth dimension for structuring the vaccine market. Vaccines can be classified by product technology (e.g., live attenuated (weakened) organisms and killed (inactivated) whole organisms), process technology (e.g., egg-based vs. cell-based production), delivery method (e.g., injectable and intranasal), number of diseases targeted (single- vs. combination vaccines), valence (mono- vs. multivalent vaccines), and other product characteristics.

The attractiveness of the various disease/consumer/country/region/product segments is typically assessed through variables including segment size and growth, and segment profitability drivers such as competitive rivalry, buyer power, entry barriers, and threats from substitutes (Porter 1980). Vaccine-specific indicators underlying assessments of segment size and growth include population/birth cohort

[36] http://www.cdc.gov/vaccines/vpd-vac/default.htm#newvacc, accessed August 28, 2011.

size and growth, actual and perceived burden of disease, per capita income and its growth, immunization programs (against what diseases? for which consumers? how funded?), and relevant characteristics of the health care delivery system (e.g., physician and nurse density, and cold chain characteristics).

13.4.2 Creating Competitive Advantage

To achieve a competitive advantage in the segments in which a firm competes, it must drive a wider wedge between willingness to pay and costs than its competitors (Ghemawat 2010). Differentiation, low-cost, and dual advantage are the three generic strategies through which firms attempt to achieve a competitive advantage (Porter 1980; Ghemawat 2010).

Multinational vaccine manufacturers tend to pursue differentiation strategies. Product-based differentiation seeks to increase vaccine efficacy, safety for consumers and vaccinators, convenience of administration (e.g., one instead of multiple doses, combination vaccines to reduce the number of visits and injections per person, and administration devices such as intradermal syringes for Sanofi Pasteur's Intanza flu vaccine), tolerability (e.g., no or less painful injection), and reduce logistics requirements (e.g., less stringent cool chain requirements and longer duration of conservation).

Among the non-product-based differentiation tools reliability of supply is particularly important. There is a history of vaccine shortages, rationing, and black markets, due both to production failures associated with the complexity of vaccine manufacturing and the small number of suppliers for many vaccines (Scherer 2007).[37] In some countries, governments expect that multinational companies invest in local facilities (e.g., formulation, fill, and pack plants) and/or technology transfers. Responding to these expectations may provide a differentiation advantage. Services provided to physicians and distributors are other avenues to achieving differentiation.

Differentiation fails if the costs associated with differentiation are high relative to the incremental willingness-to-pay. Investments in local facilities and other services may generate incremental costs, which may be higher than the incremental willingness-to-pay. Product improvement efforts may be similarly misguided. For example, believing that its nasal spray influenza vaccine FluMist (direct cost $15 per dose) would be valued highly in comparison with traditional flu injections (direct cost $3.50 per dose), MedImmune priced FluMist at $46 per dose, triple the price of a traditional flu shot, invested $43 million in measured media for the launch

[37] The H1N1 pandemic raised fears that it might spread to the flocks that produce the eggs required for flu vaccine production and thereby strangle vaccine supply. This stimulated the development of new process technologies such as cell-based production systems which are expected to increase the speed and volume of flu vaccine supply (Extance 2011).

season, and produced 4 million doses. Actual sales amounted to about 400,000 doses (Thomaselli 2004; Calkins 2004).

Differentiators are also threatened by competitors who attempt to match the differentiator's offering, while operating at lower costs. Vaccine manufacturers based in low-cost countries who have achieved WHO prequalification represent such a threat to multinational vaccine manufacturers' sales in low-income countries and progressively also in middle-income countries.

Some low-cost vaccine manufacturers may enjoy a competitive advantage vis-à-vis multinational firms even if they do not achieve willingness-to-pay parity as long as their cost advantage is larger than their willingness-to-pay gap. Their cost advantage allows them to compete successfully in low-income countries where buyers value a low price more than product- and non-product performance differences. Multinational manufacturers attempt to counter this threat through acquisitions of and partnerships with low-cost manufacturers.

13.4.3 Product and Branding Strategy

Compared with therapeutics, the size of vaccine product lines is modest even for the largest vaccine manufacturers. GSK, the number one vaccine firm, had only "over 30" approved products in 2010 (Andrews 2011). Product lines grow in size through the addition of vaccines against new disease targets, and by developing differentiated versions of existing vaccines.

Four factors encourage vaccine differentiation. (1) Differences in vaccine efficacy across consumer segments: because standard flu vaccines are less effective for elderly, Sanofi Pasteur launched High Dose FluZone for the elderly. (2) Differences in vaccine efficacy across regions: for example, a Hib vaccine effective in Finland was not in Alaska, and Chilean infants raised 3 times higher antibody responses than did children in Belgium (Moxon and Siegrist 2011). (3) Diversity in preferences for other product features, e.g., needle-phobia is higher among children than adults. (4) Diversity in ability to pay: for example, Sanofi Pasteur offers three vertically differentiated pertussis vaccines—a whole cell pertussis vaccine; a 2-component acellular pertussis (acP) vaccine; a 5-component acP vaccine—at different prices in different markets. Pfizer markets Prevnar, which protects against 7 serotypes, and Prevnar 13 with protection against 13 serotypes, at different prices. Moreover, price discrimination can be more easily sustained with product differentiation, and differentiated products can justify higher prices. For example, Sanofi Pasteur's High Dose FluZone and IntraDermal flu vaccine are sold at a premium compared to standard vaccines in the United States.

The main obstacle to vaccine differentiation is the increase in complexity and cost for vaccine manufacturers and buyers. Doubling the number of vaccines in a country and introducing single-dose vials in addition to multi-dose vials (for safety reasons and to reduce the waste that occurs when a partially used vial has to be discarded) are estimated to increase vaccine storage needs by 500 % or more (Kaufmann

et al. 2011). Product differentiation also increases costs for vaccine-dispensing physicians, because ordering, stocking, and handling several vaccines instead of one significantly increase costs and risks. This explains why physicians prefer vaccines that are licensed and recommended for a broad group of consumers over products with a narrower license. For example, GSK's adolescent and adult DTP booster vaccine Boostrix, indicated for individuals 10 years and over, represents a threat to the leadership of Sanofi Pasteur Adacel's, which is limited to individuals between 11 and 65 years.

Global branding of vaccines depends on companies' manufacturing strategy. Because brand names are linked to regulatory dossiers which, in turn, are linked to manufacturing sites, the same vaccine produced at a different site must carry a different brand name. For example, GSK markets two flu vaccine brands—Fluarix and Flulaval—each of which is produced at a different manufacturing site. Global branding therefore requires that a vaccine sold throughout the world be produced at only one manufacturing site.

The big five vaccine manufacturers pursue different branding policies. GSK, Merck, and Pfizer-Wyeth use their corporate brand, plus product brands. Novartis uses Novartis (in large letters) Vaccines (in small letters) as a master brand (Aaker 2004), plus product brands. Sanofi Pasteur is Sanofi's master brand for vaccines. It combines the corporate brand (Sanofi) with the product family brand Pasteur, which leverages the valuable equity of Louis Pasteur, the creator of the first vaccine against rabies and anthrax. GSK's product names provide a horizontal link across all vaccine products (Keller 2008) through the use of the suffix "rix," as in Cervarix (HPV vaccine), Rotarix (rotavirus vaccine), and Havrix (hepatitis A vaccine). Sanofi Pasteur uses the suffix "cim" for its 2-component acP vaccines (Pentaxim, Tetraxim, Hexaxim), and "cel" for its 5-component acP vaccines (Adacel, Daptacel, Pentacel).

13.4.4 New Vaccines

13.4.4.1 New Vaccine Development

One direction for new product development in the vaccine industry is to develop vaccines for new disease targets. The second direction for new vaccine development is to improve existing vaccines in terms of efficacy, safety, convenience, tolerability, manufacturability, transportability and storability, and cost and ease of delivery.

When target antigens are constant and do not vary over time, as is the case for MMR, yellow fever, tetanus, diphtheria, and Hib, existing vaccines maintain their efficacy. Improvements of these vaccines are therefore less frequent and focus on attributes other than efficacy. But when there are variations in the target vaccine antigens, the efficacy of existing vaccines may change. For example, influenza A antigens vary from one season to the next. To maintain efficacy, vaccines against this disease

and others with similar dynamics require periodic changes. A disease like HIV with its high and unpredictable variation of HIV antigens represents a major challenge for the development of HIV vaccines (Moxon and Siegrist 2011). The development of vaccines with sustained efficacy against dynamic target antigens would represent a major scientific breakthrough with significant commercial potential.

Berndt et al. (2009) compared development times, success probabilities, and development costs of vaccines and other pharmaceuticals. Development times for vaccines have been shorter than for other types of pharmaceuticals, while mean vaccine FDA approval times have been longer, particularly for follow-on vaccines. But the average capitalized costs are probably similar. Light et al. (2009) estimated the capitalized R&D costs (without taking into account the cost of failures) of Merck's RotaTeq rotavirus vaccine at $205–644 million and of GSK's Rotarix at between $172 and $551 million.

Because of their impact on public health, governments are more strongly involved in the development of vaccines than of therapeutics. The 2010 U.S. National Vaccine Health Plan defines as one of its goals the development of new and improved vaccines, requiring the prioritization of new vaccine targets of domestic and global public health importance (U.S. Department of Health and Human Services 2010). The U.S. Biomedical Advanced Research and Development Agency (BARDA) issues requests for proposals for prioritized vaccines that include Target Profile Specifications (TPP) including desired indications, formulations, dosing, delivery mechanisms, packaging, storage and transport, shelf life, or other considerations (Institute of Medicine 2010).[38]

Governments promote vaccine development through "push" and "pull" mechanisms. "Push" mechanisms subsidize costs, whereas "pull" mechanisms increase demand. Push mechanisms include direct financing of vaccine development, facilitating research, harmonizing regulatory requirements, and tax credits for vaccine research (Lieu et al. 2005).[39] Advance Market Commitments (Kremer 2001a, b; Snyder et al. 2011), which guarantee that manufacturers will be able to recoup production costs, as well as investments in development, manufacturing capacity, and production costs, are an example of a "pull" mechanism.

Four models of organizing vaccine research and development have been identified (Wilson et al. 2007): (1) predominantly private sector development; (2) public sector vaccine design, and transfer to the private sector for clinical trials and production; (3) predominantly public sector development; and (4) coordination by a nonprofit entity, for example, by public–private product development partnerships (PDPs). PDPs are involved in efforts to develop vaccines against AIDS (e.g., the International AIDS Vaccine Initiative, IAVI), malaria (e.g., the Malaria Vaccine Initiative), and tuberculosis (e.g., the Aeras Global TB Vaccine Foundation) (Institute of Medicine 2010; see also Eskola and Kilpi 2011).

[38] https://www.medicalcountermeasures.gov/FederalInitiatives.aspx.

[39] For example, in February 2011 Novavax received a contract from BARDA for up to $180 million for the development of a recombinant flu vaccine. And the US government invested over a billion dollars to help vaccine companies make the transition from traditional egg-based to cell-based production systems (Extance 2011).

13.4.4.2 Launching a New Vaccine

Key goals when launching a new vaccine in a country are: (1) recommendations by the country's NITAG and the medical societies, which are most important to the vaccine core prescribers; (2) WHO recommendation and prequalification; (2) favorable pricing and reimbursement conditions by public and private third-party payers; (3) strong recommendations by physicians to eligible patients, and (4) consumer willingness to be vaccinated with the vaccine.

NITAGs start working on future vaccines several years before the expected licensing date. For example, ACIP formed an HPV Vaccine Workgroup in 2004, 2 years before the first HPV vaccine Gardasil was licensed in June 2006 (Shefer et al. 2008). Most NITAGs and WHO collect and review data on the epidemiology, burden of disease, vaccine efficacy, safety, and cost-effectiveness (see sections "National Technical Advisory Groups (NITAGs)" and "The World Health Organization (WHO)"). A vaccine manufacturer can influence this process by providing appropriate data, build epidemiological, health-economic, and other economic models, and generating evidence of vaccine efficacy, safety, and other relevant aspects. Obtaining favorable recommendations from medical societies similarly requires that the manufacturer interacts with these societies prior to the launch and provide them with relevant information.

The goal is to obtain recommendations as quickly as possible following the licensing, because this facilitates price and reimbursement discussions with payers. For example, Merck succeeded in obtaining a favorable ACIP recommendation for Gardasil in the same month as the FDA approval. For vaccines destined mainly for countries procuring via UNICEF and PAHO, obtaining a WHO recommendation and prequalification rapidly is essential. It is not relevant for vaccines destined for the United States, EU, and other high-income countries.

Obtaining a high price and favorable reimbursement conditions from public and private third-party payers is the next challenge. This requires a good understanding of the decision process, who the key influencers are (e.g., through social network analysis as illustrated by Conway et al. 2008), their decision criteria and perceptions of the burden of disease, the vaccine and the manufacturer. Like for NITAG recommendations, the goal is to arrive at satisfactory price and reimbursement agreements as rapidly as possible after licensing.

A new vaccine which has obtained recommendation by the NITAG and key medical societies, favorable reimbursement conditions, namely no consumer cost sharing, and physician reimbursement that promises profits from dispensing and administering the vaccine, is in a good position to trigger strong physician recommendations to eligible consumers. Including the vaccine in the metrics used by payers to measure physician performance can generate additional physician support. According to Freed et al. (2011b), one of the reasons why the vast majority of primary care physicians stocked the pneumococcal polysaccharide (PPSV23) vaccine compared with the much lower stocking rate of most other adult vaccines was that it was one of two vaccines included as part of the Healthcare Effectiveness Data

and Information Set (HEDIS), a tool used by most US health plans to measure physician performance.

Last not least, the new vaccine needs to be accepted by consumers. Making vaccination with a new vaccine mandatory might be seen as the most effective way to speed up its consumer acceptance. This is what Merck attempted to achieve through extensive lobbying when they launched Gardasil. However, faced with growing criticism, they suspended their lobbying effort 6 months after launch (Rosenthal 2008). Schwartz (2010) recommends that vaccine mandates should be considered only after a new vaccine is well established and widespread support exists, which traditionally has taken at least 5 years.

13.4.5 Vaccine Pricing

Like for other pharmaceuticals (Frank 2001), for vaccines the "law of one price" holds neither within nor across countries. Public buyers in the United States benefit from lower prices than private buyers, and even among private buyers there is enormous variation in the prices paid by different physician practices for the same vaccine (Freed et al. 2008b).

Prices for the same vaccine can also vary greatly across countries. For example, among seven high-income countries the launch price for Gardasil was highest in Germany at $527, followed by $429 in Switzerland, $360 in the United States, $359 in Denmark, $335 in Canada, $315 in Australia, and lowest in New Zealand at $292 (Haas et al. 2009). Low- and middle-income countries procuring vaccines through UNICEF/GAVI and PAHO only pay a fraction of the public sector US federal contract price. For example, the UNICEF/GAVI prices per dose for four vaccines ranged from 2 to 12 % of the US federal contract price (Nguyen et al. 2011).

Some of the price differences may be due to differences in costs. Different contractual arrangements concerning logistics, product liability, returns policy, payment, length of contract, and guaranteed volumes may indeed engender cost differences.

Price differences can also represent price discrimination, also called differential pricing or tiered pricing. Tiered pricing exploits differences in price elasticity resulting from differences in buyer power, willingness to pay, and ability to pay. The lower US federal contract price compared to the private sector price and the lower prices of practices participating in purchasing cooperatives purchase compared to practices buying directly from manufacturers (Freed et al. 2008b) reflect mainly differences in buyer power in the United States. Differences in public prices between countries with similar high per capita income levels are probably rooted in differences of willingness to pay, which are reflected in the cost-effectiveness criteria applied in most European countries, whereas the differences between the UNICEF/GAVI prices and the US federal contract prices reflect mainly differences in the ability to pay.

Tiered pricing has a number of advantages. If firms were to charge only one price, this price would generally be what higher-income consumers can pay, which would make vaccines unaffordable to many lower-income consumers (Danzon et al. 2011). Tiered pricing increases equity by making vaccines available to most people regardless of their ability to pay. At the same time, it increases manufacturers' profits as long as the lowest price exceeds marginal cost. Profitability provides incentives for existing manufacturers to remain in the market and invest in R&D, resulting in better vaccines in the future (Lichtenberg 2011). It may also attract new entrants, a socially desirable outcome although less favorable for incumbents.

The main danger of tiered pricing is that the low prices will trigger pressures to reduce prices to buyers who previously purchased at higher prices. Such reductions lower profitability, which may result in insufficient investments in manufacturing capacity and R&D, and lead firms to exit the market. The pressure to reduce prices is particularly high when the low prices are public and used as reference prices by high-price buyers. Price transparency, as recently implemented by UNICEF (McNeil 2011), can have the unintended effect to increase prices paid by the poor, deter entry in low-income markets, reduce competition, and lower investment (Kyle and Ridley 2007).

Price referencing across countries is one reason why vaccine manufacturers tend to launch their products in high-income high-price countries first, even when the burden of disease may be highest in low-income countries. For example, the HPV vaccines were first launched in high-income countries, in which cervical cancer mortality is low thanks to the widespread use of pap tests, while the major burden of cervical cancer arises in low-income countries with little pap testing. Another reason for the launch sequencing is the difference in the burden of disease of HPV in the high-income countries, where most other infectious diseases are of lower concern, whereas other infectious diseases take precedence over HPV in low-income countries.

Vaccine manufacturers and most public buyers in high-income countries use cost-effectiveness analysis to set and assess vaccine prices. Cost-effectiveness is a value-based pricing method in which a vaccine's incremental cost per unit of health gain (often measured as quality-adjusted life-year or QALY) is compared with the buyer's maximum incremental cost per QALY gained. For example, the UK NITAG uses the guideline that the vaccine should result in an incremental cost of less than £30,000 per QALY gained (Hall 2010). The Australian NITAG initially rejected Gardasil because it found that it was not cost-effective at the proposed price of $450. When Gardasil was resubmitted at a significantly lower price, it was found to be cost-effective and publicly funded (Roughead et al. 2008).

In many high-income countries, the cost-effectiveness methods used by public buyers to assess vaccines are the same as for other pharmaceuticals. But vaccines have specific features. They may provide herd immunity (unvaccinated or poorly vaccinated people may benefit), prevent illness in young children, which causes extra care and work loss, and prevent illness in distant years, which makes the cost-effectiveness results highly sensitive to different discount rates. They may also eradicate some infections, and prevent or control pandemics with potentially major

macroeconomic impacts. These vaccine specificities are currently poorly captured in many economic evaluations, which may result in cost-effectiveness estimates that make vaccines unacceptable to buyers (Beutels et al. 2008).

13.4.6 Communication

The target audience, behavioral goals, communication goals, positioning objects, and communication channels for a vaccine depend on two market characteristics: (1) whether vaccination is mandatory or voluntary and (2) whether physicians can choose between different brands (provider choice) or not.

When vaccination is mandatory and providers cannot choose, national or regional authorities mandate vaccination and choose one brand. They generally manage the entire immunization program including vaccine distribution, selection of vaccination settings and vaccinators, and immunization communication. Vaccine manufacturers' communication efforts are minimal in such situations, and targeted at public authorities. The behavioral goals are (a) to make vaccination mandatory, (b) win the contract in case there are competing suppliers, and (c) obtain a high price. The corresponding communication goals are to increase the need for vaccination, and to create brand preference and a high willingness to pay. This requires positioning the disease (Angelmar et al. 2007) in addition to positioning the brand and supplier. Personal selling via key account management is the key communication channel.

Situations where vaccination is voluntary and providers do not choose the brand are very similar to the previous case. Examples are the 2009 H1N1 campaigns in most countries, and HPV vaccination in the UK and some other countries where governments chose one of the two competing HPV vaccines Gardasil and Cervarix. The main difference from the point of view of communication is that vaccine manufacturers may need to focus less on the need for vaccination and positioning the disease in the minds of authorities. For example, for H1N1 this was done mainly by WHO. Authorities, however, face a big challenge to convince consumers to vaccinate, especially if demand for vaccination is far lower than the amount of vaccines purchased. US health authorities mounted a significant consumer communication effort using a broad range of media to use up their large stock of H1N1 vaccine doses (Anonymous 2010).

Situations where vaccination is mandatory but physicians can choose between different brands of vaccine are more challenging for vaccine marketers and involve higher communication investments. Targeting physicians to achieve brand preference and brand recommendation to consumers typically requires face-to-face selling through medical representatives, plus other channels (medical journal advertising, congresses, continuing medical education, etc.).

Finally, the most challenging situation for vaccine marketers is where vaccination is voluntary, and physicians can choose brands. When vaccination is voluntary, this

often means that there is a private market alongside the public market. Vaccine marketers must therefore direct sales efforts at public payers, private insurers, employers (for workplace immunization), health care professionals, and consumers. This situation and the communications strategies and tactics employed by vaccine marketers are very similar to those of therapeutics marketers, and marketing and sales expenditures also reach similar levels. For example, the communication strategies employed by Merck for its HPV vaccine Gardasil were comparable to those used for blockbuster therapeutics, earning Gardasil the "Brand of the Year" award (Herskovitz 2007), the General Manager of Merck's HPV Franchise the "Marketer of the Year" award (Applebaum 2007), in addition to the accusation that the campaign "undercut the most cost-effective and appropriate use of new agents to the detriment of adolescent health" (Rothman and Rothman 2009).

13.4.7 Distributing Vaccines

Vaccinations are administered in a variety of settings including physician offices, pharmacies, supermarkets and other stores, the workplace, and schools. Easy access (minimal travel time and costs) to vaccination settings is important, which is not always the case, especially in low-income countries. In a study in rural Pakistan, only 39 % of enrolled children completed DTP3, and completion was higher among children who were living ≤10 min away from an immunization center (Usman et al. 2010). In emergency situations such as a pandemic, public health authorities typically expand the number and types of vaccination settings in order to increase the speed and rate of vaccination coverage.

Vaccines vary in stability and, thus, shelf life. Maintaining a cold chain that is robust, reliable, and routinely monitored for possible deviations is essential (Smith et al. 2011a). A recent report points out that vaccines that do not need refrigeration and may be administered orally or intranasally "could dramatically transform the immunization landscape, removing or considerably lessening the logistical challenges, training requirements, and potential safety challenges related to vaccine management and administration" (Institute of Medicine 2010, p. 210).

When its transportation and storage requirements exceed the capabilities of the supply chain participants, the commercial success of a vaccine is compromised. The need to remain frozen until used represented an important handicap for the success of MedImmune's nasal spray flu vaccine FluMist, in addition to its high price. Many practices were lacking freezers, and many of those who did have freezers received FluMist in containers that were too big to fit into them (Appleby 2004). FluMist's sales increased significantly once it was reformulated for storage in a refrigerator rather than a freezer. The required supply chain capabilities concern not only technical but also staff competencies. One of the reasons why Gardasil had a much lower penetration among 19- to 26-year-old women was that obstetricians/gynecologists, among the most important physician specialties for this age segment,

had no prior vaccination experience and therefore lacked not only stocking capabilities but also the financial and logistics skills required for profitable vaccine dispensing.

13.5 Vaccine Sales Forecasting

A number of factors make it important to have accurate vaccine sales forecasts. First, vaccine manufacturing facilities require large investments and are typically uniquely dedicated (Berndt et al. 2009). Secondly, because of the long and complex manufacturing cycles (on average 15–20 months, with the notable exception of flu vaccines), the possibility to respond rapidly to higher demand is limited (Scherer 2007). Thirdly, the limited shelf life of vaccines increases the risk that excess quantities cannot be sold and must be destroyed.

Accurate forecasts are particularly difficult for new vaccines against new disease targets, and for diseases the incidence of which fluctuates significantly such as seasonal flu and pandemics. A case in point is the 2009 H1N1 flu. The number of doses purchased by the US government based on forecasts exceeded demand by about 70 million doses, representing 43 % of supply. The excess inventory, valued at about $450 million, was subsequently destroyed (Bigongiari 2010). Other countries had similar experiences.

Sales forecasting is easiest for vaccines which have a well established tradition of routine vaccination of an easily quantifiable and reachable target. This is the case for vaccinating birth cohorts with classical infant vaccines in developed countries.

Random demand shocks occur when competitors cannot supply due to quality problems. To protect the population against product shortages, the FDA requires vaccine manufacturers to hold an inventory corresponding to several months of sales.

Global vaccine sales forecasts are built “bottom-up” by combining country forecasts. Country vaccine forecasts use the same methods as the ones used generally for pharmaceuticals (Cook 2006). New product forecasts multiply the eligible population by the expected vaccination rate and price. Such forecasts are generated by segments (e.g., by age groups, and public vs. private segment) and combined for country sales forecasts. Assumptions about the expected vaccination rates are based on analogies, market research, and judgment. Sales forecasts for in-market vaccines are generally based on statistical methods (trend extrapolation) combined with judgmental adjustments.

13.6 Trends in Vaccines and Vaccine Marketing

Children have been the traditional consumer target group for the vaccine industry. Most vaccines still target children’s diseases, and publicly financed routine immunization programs in high-income countries have provided the industry with a predictable revenue stream. But in recent years and in the future adolescents and adults will

become increasingly important target groups for the industry (Silverman 2009). Because these vaccines will be prescribed by a broader set of physician specialties than the current vaccine prescribers, vaccine marketers will need to develop new communication strategies and reallocate marketing resources.

The number of injections per person is increasing together with the number of vaccine-preventable diseases. This has triggered a move toward combination vaccines. To overcome needle-phobia, new methods of administering vaccines are being developed.

Faced with fiscal problems and escalating health care costs, public and private payers are looking for ways to allocate resources to the most cost-effective health interventions. Providing robust evidence of cost-effectiveness will be a future key factor for winning against other vaccines and other types of health interventions.

The current domination of the global vaccine market by the big five will be challenged by manufacturers from emerging markets. The Chinese government has woken up to the importance of the vaccine industry and has taken a number of measures to strengthen it (ResearchInChina 2011). Manufacturers from India—and soon from China—challenge the big five in low-income countries and in internationally funded tenders, and will be increasingly present in middle-income countries over the coming decade. Regulatory changes regarding biosimilars may facilitate the entry of biosimilars and shorten the life cycle of branded original vaccines.

The development of therapeutic vaccines targeting disease-specific proteins in such fields as oncology and immune diseases could herald a new era for the vaccine market. As discussed at the beginning of the chapter, therapeutic vaccines are similar to other therapeutic biologics in that they focus on solving consumers' current health problems, generate benefits to only to individuals and not communities, and will command prices far exceeding those of preventive vaccines.

13.7 Promising Research Questions for Marketing Scholars

We first discuss three priority questions for vaccine marketers and public health policy makers, followed by some other promising research questions, and then discuss the availability of data on vaccine markets.

13.7.1 Maintaining High Vaccination Rates Despite the Quasi-Absence of Targeted Diseases

When consumers' vaccination behavior is prevalence-elastic, voluntary vaccination programs can be victims of their own success. How can vaccine marketers maintain consumers' motivation to vaccinate despite the quasi-absence of the targeted disease? Conceivably, the same issue could pose itself for physicians.

Raising the perceived threat of the disease is one strategy. This could be done by communicating the consequences of outbreaks in other countries or in parts of a

country. MacDonald et al. (2012) cite polio outbreaks in Europe and pertussis outbreaks with infants dying in California as communication opportunities, as well as the possibility to highlight the link between outbreaks and a drop in the vaccination rate. Downward counterfactual messaging (Epstude and Roese 2008; e.g., "without vaccination, X children would have died") could also be employed.

The quasi-absence of a targeted disease reduces the perceived disease risk and, thereby, also the direct benefits of vaccination. Raising the total vaccination benefits through emphasizing the indirect social and altruistic benefits of vaccination is another possible strategy (Hershey et al. 1994; Skea et al. 2008; Reyna 2012; Caplan 2011). As Weinreb (2011) argues, "getting vaccinated … is just another important social responsibility." Altruism has been found to be an important motivator for participation in HIV vaccine trials, in addition to personal benefits (Balfour et al. 2010; Dhalla and Poole 2011).

Communicating that vaccination is a norm represents a third strategy. Hershey et al. (1994) recommend that communications should stress high vaccination rates, thus using descriptive norms (Smith-McLallen and Fishbein 2008) or social proof (Cialdini 2009).

Evidence on the relative effectiveness of the different possible strategies is lacking.

13.7.2 How to Reduce the Percentage of People Who Refuse or Delay Vaccination

Increasing numbers of parents refuse or delay vaccination for their children, mainly because safety concerns associated with vaccines loom larger than their benefits (Omer et al. 2009; Smith et al. 2011b; Salmon et al. 2005). Moreover, the many parents who let their children be vaccinated despite harboring significant safety concerns might join the camp of refusers and delayers unless their concerns are effectively addressed (Freed et al. 2010; Kennedy et al. 2011a, b).

Reyna (2012) emphasizes the importance of understanding how individuals represent the gist or meaning of risk messages and recommends two strategies for making the perceived risk of non-vaccination higher than that of vaccination. The "categorical (nominal)" strategy makes not vaccinating the risky choice ("gambling on avoiding the disease") by conveying that the risks of vaccination are "nil." The "ordinal" strategy compares the larger risks of disease to the lower risks of the vaccine. She also suggests raising the risks of non-vaccination by adding indirect risks to the community to the personal risks, a loss-framing of the social consequences (e.g., "by not getting vaccinated you are a socially irresponsible person").[40] However, because many consumers lack an understanding of herd immunity (Downs et al. 2008), increasing their background knowledge may be necessary.

[40] In Skea et al.'s (2008) study, some parents were quite critical of other parents who did not vaccinate healthy children.

Koehler and Gershoff's (2003) findings suggest that perceiving vaccination as the less risky option may not be sufficient to trigger vaccination, because consumers tend to choose options that provide less overall protection in order to eliminate a very small probability of harm due to safety product betrayal. Reasoning that safety product betrayal causes strong negative emotions, which favor emotional (system 1) appraisals, they propose that dampening the emotional response to potential betrayals promotes a more cognitive (system 2) appraisal, which would result in a preference for the lower-risk option (Gershoff and Koehler 2011). They test five tactics in a non-vaccine context which find this to be the case.

Anticipated regret has been identified as a strong predictor of vaccination behavior (Brewer et al. 2010; Chapman and Coups 2006; Weinstein et al. 2007) but not tested as a potential communication strategy for vaccines.

Because health care professionals are the most important information source for vaccination decisions (Kennedy et al. 2011a), they are the key communication channel for delivering messages that change the benefit–risk balance, manage consumers' pre-decisional emotions, and persuade them to vaccinate. But the effective use of this channel faces important obstacles: (1) Insufficient evidence regarding the effectiveness of the different possible strategies and messages, for different types of consumers. Theory- and research-based recommendations such as the ones by Reyna, Gershoff, and Koehler need to be tested in a vaccination context. There is a wealth of other recommendations about how to communicate with vaccine-refusing or -hesitant consumers (e.g., Healy and Pickering 2011), but few attempts at empirical validation (Gust et al. 2008, 2009). (2) Assuming effective messages for different consumer segments were identified, health care professionals would have to be trained to rapidly identify to which segment an individual consumer belongs, and deliver the appropriate message, analogous to what pharmaceutical sales representatives do during a sales call. (3) Not all health care professionals are strongly convinced of the safety and benefits of vaccines. A study of primary care providers found that those providing care for unvaccinated children were less likely to have confidence in vaccine safety and perceive their benefits for individuals and communities that those providing care for appropriately vaccinated children (Salmon et al. 2008). Communication strategies and messages to change the beliefs and attitudes of these health care professionals therefore also need to be developed.

13.7.3 Combating Anti-vaccination Information

Anti-vaccination information can be found in popular television programs such as the Oprah show (Parikh 2008), on anti-vaccination websites (Bean 2011; Kata 2010; 2012), online discussion forums (Nicholson and Leask 2012), in viral videos on YouTube (Briones et al. 2012), and other media. Typical claims of anti-vaccination websites are that vaccines are not safe and effective and that vaccination restricts civil liberties. The most recent study (Bean 2011) identified two emerging trends: a rise in conspiracy theories following the 2009 H1N1 epidemic threat which

is claimed to have been "manufactured" by vaccine suppliers and allied players, and the increased use of anti-vaccine testimonials by "experts" (e.g., unidentified doctors). Anti-vaccination information increases the perceived risk and lowers vaccination intentions (Betsch et al. 2010), particularly when the information consists of highly emotional narratives (testimonials, anecdotes) (Betsch et al. 2011).

The traditional strategy of fighting anti-vaccination information with education and evidence-based communication is considered to have been ineffective (Parikh 2008; Reyna 2012; MacDonald et al. 2012; Caplan 2011). Alternative proposed strategies include emphasizing "simple bottom-line meaning" instead of facts and details (Reyna 2012), stressing the obligation to act as a moral member of a community (Caplan 2011), including more emotionally compelling content (Bean 2011), for example, by having a parent tell a story of how their child died from a disease which could have been prevented by vaccination (Parikh 2008), enhancing the knowledge of the vaccine safety system (MacDonald et al. 2012), and increasing the engagement of health professionals and other vaccination advocates in online discussion forums (Nicholson and Leask 2012).

Marketing scholars can contribute to the development of effective strategies for combating anti-vaccination information by extending research on anti-rumor and brand-scandal strategies (e.g., Tybout et al. 1981; Roehm and Tybout 2006), message framing strategies that mobilize social motivations (e.g., Zhao and Pechmann 2007), and consumer persuasion knowledge models (Campbell and Kirmani 2008) which might help fight conspiracy theories, among others.

13.7.4 Other Consumer Behavior Research Questions

Consumer belief–behavior causality. Most studies about vaccination perceptions and behavior are cross-sectional. Because of this, the direction of causality—do the beliefs cause vaccination behavior or does causality flow in the other direction?—is not clear (Weinstein 2007). Longitudinal studies (e.g., Ibuka et al. 2010) could clarify causality. Funk et al. (2010) also stress the need for empirical parameterization of the many mathematical models of infectious disease-vaccination dynamics and discuss potential technologies for collecting longitudinal data.

Vaccine fatigue. A number of new vaccines for new markets are expected to be launched over the coming years. According to Humiston et al. (2009) physicians feel that, faced with an increasing number of recommended vaccines, parents are exhibiting "vaccine fatigue." Kennedy et al. (2011a) found converging results.[41] Unless vaccine marketers find ways to overcome this vaccine fatigue, the success of future new vaccine launches will be compromised.

[41] 27.8 % of parents agreed that "children get too many vaccines during the first 2 years of life," and 21.9 % of them strongly/somewhat agreed with the statement "I am concerned that my child's immune system could be weakened by too many vaccines."

13.7.5 Competitive Strategy Research Questions

Pricing. The recent publication by UNICEF of prices for individual vaccines (McNeil 2011) provides a natural experiment for testing hypotheses (Kyle and Ridley 2007) about the impact of price transparency on companies' pricing strategies and other decisions. The contract prices for vaccines published together with the manufacturers' list prices on the CDC website show great variation in the contract price discounts. What explains the differences in discounts?

Market share dynamics. Consumers and sales in a product class can be divided into "static" and "dynamic" components. The dynamic component consists of product class starters, brand switchers, and existing consumers which add a brand, while the static component comprises consumers who continue on their current treatment (Harold and Odqvist 2011). The greater the dynamic share in a class, the higher the potential for market share changes. Because most preventive vaccines are administered only once or very infrequently over a life time, virtually all sales are to product class starters (new consumers). Market shares therefore are potentially highly volatile. Analogous to studies in other markets (Sutton 2007; Srinivasan and Bass 2000; Dekimpe and Hanssens 1995), marketing scholars could investigate market share dynamics and explore determinants of market share volatility.

Budget competition. The fiscal and economic crisis in many countries increases the need for governments and other payers to make trade-offs between new and older vaccines, and between vaccines, therapeutics, and other health interventions. Pure vaccine players can position vaccines against therapeutics, but players with both types of pharmaceuticals must find ways to ensure that payers are willing to increase spending for both.

13.7.6 Vaccine Market Data

Searching the "Research and Markets" database with the word "vaccine" results in over 3,000 results.[42] Publishers of reports generally used by vaccine marketers for global market evaluation include Datamonitor, Frost & Sullivan, GBI research, and Kalorama.

IMS Health sales data, which are widely used by therapeutics marketers and marketing scholars, unfortunately do not provide reliable results for most vaccines. Sales through wholesale and retail channels, the basis of IMS Health sales data, capture only part of vaccine sales. A significant other part is shipped directly from manufacturers to prescribers, or to public purchasers who distribute them to prescribers (Berndt et al. 2009). The share of total vaccines sales captured by IMS

[42] http://www.researchandmarkets.com/search.asp?q=vaccines.<Para />

Health data is estimated at 70 % for the US, between 50 and 90 % for Western European countries, and less than 20 % for China.

Because of the lack of reliable syndicated sales data, companies like Sanofi Pasteur have developed their own complex data collection system which combines data from multiple sources.

13.8 Conclusion

In 2010, the Bill & Melinda Gates Foundation declared this decade "The Decade of Vaccines." Not long ago perceived as an unattractive segment of the pharmaceutical industry, most of the leading firms have revised their opinion and increased their investments in vaccines. In preparing this chapter, we have found very few articles dealing with vaccines in the marketing literature. We hope that marketing academics will follow the lead of the pharmaceutical industry and devote more attention to vaccines during this decade.

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Chapter 14
Patient Empowerment: Consequences for Pharmaceutical Marketing and for the Patient–Physician Relationship

Nuno Camacho

Abstract Big Pharma's *blockbuster* model—which entails developing new drugs for diseases affecting a very large number of patients, promoting it to physicians as the new best-in-class treatment, and profiting from the ensuing volume of sales—is under threat. In the last 2 decades, the largest pharmaceutical firms have lost billions of dollars in shareholder value, due to a combination of factors such as declining R&D productivity, stricter regulatory requirements, more intense generic competition, and an increasingly ineffective marketing model. I review societal, demographic, regulatory, and technological trends and discuss how such trends are contributing to the rise of a new class of empowered patients. I discuss the implications of patient empowerment for the patient–physician relationship and for therapy launch and therapy promotion. Building on real-world evidence, I discuss the benefits and challenges of direct-to-patient marketing strategies such as nurturing partnerships with key patient opinion leaders and direct-to-patient communication via social media. Through a content analysis of the 2005–2010 annual reports of the largest 20 pharmaceutical firms, I show that, despite strict regulatory requirements, several firms have started to embrace patient empowerment as a key component of their marketing models. However, much remains to be done. I propose that now is the right time for pharmaceutical marketers (and scholars) to implement marketing strategies that help empowering patients. In addition, I also discuss the importance of avoiding that patient empowerment results in healthcare consumerism, which could have destructive consequences for patient–physician (and firm–physician) relationships.

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14.1 Introduction

On December 17, 1996, the Food and Drug Administration (FDA) sent a letter to Byron Scott, the then Director of Worldwide Regulatory affairs at Parke-Davis, a division of Warner-Lambert, communicating their approval of an application he had submitted 6 months earlier. The new drug application sought market approval for a lipid-lowering drug to be prescribed to patients with primary hypercholesterolemia, mixed dyslipidemia, or homozygous familial hypercholesterolemia.[1] By 2007, the new drug, Lipitor, had become a dream brand. With almost $13 billion in global revenues, Lipitor became the symbol of Big Pharma's successful *blockbuster* model: develop a new drug for a disease affecting a very large number of patients, promote it to physicians as the best-in-class treatment, and profit from the ensuing massive volume of sales and a reasonably good margin.

Today, the pharmaceutical industry's blockbuster model, which guaranteed high profitability for many years, is under threat. Between 2000 and 2008, the top 15 firms in the industry have lost $850 billion in shareholder value, a problem typically attributed to complex challenges for pharmaceutical firms' traditional R&D and marketing models (Garnier 2008). In 2007, amid these developments, a coalition of institutional investors with more than $1.1 trillion in assets invested in the pharmaceutical industry expressed serious concern over the sustainability of the blockbuster model and asked pharmaceutical firms to consider new ways to market their therapies (The Economist 2007). This coalition is not alone in its plea for a new business model. Bain & Co.'s senior consultants (Gilbert et al. 2003) also declared that the blockbuster business model is "irreparably broken" (p. 1). They suggest that fixing Big Pharma's business model will require changes across the whole cycle of therapy development (i.e., R&D), launch, and promotion. In this chapter, I propose that pharmaceutical firms should adapt their marketing model by putting the patient at the center of their strategies for therapy launch and therapy promotion.

I review evidence that suggests we are witnessing a fundamental change in the medical decision-making paradigm. The traditional model for medical decision-making, a "white-coat" approach whereby physicians apply their biomedical knowledge to choose a therapy on behalf of their patients, is being replaced by a model in which patients are encouraged and required to play a more participatory role in therapy choice (Camacho et al. 2010). The emergence of patient empowerment as a new paradigm in medical decision-making implies that patients will play an increasingly important role in therapy choice, and consequently in the patient–physician relationship and pharmaceutical marketing.

Figure 14.1 illustrates a conceptual overview of this chapter. I first review the main trends that precede patient empowerment. Next, I build upon the discussion

[1] See Food and Drug Administration's NDA 20-702, December 17, 1996, available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020702_s000.pdf (last accessed September 19, 2011).

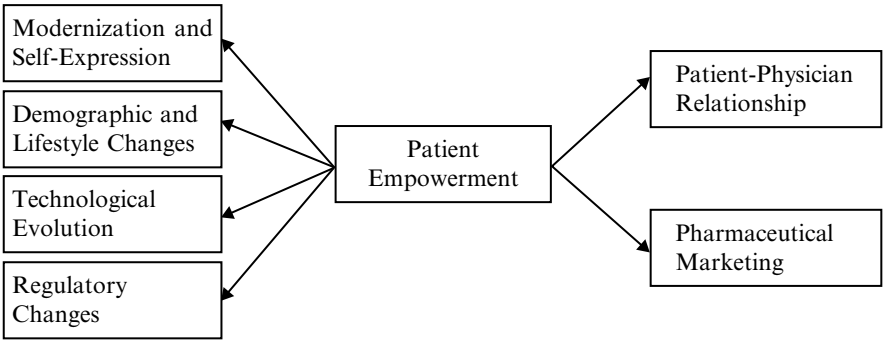

Fig. 14.1 Conceptual overview of the current chapter

of these trends towards patient empowerment and review the consequences of the patient's new role for the patient–physician relationship and for pharmaceutical marketing.

14.2 The Rise of Patient Empowerment

The traditional model of medical decision-making is physician-centric, i.e., pharmaceutical marketers tend to focus on the physician as their key customer and promote their therapies through direct-to-physician channels such as detailing and advertising in medical journals (Amaldoss and He 2009). Under this conception, the business model of large pharmaceutical companies, the so-called blockbuster approach, entails developing a new therapy, marketing it as the new best-in-class, and pushing it mainly via direct-to-physician marketing (The Economist 2007). Important topics that inform managerial decisions in this traditional model include understanding key physician opinion leaders, developing models to segment the physician population, and optimally allocating detailing and samples (Stremersch and Van Dyck 2009). These may currently be mature areas of managerial and academic interest, but that does not mean we fully understand therapy consumption and marketing. In fact, this traditional model is nowadays threatened by the increasing importance of other stakeholders in the decision-making process, like the payer (e.g., insurance companies, Governments), regulators, and the patient, which reduces the physician's role in therapy choice as well as the firm's capacity to influence therapy choice via direct-to-physician marketing.

The tenets of the white-coat model are examined in the work of American sociologist Talcott Parsons, who studied how social systems govern societies. He concluded that, traditionally, patients and physicians were expected to play different roles in society (Parsons 1951). More specifically, patients are granted the status of sick people in need of care and are allowed and expected to give up some of their normal activities to actively work towards health restoration by seeking the advice

of a doctor and complying with that doctor's advice (Morgan 1991). Parsons' model predicts a dominant role for the doctor, who uses her biomedical knowledge in a paternalistic manner to prescribe a treatment that maximizes patient welfare but is chosen with limited patient input (Charles et al. 1999). The white-coat model is increasingly being challenged.

Recent evidence from the medical and pharmaceutical industries indicates that therapy choice is increasingly the result of a joint decision-making process in which both the patient and physician are asked to actively participate (Ding and Eliashberg 2008). Despite this evidence, the vast majority of applications of therapy choice, both in economics and marketing, assume that the prescription choice is made by the physician, assumed to be a perfect agent for the patient (Manchanda et al. 2005). Even models that explicitly consider the dyadic nature of therapy choice, argue that patients are not experts in biomedical issues and, therefore, "physicians, by training and obligation, will not and should not let patients have more power over them" (Ding and Eliashberg 2008, p. 831).

However, four macro-trends are contributing to a fundamental change in societal expectations about the roles played by physicians and patients in therapy choice contributing to the emergence of *patient empowerment*, a new paradigm for medical decision-making that defends the strengthening of the role of the patient in therapy choice (Camacho et al. 2010; Epstein et al. 2004). The main trends are (1) the importance of self-expression in people's lives, (2) demographic and lifestyle changes, (3) technological developments (e.g., the availability of biomedical information on the Internet), and (4) regulatory changes (such as more flexible regulation of direct-to-consumer-advertising (DTCA) in the USA).

These four macro-trends combine to fundamentally change the medical decision-making model and the way therapies are chosen. A consequence of this new environment and the legitimate aspirations of many patients to participate actively in their healthcare is that patient empowerment is increasingly seen as the normative standard in medical decision-making (e.g., Epstein et al. 2004; Krahn and Naglie 2008). This patient empowerment paradigm also coincides with a more general trend towards higher customer participation in the marketplace (Prahalad and Ramaswamy 2000; Vargo and Lusch 2004).

The pharmaceutical industry, policy-makers, physicians, and patients cannot afford to ignore the patient empowerment trend as it has the potential to fundamentally change the patient–physician relationship and the way prescription drugs are chosen during medical encounters. In other words, patient empowerment is driving a paradigm shift in medical decision-making that will lead to fundamental changes for pharmaceutical marketing. In particular, the trend towards patient empowerment suggests the need for pharmaceutical firms to strengthen their focus on the patient as the key stakeholder.

I will now briefly discuss each of the antecedents of the patient empowerment paradigm in medical decision-making. In the next section, I will discuss the consequences of patient empowerment on the role of the patient in therapy launch and therapy promotion.

14.2.1 Modernization and Self-Expression

Modernization theorists posit that a society's value system is determined by its state of economic development and cultural heritage (Inglehart and Baker 2000). In particular, post-industrialization triggers important cultural changes, notably an inclination for more participatory values and for self-expression (Inglehart and Baker 2000). This means that as societies modernize, patients will be more inclined to actively participate in their treatment decisions, which promotes patient empowerment. Consequently, the level of patient empowerment in different societies or social groups will also be influenced by the degree to which such societies or groups value self-determination. Models of patient–physician dyadic decision-making therefore need to become culturally sensitive (Charles et al. 2006).

For instance, a recent study among undergraduates from large California universities shows that American students of European ancestry believe in the value and practice of self-expression more than their East Asian peers (Kim and Sherman 2007). Religious people also tend to value conformity more than autonomy and self-direction (Saroglou et al. 2004). I would also expect patients from countries with higher self-expression values (Protestant Europe and English-speaking cultural zones) to value patient empowerment more than patients from countries with lower self-expression values (Catholic Europe, ex-Communist countries, Latin America and South Asia). These topics deserve further scientific scrutiny.

14.2.2 Demographic and Lifestyle Changes

Demographic and lifestyle changes also reinforced the current trend towards more patient participation in medical decisions. Population aging and lifestyle changes such as increased urbanization and exposure to pollutants have contributed to an increasing prevalence of chronic conditions like ischemic heart disease, respiratory infections, chronic obstructive pulmonary disease, cerebrovascular disease, the continued spread of HIV/AIDS and several forms of cancer (Murray and Lopez 1996). In addition, increases in people's longevity mean that the 65-and-older population will dramatically increase in the coming decades globally, which will accelerate the focus on patient self-care and access to health-related information (Bodenheimer et al. 2002).

Both the increasing prevalence of chronic diseases and the aging population helps reinforce the patient empowerment trend. Patient self-management is promoted as a solution for containing the rising costs of healthcare systems and is seen as an inevitable phenomenon in modern medicine (Bodenheimer et al. 2002). Chronically ill patients tend to discuss their health concerns with peers and build their own habits and networks to secure easier access to health and therapy-related information. As a consequence, chronically ill patients are more knowledgeable about their diseases than the average patient suffering from an acute disease. Such knowledge facilitates active patient participation in therapy choice and collaboration with the physician, i.e., this knowledge facilitates patient empowerment.

Table 14.1 Percentage of Internet users who have looked for online information about…

66 %	A specific disease or medical problem
55 %	Certain medical treatment or procedure
52 %	Exercise or fitness
47 %	Doctors or other health professionals
45 %	Prescription or over-the-counter drugs
38 %	Hospitals or other medical facilities
37 %	Health insurance, including private insurance
35 %	Alternative treatments or medicines
33 %	How to lose weight or how to control weight
28 %	Depression, anxiety, stress, or mental health issues
26 %	Any other health issue
20 %	Experimental treatments or medicines
12 %	How to stay healthy in a trip overseas
83 %	Of internet users, or 61 % of adults, have looked for health information about at least one of these topics

Source: Fox (2009)

Increased concern with chronic diseases is leading medical and public health scholars to actually promote preventive medicine, e.g., the need for lifestyle changes such as smoking prevention (Pauwels et al. 2001) and eating a well-balanced diet (Grundy et al. 2004). This means that health authorities are increasingly talking to healthy consumers to convince them to implement the necessary lifestyle changes that help them to avoid future health risks. Such habits and efforts are only possible if patients are encouraged to participate in therapy choice, i.e., if patient empowerment is encouraged (Roter and Hall 2006; Sheridan et al. 2004). These trends have the potential to "irreversibly alter the traditional doctor–patient relationship" (Bodenheimer et al. 2002, p. 2469).

14.2.3 Technological Evolution

There are also important technological developments contributing to the ongoing changes in patient–physician relationships and patient empowerment. In particular, the barriers to patient access to health and therapy information are lower than ever before in the history of medicine. With the advent of the Internet, seeking health-related information is one of the most common activities on the Internet today. According to research conducted by the Pew Internet & American Life Project and the California HealthCare Foundation (CHCF), four out of five Internet users have used the Internet to search for health information, and only two other online activities were more popular for Internet users: emailing and using search engines (Fox 2011). The most sought-after information regards medical treatments or procedures and prescription or over-the-counter drugs (see Table 14.1, above). Scholars in medicine have also recognized that massive access to health information online has

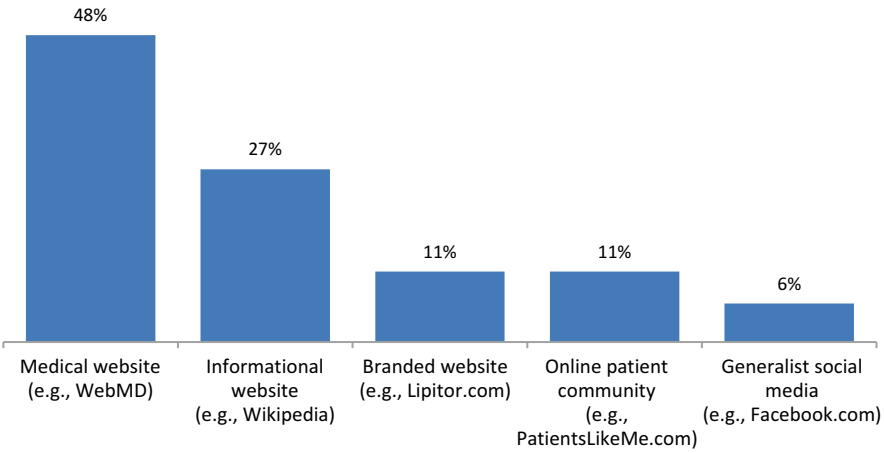

Fig. 14.2 Most frequently visited Web sites by consumers searching for health information online. *Source*: Accenture, Consumer Survey: The Evolving Consumer and the Pharmaceutical Company Relationship; Graph prepared by John Mack of the Pharma Marketing blog, available here: http://pharmamkting.blogspot.com/2010/11/guess-what-site-online-health-info.html, last accessed on October 5th, 2011

contributed to the "most important techno-cultural medical revolution of the past century" (Ferguson and Frydman 2004, p. 1149).

The Internet affects pharmaceutical marketing in multiple ways. First, easy access to biomedical information challenges traditional knowledge asymmetries that helped to sustain the paternalist white-coat model for decades. For example, patients can easily access health and therapy-related information and interact with healthcare professionals using Web sites like http://www.WebMD.com, which offer a wealth of health information and host blogs by healthcare professionals.[2]

Second, the Internet in general and social media in particular promise to become a prime channel for pharmaceutical firms to interact with patients (and for interactions among patients and between patients and healthcare providers). This channel allows patient–firm dialogue and is accessible, subject to existing regulations, even in countries in which DTCA is not allowed. Today, patients can also easily interact with other patients using generalist social media sites (e.g., http://www.Facebook.com), general online patient communities (e.g., http://www.PatientsLikeMe.com, http://www.CaringBridge.org, or http://www.Curetogether.com), or more specialized online patient communities like http://www.Crohnology.com for Crohn's and Colitis patients or http://www.Realself.com for cosmetic surgery patients. Compared with traditional sources for therapy and health information online (e.g., http://www.WebMD.com or *Wikipedia*), patient communities are still lagging behind in terms of popularity (see Fig. 14.2). Nevertheless, patient enthusiasm for

[2]See, e.g., http://blogs.webmd.com/cosmetic-surgery/, the professional blog of Robert Kotler, M.D., a cosmetic surgeon in Beverly Hills.

online interactions is expected to grow quickly and steadily in the coming years (see Terry 2010).

Besides the evolution of health information available to patients online, a critical technological development in the life sciences has been the sequencing of the human genome and, in particular, the decrease in the cost of genetic sequencing, which promises to revolutionize medicine (Zerhouni 2003). This trend is expected to reinforce the role of the patient in therapy choice. Iceland-based *deCODE genetics*, for example, promises to "empower prevention" by offering patients access to their genetic risk for 47 conditions ranging from heart attack and diabetes to alcohol flush reaction and male pattern baldness. The service called *deCODEme* Complete Scan (see http://www.decodeme.com/) costs $1,100. The company's closest competitor is *23andMe*, a company founded by bioethics analyst and biologist Anne Wojcicki, the wife of the founder of Google, Sergey Brin, and her colleague, Linda Avey. *23andMe* offers patients the possibility to discover their risk for 97 conditions and find their predicted response to drugs. The prices of such diagnostics start as low as $99. Hence, the era of preventive, gene-based medicine is here, which helps to empower patients to be in charge of their health and therapy-related choices.

14.2.4 Regulatory Changes

Patient empowerment is also being reinforced by regulatory changes. A key regulatory change has been greater flexibility towards DTCA regulation in the United States and New Zealand. Such a relaxation of regulations has sparked controversy. Some authors claim that DTCA is beneficial as a useful means to educate and empower patients to take a more active role in their treatment (Holmer 1999). Scientific research shows that patients often respond to DTCA by becoming more involved in their healthcare and voicing more drug requests to their physicians (Venkataraman and Stremersch 2007). Although there is general agreement that DTCA "has the potential to fundamentally alter the roles of doctor and patient" (Wilkes et al. 2000, p. 122), not everyone agrees that such fundamental changes are beneficial. For example, some authors claim that DTCA boosts consumerism and distorts the patient–physician relationship in undesirable ways (Hollon 1999; Moynihan et al. 2002). The controversy sometimes ends in the court room.

Take the case of Pfizer's ad campaign "Viva Viagra," launched in July 2007. Shortly after its launch, Michael Weinstein, then President of the AIDS Healthcare Foundation, criticized (and later sued) Pfizer claiming that its campaign was promoting patient requests and the usage of the erectile dysfunction blockbuster, thereby increasing consumer exposure to sexually transmitted diseases (CBS News 2007). These controversies surrounding DTCA and mass media information have also led medical scholars and lawmakers to express concern about the FDA's weak enforcement of existing laws (Donohue et al. 2007) and the need for more regulation (Government Accountability Office 2006).

Apart from DTCA regulation, regulation on *informed consent* is increasing the power of the patient. Informed consent means that the physician has a duty to provide information to his or her patients. If a certain medical treatment results in harm, and the patient is able to show in court that he or she would have opposed that medical decision, then the doctor runs a high risk of being found negligent (Faden and Beauchamp 1986).

In sum, macro-trends such as modernization and the need for self-expression, demographic and lifestyle changes, technological evolution and changes in regulation are contributing to the emergence of a new paradigm in medical decision-making: patient empowerment. In the following sections, I explore the consequences of this change for therapy promotion and therapy launch and what pharmaceutical firms are already doing in this regard.

14.3 Patient Empowerment and the Patient–Physician Relationship

Relationship marketing is widely regarded as a key strategic business mantra (Palmatier et al. 2006). Marketing scholars define relationship marketing (RM) as strategies geared towards "establishing, developing, and maintaining successful relational exchanges" (Morgan and Hunt 1994, p. 22). In healthcare, relationship marketing could mean at least two strategies: (1) strategies initiated by physicians to improve their relationship with patients and (2) strategies initiated by pharmaceutical firms to improve their relationship with patients or with physicians. This three-party interaction between patients, physicians, and pharmaceutical firms makes a relationship approach particularly challenging, but also important, in the healthcare domain.

For instance, medical scholars view the patient–physician relationship as a cornerstone of healthcare (Epstein 2002). Thus, it is pivotal to understand how patient empowerment and pharmaceutical marketing geared towards empowering patients may interfere with the dynamics of the patient–physician relationship[3] (Charles et al. 1999). The vast majority of medical scholars defend patient empowerment on the grounds that it brings important relational benefits, such as increasing patient trust in physicians (Epstein et al. 2004) and patient satisfaction with the care they receive (Flocke et al. 2002). Most of these arguments are based on conceptual articles and are not empirically grounded. However, patient empowerment could also create tension in the patient–physician relationship. Some patients, for instance, may expect a more passive role in the medical encounter and react negatively if a physician tries to share power with them during medical encounters (McNutt 2004).

[3] In 2003, for example, Johns Hopkins and American Healthways (a Nashville-based company that provides specialized care and disease management services) dedicated their yearly Outcomes Summit to defining the patient–physician relationship. To promote dialogue about their evolving roles, they invited 200 patients and physicians to discuss the ideal patient–physician relationship for the twenty-first century. See http://www.cardiophonics.com/PatientPhysician.pdf, last accessed on March 3rd, 2012.

The effect of physician initiatives to empower patients is a key area of enquiry that remains virtually unaddressed in marketing and medical literatures.

When patients take the initiative to become more empowered, many physicians still react negatively because they feel uncomfortable with the meaning of such changes to their role in the patient–physician relationship. Despite the ongoing trend towards patient empowerment, many physicians still adopt a paternalistic approach during medical encounters (Young et al. 2008). Pharmaceutical firms can also promote patient empowerment by allocating more resources to direct-to-patient marketing. Nevertheless, firms need to consider the risks to ensure that they do not damage their relationship with physicians in the process of empowering patients.

Tensions between the industry and the medical profession have a long history. In his overview of the evolution of American medicine, Starr (1982) discusses how, in the early nineteenth century, pharmaceutical firms used to promote their drugs directly to patients, which was seen as a challenge to doctor's authority. With the increasing professionalization of the medical professional, doctors became increasingly reluctant of these direct-to-patient marketing efforts. Founded in May 1847, the American Medical Association, which embraces the mission of promoting "the art and science of medicine for the betterment of the public health," has always voiced opposition to pharmaceutical firms' marketing efforts to patients. In the 1920s, the opposition was so strong that academic marketing journals, such as the *Journal of the American Medical Association*, refused to publish (direct-to-physician) ads from firms who advertised their drugs directly to patients (Starr 1982). The criticism, which still prevails today, is that doctors are biomedical experts who undergo strict training to be able to interpret and apply medical knowledge on behalf of the patient. Therefore, firm actions (such as DTCA), capable of giving more information and power to patients, are often seen as a threat because they have the "potential to fundamentally alter the roles of doctor and patient" (Wilkes et al. 2000, p. 122).

The goal for pharmaceutical firms should be to increasingly consider the patient as a key stakeholder and try to demonstrate to patients, physicians, and payers how their brands are able to create more value for the patient. Strategies aimed at promoting active interaction between the firm and patients and between patients, payers, and healthcare providers have the potential to streamline market access and improve reimbursement conditions (Bridges and Jones 2007). Hence, patient empowerment will soon become the dominant paradigm in medical decision-making and the main focus of pharmaceutical firms' marketing strategies, which I discuss next, starting with DTCA.

14.4 Marketing to Empowered Patients

After the FDA's relaxation of regulations on DTCA, the investment in the United States in such direct-to-patient channels exploded from less than $1 billion in 1996 to $4.2 billion in 2005 (Donohue et al. 2007). Despite the significant rise in DTCA

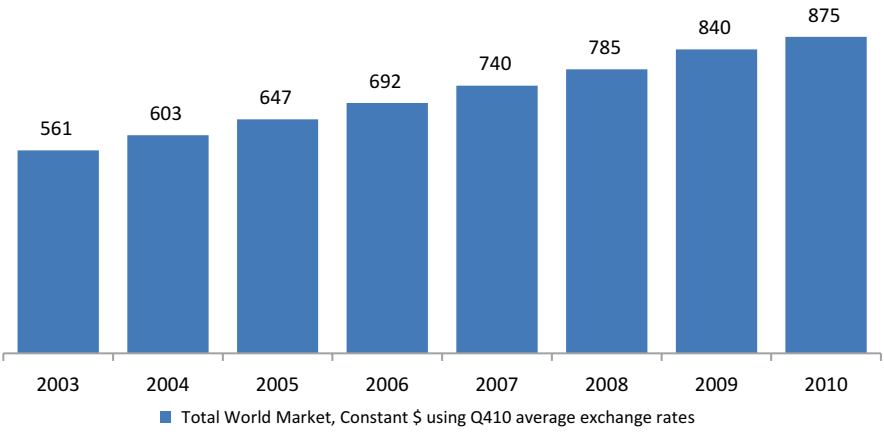

Fig. 14.3 Global pharmaceutical market (in US$ billions). *Source*: IMS Health Market Prognosis, March 2011, includes IMS audited and unaudited markets; information from March 2011: http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Top_Line_Data/Total_Market_2003-2010.pdf, last accessed on October 12th, 2011

expenditures, today DTCA still represents only 14.2 % of total industry expenditures in the promotion of prescription drugs in the United States, and direct-to-physician efforts represented the bulk of pharmaceutical marketing expenditures (Donohue et al. 2007). In most countries, in which DTCA is typically not allowed, the proportion of marketing resources allocated to direct-to-physician efforts is even greater.

The trends towards patient empowerment suggest that the relatively low share of marketing spending devoted to direct-to-patient marketing needs to be reconsidered. In addition, increased spending on pharmaceutical drugs, which, according to IMS Health, reached $875 billion in 2010 (see Fig. 14.3), led payers and regulators to increase the pressure on pharmaceutical firms to demonstrate the value per dollar of the therapies they launch (Hilsenrath 2011). Such a context requires more direct collaboration between firms and patients.

Moreover, physician responsiveness to sales reps seems to be rapidly declining (Weintraub 2007). According to recent reports by the consulting firm, ZS Associates, the number of physicians classified as "rep-accessible," those who meet with at least 70 % of the sales representatives who called them, fell nearly 20 % between 2009 and 2010, and the number of "rep-inaccessible" prescribers, those who saw fewer than 30 % of the reps who called them, increased by 50 % (Wright 2010). Finally, existing research seems to indicate that return on investment of direct-to-physician marketing efforts is modest, with elasticities clearly below 1.0 (see Kremer et al. 2008; Manchanda et al. 2005). Unfortunately, DTCA does not seem to be the solution as sales elasticities are even lower. More precisely, in a large meta-analysis of 58 studies on the effectiveness of pharmaceutical promotional investments across several therapeutic categories, Kremer et al. (2008) found an average elasticity of 0.326 for detailing, 0.123 for direct-to-physician advertising, and only 0.073 for DTCA. Apart from their direct effect on sales, promotional efforts, such as DTCA,

may bring positive effects on other performance variables like stock returns or systematic risk (Osinga et al. 2011). However, I argue that now is the time to move beyond these channels (direct-to-physician marketing and DTCA) and actively explore new direct-to-patient channels. The first step is to understand the role of the empowered patient in therapy launch and therapy promotion, which opens numerous opportunities for scholars and practitioners in pharmaceutical and health marketing.

14.4.1 Patient Role in Therapy Launch

Therapy launch is a key decision area for life sciences firms (Stremersch and Van Dyck 2009). After the long process of new therapy development and the examination of a new therapy's safety, efficacy, and incremental cost-effectiveness, marketers in pharmaceutical firms face key marketing challenges, namely, devising a strong entry and reimbursement negotiation strategy and careful key opinion leader (KOL) selection (Stremersch and Van Dyck 2009). In terms of entry and reimbursement negotiation strategy, marketers need to guarantee that they can provide regulators and payers with a clear demonstration of the health and economic value of the new therapy (Hilsenrath 2011).

The traditional model for therapy launch is largely focused on actions geared towards regulators and physicians, namely, negotiating the launch price and building ties with KOLs willing to support the new therapy. For instance, launch price and the timing for new therapies is typically co-determined by negotiations with payers and regulators (Stremersch and Van Dyck 2009; Verniers et al. 2011). In addition, firms accelerate the uptake of the new drug by closely working with KOLs. The selection of physician KOLs entails building a strong network of selected physicians who, due to their influence on others, are capable of speeding-up value-demonstration and the uptake of the new therapy (Stremersch and Van Dyck 2009). Investing marketing resources in such ties is justified by the fact that detailing KOLs triggers a social multiplier effect through which the opinions of these physicians influence the decisions of their peers, an effect that makes the return on investment of such marketing actions very attractive (Nair et al. 2010).[4] Yet, it is also important to look at social multiplier effects on the patient side of the value chain.

To involve patients in the launch of new therapies, it is important to identify the *patient opinion leaders* (POLs) for a specific indication. POLs can be of two types: (1) patient support organizations and (2) individual patients who, due to their Web

[4] Another effect KOLs may have in market access is their capacity to influence the negotiation with regulators. Clinical KOLs, for instance, are by definition influential in scientific community, and many actually belong to the committees of regulatory bodies, even though such connections are increasingly scrutinized by other scientists and health authorities (Smith 2005). As evidence accumulates regarding the relationship of the industry with KOLs, their influence on other doctors may start to decline and regulation may decrease their influence on regulatory bodies (Smith 2005).

presence, have accumulated therapy and/or disease knowledge and whose reputation exert a strong influence over other patients and physicians, payers, or regulators.

Firm interaction with POLs is particularly important during therapy launch, a time when uncertainty is higher and consumers need to learn and form beliefs about its quality (see Camacho et al. 2011; Narayanan et al. 2005). Thus, when negotiating market access, POLs may play a key role in influencing payers' willingness to reimburse the new drug.

Some firms already invest important resources in their relationship with POLs, especially with patient support organizations that represent the interests of the patient population. These organizations strive for better access to medicines, adequate care for patients, and seek to have an influence on regulators and payers (Herxheimer 2003) and clinicians (Garattini and Chalmers 2009). Take the case of Britain's Lymphoma Association, an organization that offers access to medical information for lymphatic cancer patients and their families and friends (http://www.lymphoma.org.uk/). This patient support organization offers non-branded information to patients, but also information for medical professionals, which is provided in collaboration with Roche (Herxheimer 2003).

Patient support organizations often lack adequate resources and, therefore, transparent, open, and interactive relationships between patient organizations and pharmaceutical firms are seen as win–win situations (Herxheimer 2003). In many therapeutic areas, there are opportunities for firms to collaborate with patient support organizations to provide better care for patients. For instance, National Voices (http://www.nationalvoices.org.uk/), which is a coalition of patient support groups and social care charities, received about $840,000 in funding in 2010. From this funding, only about $40,000 comes from a restricted grant given by Pfizer to fund the organization's annual general meeting and annual conference (National Voices 2010). In its 2010 annual report, the association lamented the near absence of corporate contributions.

Providing funding and working together with patient support organizations is thus a good strategy for firms to actively participate in the trend towards patient empowerment and indirectly influence all other stakeholders involved in market access. To be effective and strengthen, rather than weaken the industry's image and influence, such interactions need to be fully transparent, preserve patient organizations' independence, and treat them not as mere recipients of funding but, instead, as active partners that can help firms guarantee better care for patients (Herxheimer 2003).

On top of the patient support organizations, firms should also consider active programs to collaborate with individual POLs. In 2011, for example, Kristian Anderson, an Australian patient battling bowel cancer, became the face of a campaign pleading for a life-saving drug to be listed on Australia's Pharmaceutical Benefits Scheme (PBS; Cherry 2011a).[5] Marketed in Australia by Merck Serono, Erbitux is a monoclonal antibodies (Mab) which targets a protein called "epidermal

[5] See story here: http://manly-daily.whereilive.com.au/news/story/survivors-win-fight-for-cheaper-cancer-drug/, accessed on March 2nd, 2012.

growth factor receptor" (EGFR) that exists on the surface of cancer cells and limits their growth, thereby bringing hope to patients suffering from different types of cancer, including bowel cancer.

Despite well-established effects on quality of life and its capacity to add months or years to patients' lives, the Australian Government was hesitant to reimburse Erbitux due to budgetary concerns. Kristian Anderson became a public figure once Oprah Winfrey, after being moved by a video he produced to thank his wife for her support during his battle against cancer, had him on her show (Cherry 2011b). Kristian had also been enrolled in an early free-access program for Erbitux and was very pleased with the drug (Cherry 2011a). He then decided to embark on a mission to promote its inclusion on the PBS so that other Australian patients could access Erbitux's benefits. His mission was successful, and on September 1, 2011, Erbitux was officially listed on the PBS. This meant that Australian bowel cancer patients began to have access to Erbitux which used to cost them up to $2,000 per week, for a subsidized price of less than $34 per script. This subsidy represented a total cost for Australian taxpayers of about $32 million, but brought invaluable benefits for more than 2,000 bowel cancer sufferers across Australia. Besides therapy launch, firms may also consider engaging with POLs using channels such as the Internet and social media, to improve therapy promotion.

14.4.2 Patient Role in Therapy Promotion

After successfully launching a new therapy, marketers need to engage in *therapy promotion* to encourage patients and physicians to use the new therapy. The key challenges faced during therapy promotion are sales force management, communication management, and stimulating patient adherence to therapy (Stremersch and Van Dyck 2009). Although therapy promotion can be directed to patients and physicians, in practice budgets dedicated to physicians are still ten times larger than budgets dedicated to patients (Kremer et al. 2008). Furthermore, as already discussed, the only sizeable direct-to-patient channel, DTCA, remains highly controversial (Hollon 1999; Moynihan et al. 2002), which may explain why it is only allowed in the United States and in New Zealand and perceived as challenging by practitioners (Stremersch and Van Dyck 2009).

The discontent with DTCA coupled with the ongoing shift towards patient empowerment and the evidence of the declining effectiveness of direct-to-physician channels (Wright 2010) suggests that firms need to start allocating resources to *other* direct-to-patient channels. Such channels include social media, online patient communities, disease awareness campaigns (possibly non-branded, due to regulatory issues), mobile marketing solutions (like mobile apps), creative packaging and labeling, holistic healthcare solutions (e.g., therapy combined with medical devices or programs for lifestyle change), and patient adherence programs. I expect such efforts to have a positive impact on sales force management, patient engagement (especially via social media), firm-to-patient communication management, and patient adherence to physicians' therapy advice.

14.4.2.1 Sales Force Management

A closer relationship with patients may bring about two positive consequences for sales force management. First, it may help a firm motivate its sales force. People value working towards goals they find meaningful and feeling like they work for an organization with which they can identify (Karlsson et al. 2004). Being able to directly interact with patients or at least learn how one's brands can help them live healthier, more productive and happier lives can be a strong motivator for a sales rep. Second, closer contact with patients allows the firm to gather valuable information about patient needs and preferences, which reps can then share with physicians and increase the odds that physicians actually accept to meet them.

14.4.2.2 Patient Engagement via Social Media

Customer engagement, defined as all behavioral manifestations from customers towards a brand or firm that go beyond traditional transaction-based measures, is important in an increasingly networked society (Verhoef et al. 2010). The trend towards patient empowerment and the explosion of health discussions in social media and web 2.0 unlock new sources of patient-initiated value for firms. In fact, patients engaged with a brand through online channels and social media create at least three types of value to the firm beyond transactions (see also Kumar et al. 2010): (1) patient-to-patient influencer value—when patients recommend a therapy brand to other patients; (2) patient-to-physician influence value—when patients actively request or influence the physician to prescribe a specific therapy brand; and (3) patient knowledge value—when patients contribute with new knowledge and feedback to firms which can lead to new ideas for innovations and improvements in a firm's marketing mix. For firms, the key is to identify the most valuable patients, i.e., those capable of exerting a stronger influence in other patients and physicians or generating valuable knowledge for the firm. Therefore, research on how patients (or physicians) learn from the experiences of other patients has wide applicability in the near future.

An important question is how to identify patients capable of becoming respected opinion-makers who significantly influence other patients, physicians, and regulators. I have discussed the case of Kristian Anderson and his key role in having a drug for bowel cancer reimbursed by Australia's PBS. Let me present another example of an individual POL, Leighann Calentine. Leighann is the founder and main author of D-Mom Blog (http://www.d-mom.com/), a weblog where she gives advice and shares her own experiences on parenting children with Type 1 diabetes. In her blog, which is followed by hundreds of other parents with diabetic children, Leighann frequently voices her opinion about different therapies and devices. As of October 2011, Leighann, who also maintains a regular presence on social media, had more than 1,500 followers on twitter (@DMomBlog) and approximately 1,300 followers on Facebook (https://www.facebook.com/dmomblog).

Fig. 14.4 A dissatisfied patient (Shirley Ledlie; alias: Ann Adams) attacks Sanofi VOICES Facebook page. *Source*: John Mack's Post on Pharma Marketing Blog: http://pharmamkting.blogspot.com/2010/03/sanofi-aventis-feels-social-media-pain.html

One of the important barriers to firm activity in social media space is the need to monitor all the content generated by patients, which may seem a daunting task. In particular, there is a generalized fear of the consequences of adverse events and negative publicity. Patients with a negative opinion about a firm's therapy can indeed be the nightmare of any brand manager. Greene et al. (2010) reproduce a query posted on a Facebook page by a patient taking long-acting insulin glargine therapy that generated strong buzz around the adverse effects of this therapy (p. 289):

> Severe weight gain? Tired? Mood changes? Body aches? Insulin resistance belly fat? I have been seeing a correlation between this drug and all the above. Nothing formal as far as polls, but just asking folks that I believe are diabetic and showing signs of insulin resistance…IS THERE ANYBODY ELSE QUESTIONING THIS??????? Are you involved in the same argument with your medical team as I am? Any feedback would be appreciated! PLEASE.

Sanofi-Aventis has also faced a similar experience with its oncology drug, Taxotere (used in the treatment of breast, prostate, junction, advanced head and neck, and non-small cell lung cancers), in the form of a well-documented experience by prominent pharmaceutical marketing blogger John Mack.[6] On March 8, 2010, simultaneous posts in multiple blogs, well known within the pharmaceutical industry, documented a serious threat to Sanofi-Aventis' image coming from one of the company's Facebook pages, Sanofi Voices. Shirley Ledlie, a British patient on Sanofi-Aventis' chemotherapy drug, Taxotere, suffered from a rare side effect: persistent chemotherapy-induced alopecia, i.e., permanent hair loss. She decided to voice her anger on Sanofi's VOICES Facebook page. To avoid being blocked from posting comments on Sanofi-Aventis' Facebook pages, Shirley used the nickname "Ann Adams," and posted a vividly threatening photo of her scalp (see Fig. 14.4) and the following message on Sanofi's VOICES wall:

[6]See http://pharmamkting.blogspot.com/, in particular, the post http://pharmamkting.blogspot.com/2010/03/sanofi-aventis-feels-social-media-pain.html, last accessed on March 2nd, 2012.

> Good morning Sanofi, I had your drug Taxotere and as you can see from my photo this is what my scalp looks like 4 years later. Do you have any comment to make?

It is not surprising, then, that the fear of adverse reporting and the lack of regulation in this space are often considered the major barriers to the investment in direct-to-patient channels like social media by pharmaceutical firms. Yet, according to a recent study by Nielsen, the threats of listening to patients online are much smaller than the potential benefits of investing in such interaction (Davies 2008). Current regulation by FDA requires four conditions to be met for a report to be considered a communicable adverse event report: (1) the patient needs to be identifiable, (2) the reporter needs to be identifiable, (3) a specific drug or biological agent needs to be involved in the event, and (4) an adverse event or fatal outcome has to have occurred. If any of these conditions is not met, the company *should not* submit the report to the FDA, as it will be lacking rigor and will be impossible to follow-up on. The Nielsen study found that only 1 out of 500 healthcare messages posted in social media outlets actually meets the four criteria.

Some companies have already started to creatively explore the social media space. Jonathan Richman, of the dose of digital blog (http://www.doseofdigital.com), maintains a comprehensive list of pharmaceutical firms' social media efforts (including blogs, Twitter pages, Facebook pages, and YouTube pages). The list has been growing steadily, which suggests that an increasing number of companies are investing in social media as a prime channel through which to reach patients.[7]

In February 2012, when the third annual Healthcare Engagement Strategy Awards were announced, Boehringer Ingelheim was praised for its personalization of corporate communications through Facebook, and AstraZeneca was recognized for actively engaging patients on Twitter, specifically with its #rxsave Twitter chat on patient assistance programs.[8] Commenting on her successful experience on Twitter, Jennifer McGovern, director of AstraZeneca's prescription savings program, mentioned that it all started as an experiment about how to extend to online channels the company's engagement with advocates of reaching patients eligible for support.

Nevertheless, McGovern also admitted that most companies still have to embrace real-time open conversation with patients on social media, mainly due to a sensitive regulatory environment, the aforementioned fear of adverse reporting, and a lack of clarity regarding what firms need to do to moderate social media interactions.[9] Reflecting on their work with #rxsave, McGovern highlights three factors for success in social media: (1) having a clear social media policy that align the firm's goals with guidance from regulatory agencies, (2) clarifying to all internal and

[7] See http://www.doseofdigital.com/healthcare-pharma-social-media-wiki/.

[8] See http://engagementstrategy.com/articles/announcing-the-winners-of-the-healthcare-engagement-strategy-awards-2012-hesawards/.

[9] See http://engagementstrategy.com/articles/astrazeneca-healthcare-engagement-strategy-2012-open-dialogue-award/.

external users the rules and expectations for social media interaction, and (3) clearly connecting the social media strategy with the right organizational objectives.[10]

Hence, following a few initial success cases, it is time for other pharmaceutical firms to boldly and clearly delineate the social media strategy for their different brands, which needs to consider the new role of the patient in the patient–physician relationship and the relationship with other stakeholders, such as payers and regulators. It is also important for academic research to develop better methods and algorithms to efficiently monitor patient-generated content on social media and web 2.0 (e.g., via sentiment analysis).

14.4.2.3 Firm-to-Patient Communication via Mass Media

Despite the emergence of new channels for communicating with patients, firms also need to devise strategies for communication management via traditional channels, such as mass media, namely, DTCA strategies.[11] DTCA is still by far the most used channel for firms to communicate directly with patients, especially in the United States. In fact, branded drug slogans, themes, and imagery are now considered part of American popular culture (Myers et al. 2011). However, outside the United States and New Zealand, a key impediment to direct-to-patient communication is regulations forbidding DTCA. In Europe, for instance, public opinion typically rejects DTCA, which has led the European Commission to maintain the ban on the supply of any form of information destined to "promote the prescription, supply, sale or consumption of medicinal products" (Article 86, Title VIII on Advertising of Directive 2001/83/EC, as amended by Directive 2004/27/EC[12]). Hence, all communication efforts need to deal with the regulatory constraints in place in each region.

Even when DTCA is not allowed, there are often possibilities to fruitfully interact with patients. Despite regulation, it is possible for firms in Europe to interact with patients to provide information that is beneficial for patients and not aimed to promote a specific brand. Excluded from the ban imposed by Directive 2001/83/EC are, for instance, (1) information relating to human health diseases without reference to branded drugs (i.e., non-branded disease awareness campaigns), (2) labeling and package leaflets (which are regulated by Title V of the same directive), and (3) correspondence, perhaps accompanied by non-promotional material needed to answer specific questions about a specific drug (which opens the door for firms to explore legal possibilities for interaction with patients and possibly adherence programs).

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[10] See http://engagementstrategy.com/articles/astrazeneca-healthcare-engagement-strategy-2012-open-dialogue-award/.

[11] The academic literature on DTCA is extensive, and my goal here is to complement this literature with an overview of the effects of patient empowerment on DTCA, especially given the regulatory limitations of such communication. I refer the reader to excellent papers providing in-depth summaries of the literature on DTCA, such as Iizuka and Jin (2005), Kolsarici and Vakratsas (2010), Narayanan et al. (2004) and Osinga et al. (2011).

[12] Available at http://www.ema.europa.eu.

Non-branded channels can be important in therapy promotion, not only in Europe but also elsewhere, including in the US Non-branded disease awareness campaigns, for example, may be able to increase patients' awareness for specific health risks and benefits of treatment, possibly increasing primary demand (Gilbody et al. 2005). However, firms need to keep the goals of the campaign transparent and focused on maximizing value for the patient through promotion of patient empowerment. Failure to do so can trigger public outcry. In 2000, for instance, Novartis started a disease awareness campaign in the Netherlands for onychomycosis, a fugal nail infection for which there were two treatments: Novartis' terbinafine and itraconazole ('t Jong et al. 2004). Novartis claimed that its campaign would benefit all prescription drugs for onychomycosis. However, because medical guidelines favored terbinafine, the campaign had a significant influence both on primary demand and on market share. These effects generated heated criticism which led Novartis to voluntarily stop the campaign in May 2002 ('t Jong et al. 2004).

Another important goal of firms' direct-to-patient communication management strategies should be to increase correct use of prescription drugs. Patients' correct use of therapies is pivotal for their clinical value and cost-effectiveness to materialize. For example, patient usage of prescription drugs without a script or deviation from the physician's advice (such as non-adherence, which I discuss below) can bring about negative consequences for patients and for the image of the brand. More research is needed to better understand the drivers of correct use of prescription drugs by patients.[13]

Careful labeling and packaging can help reduce these problems. For example, a 2005 report indicates that one of the causes driving an increase in the abuse of prescription drugs is the fact that such drugs are abundantly found in family medicine cabinets and are easily shared among friends and relatives who erroneously assume that FDA-approved drugs are safe for everyone (National Center on Addiction and Substance Abuse 2005). Customized packages for different prescription regimens could help reduce this risk by limiting the amount of pills left unused in patients' cabinets. These goals can also be achieved via direct-to-patient non-promotional correspondence, which can be used to fight the use of prescription drugs without consent and other problems like patient non-adherence, a goal that can also be achieved through patient adherence programs.

14.4.2.4 Stimulating Patient Adherence to Therapy

Patient adherence programs are also a key direct-to-patient marketing strategy. Therapy non-adherence costs the pharmaceutical industry about $30 billion a year and is responsible for 125,000 deaths per year in the United States alone (Bates 2008). It also results in direct and indirect healthcare costs in excess of $177 billion in the

[13]In a rare study on this topic, Myers et al. (2011) show that in the erectile dysfunction category, individual traits are capable of predicting a patient's likelihood to use prescription drugs without seeing a physician.

United States alone (National Council on Patient Information and Education 2007), more than the annual health costs of obesity. Hence, increasing therapy adherence brings health benefits for patients, lower costs for payers, and increased patient retention (and thus higher sales) for firms. Adherence programs are one of the rare instances in pharmaceutical marketing in which the incentives of all stakeholders are aligned and scholars and practitioners see these programs as a key research priority in pharmaceutical marketing (Stremersch and Van Dyck 2009).

Several firms are already investing in adherence programs. In the latest edition of CBI's strategic patient awards, which recognizes successful adherence programs, winners included firms, like Merck, and pharmacy-sponsored organizations, like Rx Canada, and payers, like Kaiser Permanente (Ringler 2011). Adherence programs can have at least three types of goals: (1) *information-provision*—educating patients on the importance of adhering to physician recommendations, (2) *skills development and facilitation*—helping patients correctly follow the therapy advice or access to sufficient financial resources to follow the treatment plan, (3) *making therapy adherence easier for patients*—motivational and monitoring programs aimed at decreasing unintentional non-adherence, such as forgetfulness.

Most programs target multiple goals at the same time. Shire, for example, has developed "Fosrenol on Track," a comprehensive support program aimed at facilitating both patient education and patient access to financial resources, which helps to guarantee that patients "stay on track" when taking Fosrenol.[14] Pfizer has a similar program called "Staying on Track" that is aimed at helping patients monitor and adequately adhere to their therapeutic regimen (Stremersch and Van Dyck 2009). AstraZeneca also provides extensive support online for patients taking Symbicort, a combination drug and inhaler for asthma and chronic obstructive pulmonary disease. This is an important touch-point between the firm and its patients, which AstraZeneca uses to empower patients with the knowledge they need to correctly use the Symbicort inhaler and adhere to the prescription plan developed with their physician.[15] An example of a program that is aimed at reducing patient forgetfulness and making adherence easier for patients is "SIMpill," a pill bottle that keeps track of the patient's medication schedule and uses text messaging to remind patients when they forget to take their medication as prescribed[16] (see also Stremersch and Van Dyck 2009).

Despite the increasing number of adherence programs, many are not effective or are too costly for the effects they are able to produce. Researchers from IMS Health and Pfizer have analyzed all studies published between 1972 and 2007 on interventions to improve adherence to lipid-lowering medications (for cardiovascular diseases) and found that personalized, intensive, and multifaceted programs were the most effective but the most costly (Chapman et al. 2010). Reminder programs were the least costly (about $10 per patient for a 6-month intervention) but the least

[14] http://www.fosrenolontrack.com/patient/Default.aspx.

[15] http://www.mysymbicort.com/.

[16] http://www.simpill.com/.

effective (relative improvement in adherence of 1.11–1.14). Individual case management was the most costly ($90–130 per patient for a 6-month intervention) but the most effective (relative improvement in adherence of 1.23–4.65; Chapman et al. 2010). As therapy adherence is increasingly seen as a key research topic in health marketing (Stremersch and Van Dyck 2009), the literature on patient therapy adherence keeps growing (Bowman et al. 2004; Dellande et al. 2004; Kahn and Luce 2003; Lee et al. 2007; Luce and Kahn 1999; Neslin et al. 2009; Wosinska 2005). To maximize the return on investment of adherence programs, marketers need to use all available research and information to carefully ponder all direct and indirect benefits and risks and the intervention costs for designing and implementing adherence programs.

14.5 Is Big Pharma Embracing Patient Empowerment as a Key Strategic Goal?

Having reviewed the ongoing trend towards patient empowerment and the consequences of this paradigm shift in medical decision-making for the patient–physician relationship, therapy launch, and therapy promotion, my next goal is to analyze whether pharmaceutical companies are already focusing on the patient empowerment trend as a key strategic goal. To answer this question, I collected the annual reports of the 20 largest pharmaceutical companies for the 6 years between 2005 and 2010 and content analyzed them to measure the degree of each firm's strategic orientation towards patient empowerment. Content analysis of firm documents such as shareholder letters and annual reports is recognized by scholars as a good strategy to understand firms' strategic orientations (Noble et al. 2002).

I selected the top 20 firms by global sales of prescription drugs using Pharmaceutical Executive's latest ranking (Cacciotti and Clinton 2011), which should have yielded a total of 120 annual reports. However, there were six reports that I could not find in a format suitable for content analysis (Novartis 2010, Sanofi-Aventis 2005, Merck 2010, Abbott 2006 and Boehringer Ingelheim 2008 and 2009), which yielded a sample of 114 annual reports. These 20 companies account for $483.8 billion in sales of prescription drugs, which is 81.53 % of the total revenues of the top 50 global pharmaceutical firms (Cacciotti and Clinton 2011). Table 14.2 depicts the 2010 global sales of prescription drugs for each of these 20 companies (or Rx, in USD billions) and the location of their headquarters and firm expenditures on R&D in the same year.

To content analyze these reports, I converted each of the reports to plain text. Afterwards, I counted the number of times words contained in a set of keywords related to patient empowerment were mentioned in the annual report (see Appendix for the keyword list).[17] The chosen keywords include terms that directly indicate

[17]I would like to thank Viorel Milea, at the Econometric Institute of the Erasmus School of Economics, for his invaluable help in the programming of the Python code I used to perform this content analysis.

Table 14.2 The 20 largest pharmaceutical companies by global sales

Ranking	Company	Headquarters	Rx sales 2010 (USD billions)	2010 R&D expenditures (USD millions)
1	Pfizer	New York, New York	$58.50	$9,413
2	Novartis	Basel, Switzerland	$42.00	$7,100
3	Sanofi-Aventis	Paris, France	$40.30	$5,147
4	Merck	Whitehouse Station, New Jersey	$39.80	$11,000
5	Roche	Basel, Switzerland	$39.10	$8,612
6	GlaxoSmithKline	Brentford, England	$36.20	$6,126
7	AstraZeneca	London, England	$33.30	$4,200
8	Johnson & Johnson	New Brunswick, New Jersey	$22.40	$4,432
9	Eli Lilly	Indianapolis, Indiana	$21.10	$4,880
10	Abbott	Abbott Park, Illinois	$19.90	$3,724
11	Bristol-Myers Squibb	New York, New York	$19.50	$3,566
12	Teva	Petach Tikva, Israel	$16.10	$933
13	Amgen	Thousand Oaks, California	$14.70	$2,894
14	Bayer	Leverkusen, Germany	$14.50	$2,320
15	Takeda	Osaka, Japan	$14.20	$3,198
16	Boehringer Ingelheim	Ingelheim, Germany	$12.90	$3,056
17	Novo Nordisk	Bagsvaerd, Norway	$10.80	$1,709
18	Astellas	Tokyo, Japan	$10.50	$2,109
19	Daiichi Sankyo	Tokyo, Japan	$9.80	$2,124
20	Eisai	Tokyo, Japan	$8.40	$1,932

that top management has considered patient empowerment as a relevant phenomenon (e.g., "patient empowerment," "informed patient," or "shared decision-making") or that indicate that the firm has invested or is considering investing in one of the direct-to-patient channels which, as discussed in this chapter, signal that the firm considers patient empowerment important for therapy launch or therapy promotion (e.g., "social media," "disease awareness campaign," "patient support," "holistic healthcare," "patient community," or "patient adherence"). Given that different firms have different policies regarding the size and content detail of their annual reports, I normalized the keyword count by dividing it by the number of pages in each report, reaching the following *index of patient empowerment orientation* (IPEO):

$$\text{IPEO}_{it} = \frac{N_{it}^{\text{PEO}}}{\text{Pages}_{it}} \times 100$$

where N_{it}^{PEO} is the number of occurrences in the annual report of firm i at year t of terms contained in the patient empowerment dictionary (see Appendix), and Pages_{it} is the number of pages of the same annual report. The post-multiplication by 100 means that IPEO_{it} measures the number of times terms related to patient

Table 14.3 Index of patient empowerment orientation, 2005–2010, for the 20 largest pharmaceutical companies

Company	2005	2006	2007	2008	2009	2010
Pfizer	6.087	0.806	1.550	0.694	1.961	1.415
Novartis	1.429	0.424	0.385	0.000	1.119	
Sanofi-Aventis		1.316	6.250	7.143	0.000	3.571
Merck	2.778	0.000	0.000	3.390	4.911	
Roche	0.847	1.942	1.064	1.587	0.787	0.694
GlaxoSmithKline	0.521	0.521	0.543	1.415	1.449	0.926
AstraZeneca	2.083	2.717	0.481	3.922	0.943	0.292
Johnson & Johnson	1.250	1.190	1.220	2.632	2.778	1.250
Eli Lilly	1.000	0.862	0.000	0.758	1.744	2.439
Abbott	1.250		1.250	1.333	1.316	0.000
Bristol-Myers Squibb	2.419	0.735	2.419	0.926	0.806	2.344
Teva	1.487	4.242	2.959	1.449	3.497	2.717
Amgen	0.000	2.632	0.556	0.526	0.556	0.568
Bayer	0.446	0.403	1.674	3.435	3.285	3.663
Takeda	0.000	1.111	2.128	3.604	6.923	0.714
Boehringer Ingelheim	3.175	2.548	2.041			0.388
Novo Nordisk	5.172	0.806	4.032	4.839	0.893	1.724
Astellas	0.000	6.250	1.471	1.282	0.000	1.220
Daiichi Sankyo	4.167	2.941	0.000	0.000	0.000	0.000
Eisai	0.000	0.000	0.000	0.000	1.282	5.263

empowerment is mentioned per 100 pages. Table 14.3 reproduces the IPEO for each of the 20 companies in my sample and each of the years.

The first insight we can take from this analysis is that although several firms are already mentioning patient empowerment in their annual reports, the prevalence is still relatively limited. Moreover, there is heterogeneity strong volatility across companies. In 2010, the three companies with higher IPEO were Eisai, Bayer, and Sanofi-Aventis, which on average mentioned the selected keywords on patient empowerment 5.2, 3.7, and 3.6 times for each 100 pages of their annual reports, respectively. In contrast, Abott and Daiichi Sankyo did not mention any of the terms in my keyword list in 2010. However, in 2005, Daiichi Sankyo had a relatively high IPEO of 4.17.

Second, there is no clear indication of a consistent pattern for the increase in orientation towards patient empowerment. Take the example of Takeda. If I had analyzed data only until 2009, I could have concluded that Takeda was consistently increasing its IPEO over time. However, in 2010, the index for Takeda fell from 6.9, the largest value in 2009, to 0.714 in 2010, which constitutes a drop of 11 places if we rank the companies from highest to lowest IPEO. This may stem from regulatory limitations forcing companies to be more conservative in their direct-to-patient marketing or from limitations of my chosen measure (e.g., the keyword list is quite conservative). Figure 14.5 tells a similar story. It depicts the average IPEO, across all 20 companies for each year considered in the analysis. The pattern shows limited

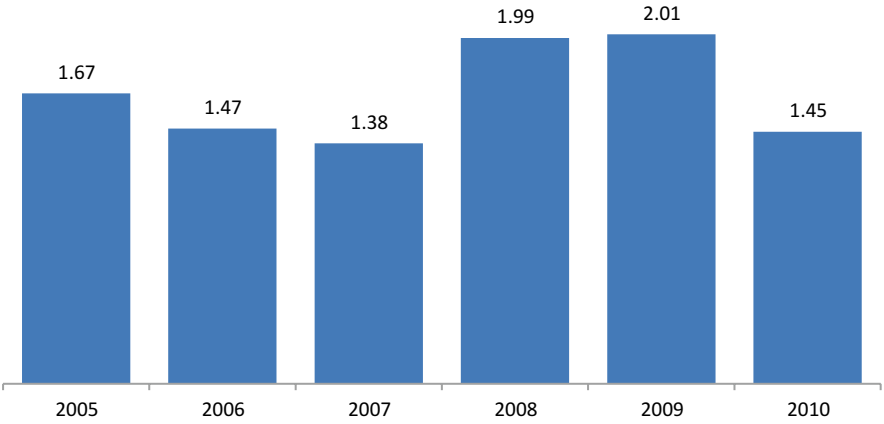

Fig. 14.5 Average index of patient empowerment orientation across all the 20 largest pharmaceutical companies, 2005–2010

and inconsistent variation over time, with a large increase in average IPEO in 2008 but a decrease of almost the same magnitude in 2010.

The main conclusion of this content analysis of Big Pharma's annual reports is that, even though most firms are already devoting attention and resources to patient empowerment strategies, the consistency and magnitude of such attention is not consistent over time and across firms. Moreover, a more in-depth analysis of the passages mentioning patient empowerment terms reinforces this conclusion. In most cases, the existing programs and actions geared towards empowerment, as mentioned in annual reports, seem to stem more from isolated initiatives in certain departments, countries, functional units, or brands rather than from a consistent strategic marketing orientation shaping the companies' future. I hope the evidence presented in this chapter stimulates managers to consider this route for the future of marketing within the pharmaceutical industry.

14.6 Conclusion

Societal trends, such as the quest for more self-expression, demographic and lifestyle changes, technological evolution and regulatory changes, are contributing to a new paradigm of medical decision-making. The traditional white-coat model, in which physicians apply their biomedical knowledge to choose a therapy on behalf of their patients, is being abandoned in favor of a model in which patients are expected and required to actively participate on therapy choice. These trends have profound implications for the patient–physician relationship and require pharmaceutical firms to rethink the way they launch and promote therapies.

In the present chapter, I have argued that patient empowerment opens up unique opportunities for firms. By pro-actively partnering with empowered patients, firms

can help determine treatment choices and effectively promote patient health and quality of life through faster access to new therapies, new health solutions, and the promotion of desirable patient behaviors, such as adherence to medical treatment.

Despite severe regulatory constraints, some firms have already started to embrace patient empowerment as a key strategic mantra. However, such efforts are not yet consistent over time and across companies. Through a content analysis of the 2005–2010 annual reports of the largest 20 pharmaceutical firms, I showed that a set of keywords and phrases aimed at measuring a firm's orientation towards patient empowerment is still unevenly and infrequently used. In addition, I reviewed evidence suggesting that it would be beneficial for firms to put patient empowerment at the center of their marketing strategies. Patient-centered marketing requires firms to move away from the current physician-focused model (complemented by DTCA in the United States and New Zealand) to a model in which patients assume a central role in therapy launch and therapy promotion, which requires new ways and new channels to address patients.

For therapy launch, firms should invest in new partnerships with key POLs such as patient support organizations and high-reputation patients with a strong Web presence. Such partnerships can help firms more efficiently enter new markets, provide faster access to new therapies for patients, and more quickly harness the information needed to demonstrate patient value and guarantee reimbursement.

For therapy promotion, firms can benefit from a focus on patient empowerment in multiple ways. First, a clear focus on the patient helps attract a passionate sales force that is motivated by clear evidence that the brands they are promoting have a direct positive impact on patients' lives. Second, strategies to empower patients via new channels, such as social media and web 2.0, help to engage patients with the brand. Such patient engagement unlocks several sources of value, such as patient-to-patient or patient-to-physician influence, and transmission of valuable knowledge about the brand from the patient to the firm. Third, despite the somewhat low effectiveness of DTCA and stringent regulation (especially outside the United States and New Zealand), firms can use non-branded channels to raise disease awareness and ensure correct usage of their therapies. Finally, a closer relationship with patients is an opportunity for firms to improve the effectiveness of their programs to stimulate patient adherence to therapy, a key customer retention effort for pharmaceutical firms, who lose about $30 billion a year due to non-adherence (Bates 2008).

Although the regulatory context of each market limits the extent of interaction that firms can have with patients, it is important for firms to creatively explore opportunities to dialogue with patients. Besides developing disease awareness campaigns, other channels include offering mobile solutions (e.g., mobile apps) aimed at improving patient knowledge and access to high-quality information about their diseases or treatments, developing creative packaging and labeling (e.g., to promote correct therapy usage and therapy adherence), offering holistic healthcare solutions (e.g., therapy combined with medical devices or programs for lifestyle change), and devising more interactive patient adherence programs.

14.6.1 Limitations

A first limitation of the current chapter is its strong focus on the effects of patient empowerment for patient–physician relationships and for pharmaceutical marketing. I refer the reader to the rich literature on patient empowerment in medicine for the implications of such empowerment for doctors (see, e.g., Charles et al. 1999, 2006; Epstein et al. 2004; Krahn and Naglie 2008). Other stakeholders in the healthcare value chain include pharmacists and other product intermediaries, hospitals, nurses and other healthcare professionals, payers (insurers, health maintenance organizations, and governments), employers, and regulators (see Stremersch and Van Dyck 2009). Although indirectly addressed in this chapter, patient empowerment may bring about unique challenges and questions for each of these stakeholders. Future research on such challenges is very important.

Second, firms trying to increase the centrality of patients in their marketing strategies will probably face several barriers that need to be openly addressed in future research. I expect firms to face three major barriers: resistance from sales and marketing managers used to steer marketing towards physicians, possible negative reactions from regulators, physicians, and even patients who are not used to dialogue with pharmaceutical companies, and initial resistance from shareholders who may fear that such a move is too costly and outside the current set of competences of pharmaceutical firms.

The present chapter does not offer all of the answers to these concerns. Yet, it provides strong evidence suggesting that medical decision-making is quickly changing. Companies that adapt faster to this new paradigm will develop a strong competitive advantage. In this new paradigm, I expect the patient to become pharmaceutical firms' best ally in therapy launch and therapy promotion.

Third, my analysis of the degree to which pharmaceutical firms are embracing patient empowerment as a strategic orientation suffers from some limitations. My content analysis was based on a relatively short and conservative set of keywords. A more extensive analysis of firms' strategic orientation towards the patient could perhaps uncover more nuanced trends. In addition, an analysis based on firms' annual reports remains focused on what top management decides to publish in those reports. Information included in an annual report may be particularly sensitive to the interests of the shareholders, who may react to information differently than do other agents. If senior management fears that shareholders may react negatively to early investments in patient-centered marketing strategies, they may be conservative when stressing such investments in the annual report. Such a behavior could explain the still relatively low prevalence of patient empowerment-related keywords in the annual reports I analyzed.

Despite these limitations, I hope my chapter has achieved at least two goals. First, I hope it has triggered the interest of pharmaceutical marketers in experimenting and developing marketing strategies capable of turning the pharmaceutical firm into an advocate and ally of the patient. Second, I hope that it stimulates marketing scholars to go beyond the study of direct-to-physician marketing and DTCA and to

actively investigate the role of other direct-to-patient channels in pharmaceutical marketing. The heyday of the physician-centered blockbuster model, which served brands like Lipitor, has passed, and patient empowerment is an inescapable reality in medical decision-making. Ignoring such a key trend is not an option.

14.7 Appendix: Dictionary of Terms Used to Identify Patient Orientation

Patient empowerment
Informed patient
Patient support
Patient community
Patient communities
Social media
Shared decision-making
Disease awareness campaign
Mobile marketing
Packaging
Labeling
Holistic healthcare
Patient adherence
Therapy adherence
Patient compliance
Therapy compliance
Patient nonadherence
Patient non-adherence
Therapy nonadherence
Therapy non-adherence
Patient noncompliance
Therapy noncompliance
Direct-to-patient
Direct-to-consumer

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Chapter 15
Leveraging Peer-to-Peer Networks in Pharmaceutical Marketing

Tulikaa Bhatia

Abstract This chapter focuses on the identification of opinion leaders in physician networks as a substantial opportunity for pharmaceutical firms rethinking their business model, and looking for improving resource allocation in order to increase their return on investment. It points out the various challenges and the advantages of identifying regional opinion leaders, especially when it comes to sustained use of branded drugs marketed by pharmaceutical firms. It includes a basic overview of network structure and the formation of physician social networks. This is a growing area of importance for various disciplines such as epidemiology, sociology, economics, and marketing. In this chapter, the reader will get introduced to several models of physician social networks which help isolate and measure the effect of opinion leaders, both self-stated and those identified by patient referral data. The author points out the managerial implications of this stream of research and promising areas of opportunity for deeper analysis for this promising nascent research stream.

15.1 Introduction

The identification of opinion leaders in physician networks is a substantial opportunity for pharmaceutical firms rethinking their business model, and looking for improving resource allocation in order to increase their return on investment. Pharmaceutical firms have focused on cost cutting to deal with the revenue loss due to patent expiry, which has reduced the size of their sales force. The overall size of the industry's US sales force declined 10 % to about 92,000 in 2009 from a peak of about 102,000 in 2007 and is projected to fall to 75,000 in the next few years (Goldstein 2009). There is also declining productivity of sales calls since there is a greater pushback from

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physicians who are restricting access in a major way. Roughly a quarter of physicians work in practices that refuse to see drug reps. Reps talk to a physician in person on about 20 % of visits to doctor's offices, and leave samples in 37 % of the visits (Goldstein 2009). "Physicians still want to see pharmaceutical drug reps, and drug companies are still convinced of the effectiveness of one-on-one sales rep visits, but the sales model and the sales rep's job will require a more focused, technical, targeted, and value-filled approach" (McKee 2010). Pharmaceutical firms are making refinements to how the sales model works at the regional level by giving greater autonomy to regional sales forces. Local peer-to-peer networks offer a significant opportunity for pharmaceutical firms to improve the effectiveness of marketing to physicians.

Especially in the drug prelaunch and new product launch, opinion leaders play a significant role in increasing new drug or new medical device adoption. Many national key opinion leaders, who are well respected as thought leaders and who publish in leading journals, are members of the clinical trials, and are used as keynote speakers in conferences in the therapeutic area. These opinion leaders increase speed of new drug adoption by lending credibility to the claims of the pharmaceutical firms. They also help obtain market access for the new drug by helping it achieve a better status on the formulary. These national opinion leaders help in the adoption of new drugs, the adoption of new health guidelines or treatment guidelines for the therapeutic area. However, when it comes to sustained use of the drug and the side effects and determining the best drug match for an individual patient, the regional opinion leaders have a stronger effect. The challenge to the adoption of a localized sales model by pharmaceutical firms is in identifying peer-to-peer networks at the local territory or district level. The problem is that information typically resides in the field and there are no consistent sets of criteria applied by sales representatives. Additionally, there is no one-stop information source to provide detailed network information at the local territory or district level. To complicate matters further, these networks of influence differ by therapeutic area. The identification of these peer-to-peer networks would thus lead to faster adoption of new drugs, new treatment guidelines, and would lead to better patient-drug match ensuring less side effects and higher efficacy of drugs prescribed.

15.1.1 Basic Overview of Network Structure

In order to understand and map physician peer-to-peer networks, we need to understand some basics of network structure. Social network analysis views social relationships in terms of network theory consisting of nodes and ties. Nodes are the individual actors within the networks, such as individuals or organizations, and ties (also called edges, links, or connections) are the relationships between the actors. These ties can be formed by friendship, kinship, common interest, financial exchange, dislike, sexual relationships, or relationships of beliefs, knowledge or prestige. The nodes to which an individual is thus connected are the social contacts

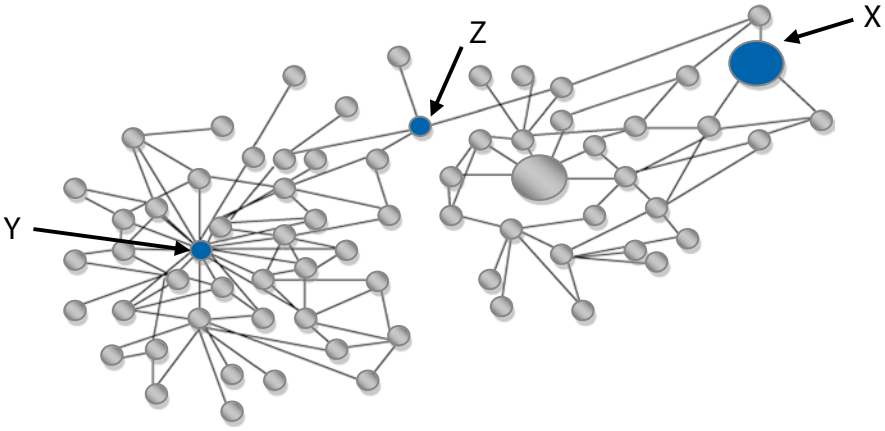

Fig. 15.1 Social network graph of physicians

of that individual. The network can also be used to measure social capital—the value that an individual gets from the social network.

These concepts are often displayed in a social network diagram, where nodes are the points and ties are the lines. Any type of dyadic relationship can be represented, but most common are communication, friendship choices, advice, trust, influence, and exchange relationships. Most of these relationships are not necessarily reciprocal. In that case, directed lines can be used. Vertices are sometimes used for points, arcs for directed lines, and edges for undirected ones. This representation makes it possible to apply graph theory, a branch of discrete mathematics. Connecting positive or negative signs to directed lines enables the representation of positive and negative ties (Stokman 2001).

Research in a number of academic fields has shown that social networks operate on many levels, from families up to the level of nations, and play a critical role in determining the way problems are solved, organizations are run, and the degree to which individuals succeed in achieving their goals. The shape of a social network helps determine a network's usefulness to its individuals. Smaller, tighter networks (strong ties) can be less useful to their members than networks with lots of loose connections (weak ties) to individuals outside the main network. More open networks, with many weak ties and social connections, are more likely to introduce new ideas and opportunities to their members than closed networks with many redundant ties. In other words, a group of friends who only do things with each other already share the same knowledge and opportunities. A group of individuals with connections to other social worlds is likely to have access to a wider range of information.

This can be illustrated in a social network diagram of physicians shown in Fig. 15.1. The circles (nodes) represent physicians and the size of the circle represents the size of prescriptions they write. The lines represent the connections between physicians (ties). The ties shown here are nondirectional but they may be

directional in nature leading to a better idea of the influence of these physicians. Physician X may be a high prescribing physician but he is not connected to many other physicians whom he can influence (only three other physicians as shown in Fig. 15.1). Physician Y on the other hand is socially central and is very well connected. Physician Y is in a better position to influence a large number of physicians and be influenced by them. Physician Z, is neither socially central nor high prescribing, but she is the key link between two groups of physicians. Physician Z seems to be a node who is key to access to two large groups of physicians and so may be an important physician to target by pharmaceutical firms trying to increase their reach.

Freeman (1978) defines three main measures of "network centrality" which gives a rough indication of the social power of a node based on how well they "connect" the network—"Degree," "Closeness" and "Betweenness." Measures based on the degree, the number of points with which a point is directly connected, indicate the communication activity of a point. In directed networks, centrality in terms of outdegree and indegree is different. In friendship choice networks the number of choices received (indegree) generally indicates centrality (popularity); in influence networks centrality is based on the number of outgoing relationships (outdegree). *Degree-based measures* indicate local centrality, as the global structure of the network is not taken into account. In Fig. 15.1, physician X has degree 3, physician Y degree 18, and physician Z degree 4. So, physician Y is more central in the network since she is connected to more physicians than physician X or Z. *Distance-based measures* indicate the relative proximity of points with other points in the network and the extent to which a point can communicate with other points independently of others. In this context, the distance from a point to another point is the minimum number of ties that must be used to transmit a message to that point, the length of a shortest path. Using Fig. 15.1, we can calculate that the closeness between physicians X and Y is 6, while that between physician Z and physicians X or Y is 3. So, we know that physicians X and Z are more close than physicians X and Y, and so information will take a longer time to travel from physician X to physician Y, as compared with physician Z, and in this case will have to go through physician Z. Betweenness or rush is the third type of centrality and measures how important a point is for the transmission of information between other points. Betweenness measures assume that information is mainly transmitted through shortest paths, connections based on the lowest number of consecutive ties. So, in the example in Fig. 15.1, physician Z will have a higher betweenness measure than physicians Y or Z. A fourth measure suggested by Freeman (1978) is based on prestige or status. Status-based measures take all direct and indirect connections into account. They were originally developed to indicate centrality in influence networks.

15.1.2 Physician Social Networks

Physician social networks are built in several ways. There are three main ways in which physician networks are formed—by social links, by job and location links, and by professional links. First, physicians who study together in a medical school

or do residency in the same hospital know each other and develop social ties. Also, these physicians probably look up to the physicians who belong to the faculty of the school or hospital as opinion leaders. Second, physicians who work together in a group practice or in a hospital may have similar patterns of prescribing drugs and treating certain illnesses. The senior physicians in the group practice or hospital may be the opinion leaders and may decide on specialists whom they would refer their patients to. These specialists are usually regional specialists who often end up influencing the physicians in the group practice. Third, physicians routinely attend seminars for continuing learning credit or are members of a professional society where they meet other physicians and develop social connections. The speakers at these seminars and conferences end up influencing the prescribing pattern of physicians as well. Depending on the level of the seminar, the speakers are usually regional or national key opinion leaders. The national key opinion leaders are usually physicians who publish research in the therapeutic area, are involved in clinical trials, write guidelines for treatment of the disease and are thought leaders in their area. The key opinion leaders vary by therapeutic area and tend to be specialists.

There are different ways in which information diffuses in the physician social networks. One way in which information is disseminated in the network is when new information about drugs or therapies is released in the physician community. These could be new drug launches (or lately drug withdrawals), new drug efficacy or comparison studies, new therapy or treatment guidelines, etc. The new information creates uncertainty about efficiency of these therapies, wherein an opinion leader steps in to answer the questions raised by other physicians about which patients would be most suited for drug withdrawal or for prescribing the new drugs, when and on whom to apply the new therapies, whether to change current prescription behavior gradually with new patients or change therapy for existing patients. The information is disseminated through meetings and conferences by the key opinion leaders who are sometimes part of the clinical trial team, or who have published new studies in top academic journal, or have helped shape the new guidelines.

Another way in which information is disseminated in the network is sourced from the physicians who treat a lot of patients, perhaps specialists who are affiliated with hospitals and large clinics, or those heading large physician practices. These physicians are aware of the side effects of different drugs and have learned which therapies work on a certain patient profile. So, these physicians act as opinion leaders for physicians unsure about the patient-drug match, or those uncertain about therapy side effects. Typically the information disseminates through a physician referral for a patient from a general practitioner to a specialist. The general practitioner is unsure about the best drug for this particular patient, or the patient is suffering from some side effects on the current therapy, and the general practitioner refers him to a specialist whom she looks up to. The general practitioner receives feedback from the specialist (Bhatia and Wang 2011) and learns how to treat similar cases in the future. Hence knowledge disseminates from a specialist to a general practitioner in the direction opposite to the referral. Specialists also work in teams and can be influenced by physicians of other specialties or subspecialties whom they refer patients to.

Opinion leaders are physicians who asymmetrically affect the prescribing or treatment behavior of other physicians. These opinion leaders can be of two types: "clinical leaders" who are experts in the therapeutic area by virtue of their publications in top ranked journals and their membership of editorial boards and clinical trials, and the "market leaders" who are typically large practitioners who are closely connected to the local physician population and gain recognition by the satisfaction and loyalty of their patients (Stremersch and Van Dyke 2009). While the clinical leaders are well respected as academicians/thought leaders who publish in leading journals, physicians have a stronger referral relationship with local market leaders. In addition, physicians' interactions with national key opinion leaders are not sustained in nature because these leaders are not local. They hear them and meet them at conferences or read their publications. Stremersch and Van Dyke (2009) propose that the clinical leaders will have greater impact on other physicians' prescriptions than market leaders when there is uncertainty about the effectiveness of the therapy. The market leaders, on the other hand, are proposed to have a higher influence on physicians' prescriptions than clinical leaders when there is uncertainty on therapy side effects. Stremersch and Van Dyke (2009) also propose that clinical leaders may have greater impact on the prescription behavior of hospital-based physicians than market leaders. On the other hand, market leaders may have a greater impact on the prescription behavior of general practitioners than clinical leaders.

15.2 Existing Literature

The study of social interactions and contagion has been of interest to various disciplines such as epidemiology, sociology, economics, and marketing. The literature in *epidemiology* which studies and models the spread of diseases through contagion has been the basis for much further research in this area. The Bass (1969) model in marketing is based on an epidemiological framework and uses data on aggregate diffusion of sales. The framework has a specification of the probability of social contagion implying a positive concave relationship between sales and the installed base, and measures the implied word-of-mouth diffusion parameters. But the Bass (1969) model and the models based on this framework are pure mixing models which do not model the network explicitly.

The *sociology* literature models the social interactions actively. The simplest model in this stream of literature is the linear-in-means model, in which the actions of an agent are linearly related to the characteristics, as well as the mean behavior of others in her reference group. Another popular stream of sociology literature is that of discrete choice models of social interactions. Schelling (1971) and Granovetter (1978) developed threshold models of social interactions in which the marginal utility that some agents obtain from an action is an increasing function of the proportion of the population taking the similar action. Once a critical mass of people is involved in this action, the threshold or "tipping point" is reached. The basic threshold models is the basis for cascade models in the mathematics, physics,

and computer science literatures that model networks as collections of connected agents differentiated by their vulnerability (Dodds and Watts 2004, 2005). For example, the vulnerability of a physician *i* will be defined as the threshold number of connected physicians that would have to take an action (therapy or dug adoption, increase/decrease prescription of a particular drug) before physician *i* himself would succumb to the action. The critical mass model was extended by Brock and Durlauf (2001) who cast the model in terms of discrete choice.

There are various approaches to modeling social interactions in *economics* literature. The spatial models specify correlation structures such that responses by individuals near one another generate similar outcomes. The measure for nearness could be physical location (as in Manchanda et al. 2008), or attributes similar to those used to prepare a perceptual map, or underlying preferences (as in patriotism in Yang and Allenby 2003). A limitation of these models is that they cannot identify whether an interaction is present. Another class of models in economics is that of models with "forward-looking consumers." These models set up repeated static games where the consumer learns over time by interacting repeatedly in an uncertain environment. For example, physicians learn over time by referring patients to various physicians, which of those physicians are better than the others, or which physicians are better for which kind of patients, and apply that knowledge in the present when deciding who to refer the current patient to. Blume (1993) and Brock and Durlauf (2001, 2002) apply mean field theory to check expectations formed by agents about group behavior, and the expectations are consistent with outcomes. There have been economic models of the process of group formation (Bala and Goyal 2000; Conley and Udry 2010). The network effects can work in either direction. Most papers show positive effects, but some, such as the one authored by Frank (1985), show negative social effects due to status-seeking. Show how network externalities can actually slow diffusion of innovation. Stremersch et al. (2010) suggest that more work is needed on the separation of social contagion and network effects.

There has been great interest in marketing in modeling social interactions. The focus of this literature has changed over time from whether people's behavior was affected by social interaction to who was affected, followed by why and how. Some recent research models social contagion in a piano tuning service (Reingen and Kernan 1986), student grade point averages (Sacerdote 2001), automobile purchases (Yang and Allenby 2003), an internet grocer (Bell and Song 2007), and a video-on-demand service (Nam et al. 2010). Godes and Mayzlin (2004) use field studies to measure word-of-mouth effects from loyal and non-loyal customers of a retail chain. They find that word-of-mouth seems more persuasive on "far" peers rather than "close" peers. Also, surprisingly, word-of-mouth generated by non-loyal customers is more effective than that generated by loyal customers. The Medical Innovation Study (Coleman et al. 1966) in sociology was among the first to focus on whether there are opinion leaders. The study was followed by Burt (1987) who used more accurate identification, and Van den Bulte and Lilien (2001), who added marketing variables to the model, while employing the data from the Medical Innovation Study to better identify the social effects.

A key issue in identifying peer effects is that of defining peers. Manchanda et al. (2008) use physical distance between physicians to identify physician networks. Trusov et al. (2010) use observed "friends" lists on online social networking websites to define the network and the activity (log-on data) to estimate the peer effect. Other research uses surveys and/or experiments to identify the opinion leaders; examples include Valente et al. (2003), Lomas et al. (1991), Celentano et al. (2000), Dufflo and Saez (2003), Nair et al. (2010), and Iyengar et al. (2011). Bhatia and Wang (2011) use patient movements between physicians to identify the physician network. Wuyts et al. (2010) provide a summary of the data used in the literature to study customer networks.

15.3 Models of Physician Social Networks

15.3.1 Identifying Physician Networks and Opinion Leaders

Various ways have been used in marketing literature to identify opinion leaders in industry as well as in academia using surveys (Nair et al. 2010; Iyengar et al. 2011), distance between physician office locations (Manchanda et al. 2008), and patient movements between physicians (Bhatia and Wang 2011). The clinical leaders can be identified by surveying physicians (Nair et al. 2010; Iyengar et al. 2011). The market leaders can be identified by the referral patterns of physicians (Bhatia and Wang 2011).

There are three main difficulties in identifying the effect of opinion leaders on other physicians as pointed out in, which provides a recent and broad summary of the various models of social interactions. The three difficulties are endogenous group formation, correlated observables, and simultaneity. The endogenous group formation problem arises because physicians with similar tastes may tend to form social groups; hence, subsequent correlation in their behavior may reflect these common tastes, and not a causal effect of one's behavior on another. General practitioner physicians tend to meet and form their relationships with specialist physicians at conferences, some hosted by drug companies, which are organized around specific disease conditions and therapeutic treatment options. These relationships between physicians may have correlated prescriptions due to similar tastes rather than due to the opinion leader effect. One solution to the endogeneity of group formation is facilitated by the availability of panel data. With panel data, one can control for endogenous group formation via agent fixed effects (e.g., Nair et al. 2010).

A second source of correlation is correlated unobservables that drive the actions of all physicians in a reference group similarly. There may be common location and time period specific effects which affect all physicians in the group. For example, if some geographical region such as Florida or Arizona has a higher percentage of elderly patients with higher incidence of hypertension or high cholesterol, or if a certain region has a higher ethnic concentration, the physicians may be prescribing more of

certain types of drugs. Also, there may be several time trends where the prescription of certain type of drugs, say combination drugs, may be going up over time. This will lead to correlations in physician prescriptions which are not caused due to opinion leader effects. The inclusion of fixed or random effects mitigates the correlated unobservables problem to some extent, since these control for time-invariant aspects of unobservables driving agents' behavior. In some contexts, one can use a difference-in-difference strategy of using the behavior of other agents not in the focal agent's reference group to control for common unobservables (e.g., Nair et al. 2010).

Finally, a simultaneity problem arises due to the potentially simultaneous nature of decisions by the opinion leader and others in his reference group. Due to simultaneity, correlation in subsequent actions could simply reflect the fact that the opinion leader's decision affects the group's behavior, and at the same time, the group's behavior affects the opinion leader's behavior. This has been referred to as the "reflection problem" in the literature (Manski 1993). This problem may be solved by using an instrumental variable that affects the opinion leader's decision but can be excluded from the decision of others in his reference group. For example, Nair et al. (2010) use the pharmaceutical firm sales representative visits to the opinion leader as an instrumental variable which affects the opinion leader's prescriptions but not the other physicians' prescriptions.

15.3.2 Datasets Available for Research

There are several datasets available to managers and researchers for analyzing physician networks in the United States. These datasets are of various types. The physician level datasets provide information on number of prescriptions written by each individual physician per month for a particular drug. IMS Health is the leading provider of such longitudinal physician prescription data in a dataset called IMS Xponent. This data is considered the standard in the industry and is one of the most comprehensive sources of prescriptions including retail prescriptions filled in pharmacies, mail order service, and the long term care market. IMS Health prescription data represents more than 73 % of the total US retail and mail prescription activity, and contains records from over 50,000 retail pharmacies. IMS Health also provides Xponent Plantrak, which provides information about the managed care plans by physician. Information includes third-party method of payment, including Commercial, Medicare Part D, and Managed Medicaid data. This information could be used to study location-based models of physician networks as in Manchanda et al. (2008). IMS also conducts a promotional audit to ascertain the money spent on detailing, sampling, physician meetings and events, and journal advertising which gives the researchers/pharmaceutical firms aggregate marketing activities (and share of voice) for the brands over time. This data can also be combined with a primary market survey of physicians (as in Nair et al. 2010; Iyengar et al. 2011) to identify and estimate the effect of physician opinion leaders. These researchers (and corresponding pharmaceutical firms) also have the marketing activities for the brand they promote at a physician level.

Physician surveys are the most common method used by pharmaceutical firms to identify opinion leaders. It is a simple and effective method. Usually the physicians are asked questions about who influences them in a particular therapeutic area. Sometimes they ask for more information about how they know the opinion leader or how often and through which channel they get information from the opinion leader. These channels typically could be by direct contact; through patient referral; medical school, hospital or group practice colleague; medical journals; or meetings and conferences. Survey data has the advantage of simplicity and the ability to choose which physicians to survey. Using survey data has several disadvantages too. The first of these is the bias of physicians due to self-reporting. Physicians tend to be more comfortable in naming the national key opinion leaders and more prominent and senior physicians than their peers. Also this kind of survey methodology leads to an incomplete list of opinion leaders because only a few physicians fill out the survey, and possibly nonresponse bias because the physicians filling out the survey may have more time or may be more responsive to detailing.

Another promising avenue for data for mapping physician networks extensively is the anonymous patient level data (APLD). There are various data vendors providing longitudinal de-identified patient level data (in order to conform to HIPAA regulations). Surveillance *Data* Incorporated (SDI) is a leading provider in this area with the largest stream of patient-centric data available, with information from more than 11 million unique patients per year. The SDI Patient Parameters: Source of Business series of products offers information on the patient prescriptions written by individual physicians. SDI is currently in the process of being acquired by IMS Health. There are several other vendors which provide APLD such as Wolters Kluwer and Dendrite. This patient level data can be used to monitor patient movement between physicians, which can be used in turn to infer physician networks as in Bhatia and Wang (2011). There is an opportunity to use this massive/passive data (Chritakis and Fowler 2011) to map the full network of physicians and to look at more facets of the physician network rather than just indegree and outdegree.

15.3.3 Latest Models of Physician Contagion Effects

We will describe the model and main results in the three latest research papers modeling contagion effects in physician networks in detail here. These research papers are Nair et al. (2010, henceforth NMB), Bhatia and Wang (2011, henceforth BW), and Iyenger et al. (2011, henceforth IVV). We will drop most subscripts here for ease of presentation. The reader is encouraged to read the respective research papers for more detail.

These models differ in the data and methodology used to identify the opinion leaders. NMB and IVV use self-reported survey data while BW use patient movement data between physicians to identify opinion leaders. NMB use a two-stage fixed-effects panel data linear instrumental variables regression to estimate their model. IVV estimate a discrete-time hazard model with a logit link function estimated using

standard maximum likelihood. BW estimate their simultaneous equations model using three-stage least squares. There are also several similarities in the models. All three models assume that the social network is exogenous and static. All three models assume that the physicians learn from the prescription experiences of other physicians in their social network, and that the prescriptions written by the opinion leader will influence the prescriptions written by the influenced physician/s.

NMB quantify the impact of social interactions and peer effects in the context of prescription choices by physicians. They specify a parsimonious model for measuring the effect of physician *i*'s self-reported opinion leader(s) (represented as *j*(*i*)). The dependent variable is physician *i*'s prescriptions *y*, and the independent variables are detailing *D*, prescriptions *x*, and control variable *z*. The control variable *z* helps mitigate the problem of correlated observables and is calculated as the mean prescription of all other physicians in physician *i*'s zip-code. NMB control for endogenous group formation using physician fixed effects, and for simultaneity by using instrumental variables for the endogenous variable *x*. The instrumental variables they use are detailing to the opinion leader, $D_{j(i),t}$, as well as the mean prescriptions of all *other* physicians in the opinion leader's zip-code, $z_{-j(i),t}$ which influence *x* but not *y*.

$$y_{it} = \alpha_i + \gamma_t + \beta D_{it} + \delta x_{j(i),t} + \gamma z_{-i,t} + \varepsilon_{it}, \quad i = 1,..,N; t = 1,..,T \tag{15.1}$$

The corresponding specification for *i*'s opinion leader is:

$$x_{j(i),t} = \alpha_{j(i)} + \tau_t + vD_{j(i),t} + \varsigma y_{it} + \xi z_{-j(i),t} + \varepsilon_{j(i),t}, \quad t = 1,..,T \tag{15.2}$$

They estimate both specifications via fixed-effects panel data linear instrumental variables regression. NMB find asymmetric peer effects where they find the effect of opinion leader's prescriptions on physician *i*'s prescriptions (δ) to be positive and significant while the effect of physician *i*'s prescriptions on the opinion leader's prescription (ς) is not significant. The interesting finding in this paper is that these effects are significant only when there in uncertainty in the system, which they specify as the release of new guidelines for treatment of the disease.

NMB calculate a *social multiplier* for each opinion leader. The social multiplier measures the ratio of the effect on the average action caused by a change in a parameter to the effect on the average action that would occur if individual agents ignored the change in actions of their peers. In this case, for example, there is a direct effect of targeting the opinion leader, which is the increase in the number of prescriptions written by the opinion leader. There is also an indirect effect of targeting the opinion leader. The opinion leader influences other physicians to prescribe more of the focal drug. The social multiplier for each opinion leader will be the ratio of total revenue (direct and indirect) received by targeting the opinion leader to the revenue received directly from just the prescriptions written by the opinion leader. This gives an idea of the true value of the opinion leader. So, an opinion leader with a social multiplier of 1.25 generates 25 % more revenue from influenced physicians (indirectly) than from his prescriptions alone (directly). The higher the social multiplier, the more the influence of the opinion leader, and the higher the amount of indirect revenue from

prescriptions of influenced physicians. NMB calculate a social multiplier for each opinion leader by multiplying the additional revenue from the influenced physician(s) as a result of the increase in opinion leader prescriptions (marginal effect of detailing $*\delta*$ revenue generated by one prescription) by the number of physicians the opinion leader influences in their sample. Their social multipliers range from 1.04 to 1.35.

IVV study the adoption behavior of a new drug designed to treat a chronic viral infection. They collected physician self-reported data on the referral and discussion networks and self-reported assessment of leadership in three cities. This enables IVV to distinguish between self-reported leadership and referral leadership (or sociometric leadership). IVV model the adoption of the new drug at time t as a hazard function. The discrete-time hazard of adoption is modeled as below. The probability that the new drug is adopted at time t given it was not adopted at time $t-1$ is a standard normal function of covariates x and parameters β to be estimated.

$$P\left(y_{it}=1 \mid y_{it-1}=0\right)=F(x_{it}\beta) \tag{15.3}$$

The covariates used by IVV are the indegree (number of physicians who nominate a particular physician), self-reported leadership construct, social contagion measures, detailing, and control variables (physician characteristics, category level prescription volume, outdegree (number of nominations given), city and time dummies). IVV find that physicians with high indegree adopt earlier. These are the opinion leaders identified by surveys based on their peer-to-peer connections. IVV test three types of social contagion measures based on adoption (did the opinion leader adopt or not), current prescription (did the opinion leader prescribe in the time period $t-1$), and prescription volume (how much did the opinion leader prescribe). They find only volume contagion out of the three measures of social contagion to be present. This is an interesting finding showing that adoption by a physician is dependent on the prescription volume of the opinion leader, not just the fact that she has adopted the drug and has prescribed it in the last time period. Volume contagion is moderated by self-reported leadership and not be indegree. The correlation between heavy users and influential users (high indegree physicians) is only moderate, suggesting that "just focusing on heavy users will fail to leverage all potential influential seeding points (IVV p. 196)."

Chritakis and Fowler (2011) argue for new techniques to identify the connections among entire networks of physicians. BW set out to do just that by using patient movement data between physicians. Since patient movements can be generated by patients or by physicians, and only the latter will contain information about physician networks, BW impose a simple framework dividing patient movements into three groups: (1) primary care physician (PCP) to specialist and back, (2) specialist to specialist, and (3) PCP to PCP. They suggest that the PCP to PCP movements are purely patient-generated, PCP to specialist movements are mostly physician-generated, and specialist to specialist movements are a mix of patient- and physician-generated movements based on a physician survey.

BW model the contagion between pairs of physicians i and j where there is at least one patient movement from physician i to physician j. Similar to NMB's

specification, physician *i*'s number of prescriptions of the focal drug are a function of time dummies d, marketing variables *x* (including detailing and sampling), physician *j*'s current and lagged prescriptions y_t and y_{t-1}, prescriptions of all other physicians y_{other}, and control variable *z*. Here *z* are the mean number of prescriptions issued by the other physicians in the same zip-code as physician *i* (and *j*) but not in the sample.

$$y_{it} = \alpha_i + \alpha_1 d_t + \alpha_2 x_{it} + \alpha_3 z^i_{-\text{sample},t} + \alpha_4 y_{jt} + \alpha_5 y_{\text{other}\_i,t} + \alpha_6 y_{jt-1} + \alpha_7 y_{it-1} + \varepsilon \quad (15.4)$$

The corresponding specification for *j*'s number of prescriptions issued is

$$y_{jt} = \beta_j + \beta_1 d_t + \beta_2 x_{jt} + \beta_3 z^j_{-\text{sample},t} + \beta_4 y_{it} + \beta_5 y_{\text{other}\_j,t} + \beta_6 y_{it-1} + \beta_7 y_{jt-1} + \varepsilon_{jt} \quad (15.5)$$

In this specification, α_4 and β_4 are the key parameters that measure the peer effect.

BW estimate a simultaneous equations model on these three types of movements and find that the specialist has a significantly positive effect on the PCP but not vice versa suggesting an opinion leader effect. BW compute the social multipliers for these opinion leaders which range from 1.16 to 1.83, much higher than those computed by NMB. BW attribute these to the nature of the identification process where the surveys do "not reveal all of the physicians influenced by a particular physician but only a subset of them." A regression of the social multipliers on specialty categories, the number of physicians in each zip-code, and the category prescription deciles find focal specialists who are high prescribers are more likely to be opinion leaders.

15.4 Managerial Implications

There is a high economic benefit to pharmaceutical firms in identifying opinion leaders and physician networks of influence. First and foremost, these opinion leaders are very influential to the success or failure of any new therapy, new drug launch, or new medical device use. There are two ways in which opinion leaders can ensure quick product uptake in a new drug or medical device launch. First, the opinion leaders can act as spokespeople spreading the word about the better efficacy and/or beneficial side effect profile of the new pharmaceutical drug or medical device. These opinion leaders drive the word-of-mouth for the new drug or medical device, creating a cascading effect, helping it gain the critical mass of patients required to lead that drug over the "tipping point" to make it a commercial success. Pharmaceutical firms actively engage key opinion leaders in clinical trials and as speakers in various industry conferences in order to influence other physicians to follow the lead of these opinion leaders in adopting and using the new drug or medical device. Iyengar et al. (2011) find that the time of adoption by influenced physicians goes down as a result of opinion leader adoption. Second,

the opinion leaders can influence market access by convincing the pharmacy benefit managers to give a favorable formulary status to the new drug or approve use of the medical device.

Pharmaceutical firms target physicians based on their potential and responsiveness to detailing. Typically, pharmaceutical firms target physicians based on their prescription deciles. The high prescribing physicians get higher frequency of sales calls as compared with the low prescribing physicians. However, as Nair et al. (2010) and Iyengar et al. (2011) find in their research, not all influential physicians are high prescribers. There are a lot of influential physicians who teach in hospitals, publish in top academic journals, and participate in clinical trials, acting as key opinion leaders disseminating information, but themselves do not prescribe too many drugs. These low prescribers are valuable for sourcing prescriptions from other high prescribing physicians, rather than their own prescriptions. These physicians have a high social multiplier. As described earlier, the social multiplier measures the ratio of the total sales (direct as well as indirect sales) generated by targeting the opinion leader to the sales from the opinion leader alone (ignoring the change in actions of their peers). Bhatia and Wang (2011) find an average social multiplier of 1.27 which is significantly greater than one. This implies that ignoring the social multiplier effect would lead to suboptimal resource allocation since sales calls to the opinion leaders will be undervalued. Hence, knowledge of the social multipliers of opinion leaders leads to better allocation of scarce marketing and sales force resources, and leads to better return on investment on sales force even for a drug which is already in the market.

Lastly, Iyengar et al. point out that it is not just the fact that the opinion leader has adopted the new drug that influences other physicians, but also the volume of prescriptions of the new drug prescribed by the opinion leader. Hence, there is an advantage to targeting the heavy prescribing "market leaders" along with the "clinical leaders" in order to create the critical mass to reach the tipping point (threshold) leading to widespread use of the new drug.

15.5 Concluding Thought

There is a strong interest in studying social interactions and social contagion driving a large stream of research in marketing, as well as economics and sociology, in this area. This is a promising research area since this research is very nascent and there is a large opportunity for deeper analysis. I believe we have just scratched the surface when it comes to understanding the various motivations and dynamics of peer-to-peer influences, both in terms of the peer group formation, its influence on decision making, and in terms of who become influential and why. The literature so far has tried to identify the physician network and to quantify the impact of the opinion leaders. The next step is to study the formation and utilization of these networks. We describe six different areas of research which hold great promise for researchers in this area.

15.5.1 Mapping the Full Physician Network

Research has found different kinds of opinion leaders based on different techniques used. Self-reported opinion leaders were found to be less affected by contagion (Iyengar et al. 2011). Survey-based identification of opinion leaders does not lead to a full mapping of the physician network, and hence reports lower social multipliers than a method which maps the physician network more completely (as in Bhatia and Wang 2011 using patient movements between physicians, or by using physician referral network data, if available). Also, combining various sources of data such as surveys, physical distances between physicians, physician referral patterns, and other sources may lead to a more complete picture not just of the physician network but also of the physician referral decision making process. Iyengar et al. (2011) find that the tendency to adopt early is more pronounced among those who are central to the network than the self-reported opinion leaders. Chritakis and Fowler (2011) argue that "To know whether a doctor is central, one must map the whole network, not simply ascertain attributes of the doctors, such as their specialty or prescribing behavior" (p. 214). This will lead not just to the identification of who is influential, but also who is influenceable. If there is no contagion in individual level adoption, then no increase in detailing to opinion leaders can lead to cascade effects.

15.5.2 Social Network Analysis

Various complex strategies for targeting also need investigation, and not just the idea of targeting the most central or highest degree nodes (Valente et al. 2003). Tracking the method of propagation of prescribing behavior or adoption may be useful. For example, the possibility that it may spread via "complex contagion" could be examined. Aral (2011) suggests studying how different types of physicians are distributed in the network since it can affect cascades of social behavior and contagion. Networks in which low-status physicians are clustered around high-status physicians will possibly exhibit different adoption dynamics from isolated peripheral clusters of low-status physicians distant from a densely connected core of high-status physicians (as in prestigious clinics and hospitals such as Mayo clinic, or John Hopkins hospital). If physician referral networks typically connect competitors who typically service the same type of needs (such as PCPs or between specialists of the same specialty), prescription referrals may not flow to peers as easily as referral networks connecting physicians to specialists who do not directly compete (Bhatia and Wang 2011).

All the current literature assumes that all the mechanism of influence for the social ties is the same as that of professional ties. Depending on how the social ties among physicians are formulated, it might lead to different levels of peer influence. For example, the tie can be created socially, such as the case when two doctors get to know each other at the same graduate school or in the same hospital for residency; or the tie can be formulated professionally, such as the case when they work in the

same medical group. The differences in peer influences could be among the strength of influences or types of drugs.

15.5.3 *Influence of Product/Patient/Physician/Payor Characteristics*

A major area for research is the effect of patient and product characteristics, and the features of the health care system on peer influence and contagion. This would extend the more general literature on characteristics of products or innovations that influence collective adoption or diffusion. The existing studies do not take into account the patient profile, the patient insurance status, the physician insurance acceptance status, and many other factors which may be important in the formation of the physician network. The physician referral network may be different based on the patient insurance status. There may be differential effects in how contagion works for different drugs, perhaps depending upon the therapeutic category, chronic vs. one-time use drugs, critical vs. healthy patients, high vs. low uncertainty in therapy, and so on. These findings may also apply to the adoption of medical devices, surgical procedures, guideline adherence, and generic adoption, which may be of interest not just to pharmaceutical firms but also to hospitals, health systems, insurers, and the government. There may be differences based on stage in the product life cycle of the drug. For example, Iyengar et al. find contagion in introduction of a new drug, while Nair et al. (2010) find that opinion leaders are influential only in the times following an uncertainty.

15.5.4 *Mechanism of How Social Contagion Influences Physicians' Prescription Decisions*

None of the existing studies on physician social networks have tried to understand the mechanism of how social contagion influences physicians' prescription decisions. Does the follower just do what the opinion leaders do? For example, the follower prescribes the same drug as the opinion leader does in all the existing literature discussed here. Or does the opinion leader's prescription behavior help the follower to learn about the efficacy of the drug by reducing the uncertainty of the drug? Depending on which mechanism is at work, the results would have different implications. If it is the latter, the reduction of uncertainty through social network could be different from the uncertainty reduction through detailing or prescription experiences.

15.5.5 *Hierarchy and Variety in Physician Opinion Leaders*

The physician opinion leaders have been classified by Stremersch and Van Dyke (2009) as "Clinical Leaders" (more academic and well known at the national level) and "Market leaders" (regional opinion leaders affecting physicians through the

patient referral network). Perhaps a hierarchical model of opinion leaders at the regional and at the national level may provide a more complete picture of the physician network. Bhatia and Wang (2011) find continuous influence of regional opinion leaders found by tracking patient movements between physicians, while Nair et al. (2010) find that survey-identified opinion leaders are influential only in the times following an uncertainty. It could be that the former process is identifying "Market leaders" while the latter is identifying "Clinical leaders." Identifying both kinds of leaders in one research study with different drug categories may be useful to gain a better understanding of this hierarchy of opinion leaders. There may also be some benefit to exploring "strong" and "weak" ties between physicians along with network size. There is some evidence that weak ties lead to stronger contagion than strong ties (Godes and Mayzlin 2004).

15.5.6 Role of Sustained Use in Contagion

Aral (2011) suggests studying the role of sustained use in creating sustainable contagions. The sustained use may be correlated with consumer satisfaction, increasing the probability that a user will persuade others to adopt the product. The opposite could also be true, where sustained use of the product leads to waning enthusiasm for the product, making the user less likely to spread word-of-mouth in later periods. This is also related to the volume contagion findings in Iyengar et al. (2011). It will be informative to study how the volume of the drug prescribed over time affects the propensity of the physicians to recommend it to colleagues. The side effects of drugs and patient match characteristics are revealed later in the life cycle through physician learning, and physician enthusiasm about the product could be key to increasing the product market share in a more mature and competitive market with newer competitors. Also, it may be useful to include feedback effects in the model. For example, assume that physician X has recommended brand A to physician Y. How does the performance of brand A as perceived by physician Y impact continued reliance on word-of-mouth from physician X when he/she recommends a second brand at a later point in time?

15.5.7 Susceptibility to Social Influence

Another avenue for research is to study which customers are more susceptible to contagion and why (Godes 2011). The focus of research so far has been on the sender and not the receiver of the contagion—the influencer and not the influenced. It may be interesting to see how self-reported opinion leadership and sociometric centrality moderate vulnerability to contagion. To propagate the message most efficiently, those with significant influence need first to adopt it. IVV find that opinion leaders adopt sooner, but this may not always be the case. If those with influence are aware of their social status, they may want to wait and have more

information about innovations before they adopt. The later will not be true if the opinion leadership is based on expertise, which seem to be true in the case of physician opinion leaders.

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Chapter 16
Leveraging Social Media in the Pharmaceutical Industry

Venkatesh Shankar and Jiaoyang (Krista) Li

Abstract Social media and social networks are the rage these days. The healthcare industry in general and the pharmaceutical industry in particular, are being reshaped by the proliferation of electronic communication through social media. Consequently, marketing practices are also evolving rapidly. Pharmaceutical marketers need a better understanding of how social media work and how they influence marketing strategy. This chapter reviews the burgeoning literature on word of mouth, in particular relating to social media and on how social media and social networks are redefining marketing strategy in this context. It provides a framework for analyzing the effects of social media on patients, physicians, and marketers. It offers actionable implications for pharmaceutical companies, provides pointers to successfully develop and implement an integrated social media marketing strategy, and highlights fruitful avenues for future research.

16.1 Introduction

Social media and social networks are the rage these days. The emergence of social media and the surge of social networks on different themes have transformed markets by engaging consumers through interactive communications. Unlike the traditional media for which consumers are passive recipients of messages, social media have put consumers in control by allowing them to set the dialog agenda and influence marketing decisions and outcomes through word of mouth. Using social media, consumers actively create and share information and experiences that invite further inputs from other members of their social networks. Advances in new telecommunication technologies and mobile devices have expedited the diffusion of social

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media (Shankar and Balasubramanian 2009). People with smart phones and mobile tablets can connect to social media easily to participate in online conversations without time and location constraints.

Formally, social media are media for social interaction that use highly accessible and scalable communication techniques. Social media use web-based and mobile technologies to turn communication into interactive dialog (Wikipedia 2011). Social media comprise different types of websites that perform different functions such as blogging (e.g., Blogger, WorldPress, and LiveJournal), microblogging (e.g., Twitter, Google Buzz, Qaiku), social networking (e.g., Facebook, MySpace, Sermo), professional networking (e.g., LinkedIn, Plaxo), creativity work sharing: video sharing (e.g., YouTube), audio sharing (e.g., Podcast), photo sharing (Flickr), music sharing (Jamendo), content sharing with assistance (Piczo), social bookmarking (e.g., Digg, Delicious), collaborative content creating (e.g., Wikipedia), virtual world sites (e.g., Secondlife), and commerce communities (e.g., eBay, Amazon, Craig's list).

A social network refers to a community of people connected by a common theme or focus through social media vehicles. For example, the group of doctors on the social networking site Sermo, constitutes a social network as they are connected by the common theme of being certified physicians practicing in the healthcare industry. The members of Sermo are similar in their profession, so they are interested in common issues and benefit from connecting with their fellow members.

Social media are growing rapidly. Consider the following statistics that attest to the growing importance of social media.

- By 2010, 96 % of Generation Y[1] were on a social network.
- There are over 200 million blogs.
- 54 % of bloggers post connect/tweet daily.
- 34 % post opinions about products and brands.
- 25 % of search results for Word Top 20 brands are links to user-generated content.
- 90 % of people trust peer recommendations, while only 14 % trust advertisements.
- The online market, now at $1.2 billion is expected to reach $2.2 billion by 2011.
- To reach 50 million users, radio, TV, Internet, and iPod took 38, 13, 4, and 3 years, respectively. But Facebook has added 100 million users in less than 9 months (Socialnomics 2009). Facebook is likely to touch a user base of one billion by August 2012. If Facebook were a country, it would be the world's third largest after China and India.

When virtually everyone is online, belongs to a social network, consumes and contributes to the digital world, and influences each other by word of mouth through

[1]Generation Y, also known as the Millennial Generation (or Millennials), Generation Next, Net Generation, Echo Boomers, describes the demographic cohort following Generation X. As there are no precise dates for when the Millennial generation starts and ends, commentators have used birth dates ranging somewhere from the mid-1970s to the early 2000s (http://en.wikipedia.org/wiki/Generation_Y).

highly accessible and scalable social media, firms need to rethink the way they communicate with and reach customers. Using social media, marketers can more effectively connect with customers, join and build communities, collect market research data, deploy an application, advertise products, announce promotions, monitor, influence, and initiate word of mouth (WOM), and let social media drive sales.

In this chapter, we provide researchers and managers with a comprehensive review of social media, in particular, in the pharmaceutical industry. Although our discussion is relevant to different constituents of the pharmaceutical industry, such as drug manufacturers, pharmacies, pharmacy benefit managers (PBMs), and government agencies such as Federal Drug Authority (FDA), Center for Diseases Control (CDC), and National Institute of Health (NIH), since pharmaceutical firms are major players in the industry and to keep the scope manageable, we focus on pharmaceutical manufacturers and marketers. Importantly, we shed light on how researchers can explore important issues and unearth key insights on social media and how practitioners can leverage social media for favorable outcomes.

The rest of this chapter is organized as follows. In Sect. 16.2, we discuss social media in the context of pharmaceutical industry. In Sect. 16.3, we review the social media and the word of mouth literatures and discuss studies relevant to the pharmaceutical industry. In Sect. 16.4, we discuss how pharmaceutical firms can leverage social media effects.

16.2 When Social Media Meet the Pharmaceutical Industry

16.2.1 Benefits of Social Media for Pharmaceutical Firms

For pharmaceutical firms, social media marketing presents several advantages over the traditional media. First, social media allow firms to listen as well. Engaging online customers in dialogs about the company, product, and brand, firms can build relationships with online influencers, hear feedbacks from customers who use their products and services and understand the needs of customers and the market.

Second, social media allow firms to speak more cost efficiently, to more customers, and louder than that of traditional media. Social media are cost efficient because most social media are free while the traditional promotional activities such as professional detailing and direct-to-consumer advertising (DTCA) are more expensive.

Third, social media offer a new channel for firms to reach customers who cannot be reached easily via traditional media. In the past, pharmaceutical firms connected with physicians mainly through sales representatives and rarely had any direct link to patients other than the one-way mass media broadcasting. As the prescription decision is increasingly becoming a result of joint decision made between the physician and the patient, pharmaceutical companies are investing significant amount of resources to promote drugs to patients as well (Ding and Eliashberg 2008). However, consumer adoption of the digital video recorder (DVR) such as TiVo has attenuated the effectiveness of TV broadcasting.

Fourth, social media can be synergized with traditional media to drive sales and financial returns. Consider the following example of a pharmaceutical firm's social media experience. In early 2011, Bristol-Myers Squibb (BMS) aired a new TV cartoon commercial to promote Abilify as an add-on antidepressant drug. In this cartoon, the main character is a white lady and her depression is represented by a dark blue blob. Viewers, who found the commercial interesting, posted it on YouTube, leading to approximately 10,000 views in a few months. Viewers also discussed this commercial on Twitter and Facebook. Online buzz of this kind can heighten brand awareness, drive viewers to the TV commercial, and also enhance the effectiveness of TV advertising.

Finally, drug prescription decisions are made under uncertainty about the efficacy of drugs to treat different patients and are associated with high level of risks such as side-effects (Ching 2010; Narayanan and Manchanda 2009). WOM from peers is perceived as more reliable information than that provided by drug companies. Social networks offer a platform for WOM to spread boundlessly among people drawn together by a common interest. WOM in social media, if leveraged appropriately, can play a stronger important role to boost sales than that can be accomplished by traditional media and deliver strong returns on investment (ROI). Different from traditional marketing, social media is a platform for two-way dialogs.

16.2.2 Social Media Usage by Physicians and Patients

The healthcare industry in general and the pharmaceutical industry in particular are not immune to the influence of the growing World Wide Web and social networks. It is unsurprising that the Internet has become a critical component of how both physicians and patients seek medical information. About 86 % of US physicians use the Internet to gather health, medical, or prescription drug information (American Medical News, 2010). Furthermore, 65 % physicians search the Web more than once a day. Other reports also show that physicians increasingly trust information on the Internet. For example, about one-third of the physicians have made a change to a patient's medication or initiated new treatment, as a result of an online search (Dolan 2010).

Healthcare providers are using social networking sites to reach other physician colleagues. Sermo, the largest physician networking community, has about 120,000 physicians as its members (Sermo 2011). Other physician social networks such as Ozmosis, SocialMD, and DoctorNetworking report memberships between 3,000 and 10,000 physicians each. Physician-only social network is growing so rapidly that it is likely to overtake American Medical Association (AMA) as the largest physician community. Sermo even released a survey, noting that 89 % of physicians believed that the AMA does not speak for them, less than 20 % of practicing physicians are members of the AMA, and 91 % of them do not believe the AMA accurately reflects their opinion as physicians (Sermo 2009).

Physicians are moving online to share their voice, to learn from experts and peers, to discuss clinical issues and to talk about practice management issues.

Physicians also utilize social media and social network to connect to patients. They frequently use Facebook, Twitter, and blogs to share medical advice, success stories, and patients' testimonies, and to explain medical procedures to their patients.

Patients are also increasingly using online information and social media to manage their health conditions. The Pew Research Center's Internet & American Life Project estimates that 61 % of all adults (80 % of internet users) looked online for information about health topics such as a specific disease or treatment. One in every four adult Internet users looks up social media's online reviews of drugs or treatments (PewInternet 2010). In 2008, the Internet surpassed doctors as the top source of health information (Manhattan Research 2008). A survey of more than 22,000 Americans reports that one in five Americans use social media sites as a source of healthcare information. Of those, 94 % said Facebook was their preferred source, followed by YouTube with 32 % and Twitter with 18 % (National Research Corporation 2011). Health condition-specific Facebook pages are popular among patients. For example, the unbranded Breast Cancer Site has more than 2.8 million "likes" on its Facebook page while the branded Weight Watcher Facebook page has 880,953 "likes."

Patients are also active contributors to various online communities. They share opinions about the benefits and adverse effects of drugs and also listen to fellow patients regarding their experiences. For example, PatientsLikeMe.com is a social network site with 104,277 patients across over 500 conditions (www.patientslikeme.com). This site invites patients to find others with similar disease and health conditions by sharing their own conditions, symptoms, or treatments. The more the patients share information about themselves, the easier they can find "matches" to their situations. Other patient networks include HealthChapter, IMedfix, Inspire, Disaboom, and DiabeticConnect. Some of these are general, whereas others are disease-specific.

16.2.3 Challenges of Social Media for Pharmaceutical Firms

The surging presence of physicians and patients on the social network calls pharmaceutical firms to rethink how to harness social media and leverage the momentum created and carried by social media while planning the strategic allocation of their marketing resources (Shankar 2008). However, some external and internal hurdles hinder the usage of social media by pharmaceutical firms. Traditionally, drug companies have heavily relied on sales force teams to promote drugs to physicians and on conventional media agencies to execute direct-to-consumer (DTC) advertising campaigns. Social media are completely new vehicles that drug companies have had little exposure to or experience with. Social media pose several questions: How to engage in social media within the regulatory framework? How to integrate social media into traditional marketing strategy? How and where to start a social media campaign? What are the ROI of social media efforts? Pharmaceutical firms need answers to these questions so that they can get their stakeholders aligned to support social media marketing initiatives.

The external barrier for drug companies to embrace social media is the high regulation standard in this industry. Pharmaceutical companies are required to report to the FDA any monitored social media conversation concerning possible or potential adverse outcomes related to their drugs. Furthermore, their direct communication to patients on their drugs is controlled. As the general public increasingly trusts social media, engaging patients without crossing FDA regulations is a challenge unique to pharmaceutical marketers. It is more of a puzzle for pharmaceutical marketers when there is a lack of clear guidelines. According to the eyeonfda.com posted on May 31 2011, the FDA has repeatedly delayed issuing any guidance on the Internet and social media. "In October, 1996, the agency held its first public meeting on the regulation of the Internet and the Promotion of Medical Products. In March 2009, they said it isn't the medium, it is the message. In November 2009, they did the same 1996 meeting over again, only this time throwing in social media and targeting the end of 2010 for the issuance of a draft guidance. It didn't happen. Then the end of the first quarter for a guidance. It didn't happen."

Frustrated by FDA inaction on guidance for digital marketing and social media, industry players such as Merck, Roche, AstraZeneca, Lilly, Sanofi, and GlaxoSmithKline (GSK), Google, Epocrates and HealthCentral and agencies such as Edelman and Digitas Health are forming a nonprofit organization called the Digital Health Coalition that aims to develop an industry consensus on marketing via social and web media (Arnold 2011). The key unresolved issues for which marketers await FDA guidance surround adverse effects and off-label usage. It is unclear that whether pharmaceutical companies should be held responsible for third-party claims about a drug's risks or benefits on outlets like Facebook and Wikipedia. These problems could be mitigated by filtering or disabling commenting functions on social outlets. However, to utilize major social media like Facebook, drug companies have no control over the functionality of the medium. Facebook previously allowed pharmaceutical brands to disable commenting on their Facebook page that would avoid patients introducing off-label usage. However, starting June 2, 2011, Facebook no longer allows new pharmaceutical pages to disable commenting on the content their page shares with people on Facebook. For existing branded pages, removing commenting functionality may continue to be allowed subject to Facebook's approval (Thomaselli 2011).

There are some other unresolved practical issues involving basic online procedures such as patient registration. Other practical questions include: How can pharmaceutical marketers embrace social outlets such as Twitter and Google blogs and sufficiently explain a drug's risks within the bounds of the 140-characters for a tweet or roughly two lines of Google ads' text?

16.2.4 Social Media Use by Pharmaceutical Firms

Despite the challenges of social media in the pharmaceutical industry, several firms have used social media to expand their social share. *Baxa* Corporation, a developer of

technology for the safe handling, packaging, and administration of fluid medications, hosts both a corporate Facebook page "Culture of safety" and a LinkedIn Business Group. Adding social media tools to the company's marketing tools provides a new channel for determining how customers feel about Baxa and its products. Furthermore, connecting and interacting online with customers builds trust and understanding.

Another example is *Atkins* that focuses on the simplicity and flexibility of the Atkins diet. By offering free starter kit and carb counter guides and three free snack bars, Atkins helps customers get started on their New Year's resolutions. The company works with consumers by filming them on a weekly basis to document their weight loss journey and struggles, and posting these videos on the Web. Since launch, Atkins' social networking community's membership (http://community.atkins.com/) has grown by more than 1,000 %.

Other pharmaceutical companies have also made efforts to use social media in their marketing campaigns. *Johnson & Johnson* (J&J) has made successful moves that put its online presence ahead of its competitors. In July 2006, J&J launched the Kilmer House blog that introduced the company's history as the first step to start its social media experience small and start it simple to prove the concept. One year later, J&J opened its corporate blog, JNJBTW, with more complexity and confidence in the social media to cover recent topics about the company and the industry. In 2008, J&J rolled out several social media initiatives, including the purchase of the online community, Children With Diabetes, opening its YouTube channel with 487 videos, more than 4,000 subscribers and nearly four million video views (as on June 5, 2011). J&J also supports several Facebook network such as ADHD–MOM, Johnson's Baby, and Neutrogena. J&J has maintained active presence on Twitter that attracted over 6,000,000 followers.

GSK quickly followed J&J to befriend various social outlets. GSK introduced a popular 104-s domino video on YouTube for Restless Legs Syndrome in October 2006. The domino starts with the sleeping father's restless legs kicking a book off the bed to trigger the dominoes, and ends with a TV being flicked on that shows a spot that reads, "My dad is one of a million people in the U.K. who have Restless Legs Syndrome. www.legsinfo.com." This video has drawn more than 483,000 views on YouTube today. GSK opened its YouTube channel, GSKvision in August 2008 with 33 videos. Furthermore, to promote the new OTC weight loss treatment, Alli, approved by FDA in early 2007, GSK created the branded AlliTube channel, a patient community and a blog to offer support for their patients to fight obesity. The emotional support provided by the virtual community is well staged on the website of myalli community: "with alli, you're never alone—change can be challenging. And you need support from people who care. There are thousands of people just like you in allicircles-the alli community. They're always here to encourage, lend advice and support you at every step of your journey." Such support leads to increased patient compliance and success in treatment. GSK also has active presence on Facebook with 1,289 members and over 8,000 followers on Twitter.

AstraZeneca invited asthma sufferers to submit videos about their positive experiences with its product Symbicort and essentially create their own advertisements for the drug. In the 3 months since the site has been live, AstraZeneca has received

a handful of submissions and over 53,000 page views (Miley and Thomaselli 2009). Similarly, AstraZeneca launched CelebrationChain.com, an interactive effort for breast cancer awareness that allows patients to create virtual paper doll likenesses of fellow survivors and e-mail them to recipients.

In September 2008, *Bristol-Myers Squibb* (BMS) launched the Advanced Breast Cancer Community, an information source and online community for advanced breast cancer patients, caregivers, family, and friends. The AdvancedBreastCancerCommunity.org represents the collective thinking of a partnership among 13 of the leading breast cancer patient advocacy organizations in the United States, the Advocate Partners and Inspire. The website also reflects new research, treatment, and clinical trials information.

Other innovative followers have introduced new ways to reach their patients and physicians. *Sanofi-Aventis* rolled out a multimedia GoInsulin campaign designed to encourage Type 2 diabetes patients to use insulin and control their blood sugar. This campaign includes a Youtube channel (www.youtube.com/user/goinsulin). *Pfizer* entered into a deal with Sermo to peephole into Sermo's strong community of physicians and their ideas about its products. This collaboration is designed to complement, not replace, Pfizer's sales force activities. *Novartis* dabbled in user-generated content with its November FluFlix.com contest on YouTube, asking users to post 2-min videos on how the flu makes them feel and offering three $500 prizes.

Statements by pharmaceutical executives support their focus on social media. "I don't think there's a question any more as to whether or not we have to get involved in social media. We have no choice" (Ray Kerins, VP, Worldwide communications, Pfizer). "I think pharma will proceed more deliberately with social media, but they won't abandon it," said a former pharmaceutical-company advertising executive from BMS (Thomaselli 2011). Michael Berelowitz, Pfizer's senior vice president for global medical, says the company wants to communicate more openly (by utilizing social media), despite the risk. "We live in an environment where we're closely monitored all the time and have constraints around what we say and how we say it," he says. "Given that this kind of (social) medium is the way forward…we have to learn how to behave in it" (Wall Street Journal 2007).

By 2011 end, the top 20 pharmaceutical companies owned one more corporate Facebook page, 17 (85 %) are on Twitter, 13 (65 %) run a Youtube channel, eight (40 %) sponsor online physician or patient communities, and six (30 %) maintain a corporate blog. As social media gradually become accepted in the corporation and as FDA starts to provide guidelines on social media practices, pharmaceutical firms will increase their use of social media (Table 16.1).

16.3 Word of Mouth

Word of mouth (WOM) is the building block for understanding the effects of social media. There have been extensive studies on the topic of word of mouth for nearly half a century. Early studies found evidence for WOM to be an important driver of

Table 16.1 Utilization of social media platforms by top 20 pharmaceutical companies

Rank	Company	Revenue (million)	Blog	Youtube	Facebook page	Twitter	Physician or patient community
Top 20 pharmaceutical companies based on 2010 revenues							
1	Pfizer	$58,523	Yes	Yes	Yes	Yes	No
2	Novartis	$44,420	No	Yes	Yes	Yes	Yes
3	Merck & Co.	$39,811	No	Yes	Yes	Yes	Yes
4	Sanofi	$37,403	No	Yes	Yes	Yes	No
5	GlaxoSmithKline	$36,156	Yes	Yes	Yes	Yes	No
6	AstraZeneca	$32,515	Yes	Yes	Yes	Yes	Yes
7	Johnson & Johnson	$22,396	Yes	Yes	Yes	Yes	Yes
8	Eli Lilly & Co.	$21,685	Yes	Yes	Yes	Yes	No
9	Abbott Laboratories	$19,894	No	Yes	Yes	Yes	No
10	Bristol-Myers Squibb	$19,484	Yes	No	Yes	Yes	Yes
11	Teva	$16,121	No	Yes	Yes	Yes	Yes
12	Takeda Pharma	$14,829	No	No	Yes	No	No
13	Bayer Schering	$14,485	No	Yes	Yes	Yes	Yes
14	Boehringer-Ingelheim	$12,883	No	Yes	Yes	Yes	No
15	Astellas	$11,161	No	Yes	Yes	Yes	No
16	Daiichi-Sankyo	$10,794	No	No	Yes	Yes	No
17	EISAI	$8,542	No	No	Yes	Yes	No
18	Otsuka Pharmaceutical	$8,440	No	No	Yes	No	No
19	Gilead Sciences	$7,390	No	No	Yes	Yes	Yes
20	Mylan	$5,404	No	No	Yes	No	No

Source: Revenue figures are from ContractPharma.com

firm sales in offline settings (Arndt 1967; Coleman et al. 1966). WOM is impactful because consumers are more likely to trust information from their peers than from advertising. The more similar the sender and the receiver are to each other, the more persuasive WOM is (Kruglansk and Mayseless 1990).

With the rise of social networks and social media, researchers have shifted the context of study for WOM from offline settings to online settings where WOM operates through social networks and social media. WOM in social media differs from the general WOM in offline setting in three important aspects. First, WOM in social media is much more accessible and scalable than the general WOM in offline settings. WOM in the form of user-generated contents created by users of social media are exposed to an enormous audience—all other network members or even all Internet users. In contrast, offline WOM is only confined to parties involved in the interpersonal communication. For example, A can tell B about A's usage experience of a product, and that general WOM can only have impact on B's evaluation about the discussed product. If A goes online and posts a review about that product on a popular online review site like Amazon.com, then the same piece of WOM information can be viewed by millions of others and therefore could have a much stronger impact than it could offline.

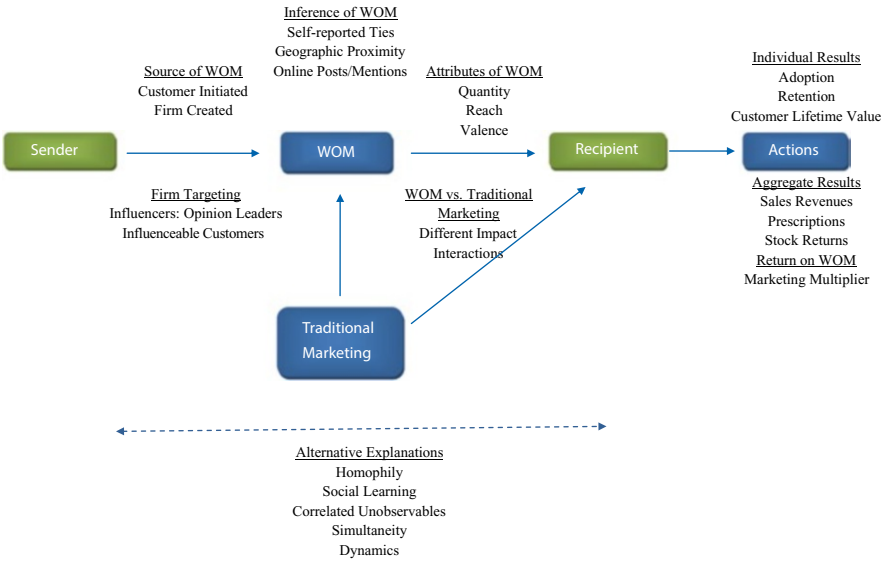

Fig. 16.1 Conceptual framework of how word of mouth works

Second, WOM in social media and social networks can be more persuasive than general WOM that takes place offline. Social media and social networks connect people with a common interest. Word of mouth that flows through social networks is powerful because people believe more credible information comes from people "like themselves" (Sarasohn-Kahn 2008), and 3 times more likely to trust the opinions of their online friends than advertising (Bart et al. 2005; Jupiter Research 2007). In contrast, general WOM that takes place offline may not be effective because of the difference among parties involved in the WOM conversation.

Third, unlike offline WOM, the influence of WOM in social media and social networks is not limited to particular location. Offline WOM takes place through interpersonal communications. WOM in social media and social networks take place on the Web, and it can take effect on users of the Web, anytime, anywhere without time or location limitation.

Given the power of WOM in social media and social networks, there has been a surge of marketing literature in this area. Studies on WOM in social media can be summarized using the following framework based on the sender–recipient pair engaged in WOM communication in a social network (Fig. 16.1).

Studies on WOM in social media and social networks have investigated different aspects of the WOM communication process. These aspects include sources of WOM (customer-initiated vs. firm-created), inference of WOM (online metrics vs. offline metrics), attributes of WOM (volume vs. valance), impact of WOM (on individual decisions vs. aggregate results), comparison of WOM vs. traditional marketing (differences and interactions), and firm targeting strategies (seeding strategies, targeting influencers vs. the influenciables). We will discuss each aspect separately below.

Sources of WOM. WOM as a form of interpersonal communication can be initiated by either customers or firms. Customer-initiated WOM, often referred to as generic or exogenous WOM or user-generated content (UCG) is both generated by customers and implemented by customers. Natural WOM occurs because customers like to talk about interesting products or products that are frequently cued by the environment (Berger and Schwartz 2011). People tend to contribute more content to shared platforms with a larger audience base (Zhang and Zhu 2011). Because WOM may be a cost effective driver of sales, firms seek to initiate WOM about their products that could be spread by customers. Firms can create WOM by anonymously posting positive comments on the Internet about their own products (Mayzlin 2006; Godes and Mayzlin 2009). Mayzlin (2006) shows that firm-created anonymous online WOM may be a profitable equilibrium strategy even when consumers are aware of the possibility that the firm is creating the positive WOM. Firms can also generate positive WOM by offering incentives for existing customers to refer friends (Schmitt et al. 2011; Trusov et al. 2009; Van der Lans et al. 2010). Customers acquired through referral programs have higher customer lifetime values than those acquired through non-referral methods (Schmitt et al. 2011).

Inference of WOM. Face-to-face communications can be rarely observed by researchers in nonexperiment settings. In the context of online WOM in social media and social networks, direct measures of WOM are readily available. Measures of online WOM studied include number of tweets on Twitter (Rui et al. 2011), posts on message boards or chat rooms (Godes and Mayzlin 2004; Liu 2006), book reviews on Amazon.com and bn.com (Chevalier and Mayzlin 2006), e-mail invitations (Schmitt et al. 2011; Trusov et al. 2009), and online comments (Sonnier et al. 2011). The availability of online WOM data provides tremendous opportunities for researchers to answer many questions that are not possible to address in offline settings.

Attributes of WOM. WOM can be characterized by its quantity or volume (such as the number of times a product is mentioned on an online message board), dispersion/reach (the extent to which product-related conversations are taking place across a broad range of communities), and valence (positive, negative, or neutral comments). The relationship between attributes of WOM and product performance is of great research interest. Prior research in this area offers conflicting results. Godes and Mayzlin (2004) find that dispersion of WOM rather than volume of WOM has a significant effect on TV ratings. Chevalier and Mayzlin (2006) find that both volume and valence of reviews are significant predictors of sales ranks of book titles from Amazon.com and bn.com. However, Liu (2006) analyzing over 12,000 messages posted on the Yahoo movie message board, finds that volume of WOM, not its valence, is a significant predictor of box office revenues. Some results show that even negative WOM can lift sales by building awareness and increasing accessibility a product (Berger et al. 2010; Liu 2006). However, other studies show that negative WOM's destructive power could be more than twice as large as that of positive WOM and harmful in the long term (Luo 2009; Nam et al. 2010; Sonnier et al. 2011).

Impact of WOM. WOM is particularly important for forming new attitudes and perceptions toward new products, so researchers have focused on how WOM affects

new product diffusion (Bell and Song 2007; Foster and Rosenzweig 1995; Garber et al. 2004; Manchanda et al. 2008; Van den Bulte and Joshi 2007). Besides modeling the time to adoption of a new product or service as a function of word of mouth, other dependent variables analyzed include sales (Berger et al. 2010; Chevalier and Mayzlin 2006; Liu 2006; Rui et al. 2011; Sonnier et al. 2011), prescriptions (Nair et al. 2010), retention rate (Schmitt et al. 2011), product rating (Godes and Mayzlin 2004), and stock price (Luo 2009). Research on the impact of WOM has predominately documented the significant explanatory power of WOM on the dependent variable of interest.

Firm targeting strategy. It is widely recognized that social influence exists and WOM is a cost efficient way to drive sales. Firms need to understand who to target to maximize the lift from WOM and social influence. Two key factors determine the success of a WOM campaign. First, firms should allocate marketing resources to influence the influential members (influencers) of a network. However, there is inconclusive evidence on who constitute the influencers. Consumers with greater product expertise could be more influential than others. Consistent with this assumption, it is common for sales force in the pharmaceutical industry to target high prescribers and those in other industries to target heavy users of their products, under the belief that heavy users have high "stand-alone" customer lifetime value as well as "network value" or social influence. This view suggests that loyal customers who have more experience with a product tend to be more satisfied with the product. These customers are looked upon as opinion leaders or experts with respect to the particular product. However, Godes and Mayzlin (2009) find that opinion leadership is associated with a higher propensity to spread WOM only among more loyal consumers, but not among less loyal customers. Iyengar et al. (2011b) show that the volume of product usage and self-reported leadership are only moderately correlated with social-metric leadership. More research is needed for a comprehensive framework that can guide marketers to effectively identify and target the influencers. By the same token, members of a network are not equally susceptible to influences. Iyengar et al. (2011b) find that physicians who perceive themselves as opinion leaders are less sensitive to influence from peers. Nair et al. (2010) find that physicians' prescription volume is influenced by that of a peer they regard as an influencer only after a change in FDA policy about usage.

The second factor that determines the success of a WOM campaign is an understanding of those susceptible to a firm's targeted efforts (Christakis and Fowler 2011). This aspect has been overlooked by many researchers and practitioners who have concentrated on influencing the influencers. However, understanding the susceptibility of network members to marketing effort is equally important.

WOM vs. traditional marketing. WOM and traditional marketing are two contrasting types of communications that can drive sales. Trusov et al. (2009) find that WOM referrals have substantially longer carryover effects and produce substantially higher response elasticities than do traditional marketing actions. Villanueva et al. (2008) document that marketing-induced customers add more short-term value, but WOM-induced customers add nearly twice as much long-term value to the firm. Manchanda et al. (2008) find that marketing plays a relatively large role in affecting early adoption while contagion plays a dominant role from Month 4 onward.

More research is needed to shed light on the interaction between WOM and traditional marketing, i.e., how traditional marketing affects the effectiveness of WOM and vice versa. Such research can help firms design multichannel marketing campaigns that synergize WOM with traditional marketing.

In the offline context, collecting word of mouth data to study the influence of WOM is a challenge for researchers. Offline WOM occurs in private conversations, so it cannot be directly observed. However, online WOM that takes place through social media are becoming more readily available nowadays. When researchers embrace the rich online WOM data, they need to determine if the same WOM mechanisms operate in both the online and offline settings, and whether the assumptions and findings from traditional marketing hold for social media marketing as well. For example, in the realm of traditional advertising, firms spend more resources promoting their superior products, resulting in advertising being a credible signal of quality (Milgrom and Roberts 1986; Nelson 1974). However, analysis of social media marketing suggests that firms promote their inferior products anonymously in online communities (Mayzlin 2006).

16.3.1 WOM in the Pharmaceutical Industry

In the pharmaceutical industry, WOM influence can emanate from different players such as patients, physicians, healthcare providers, insurers, regulatory authorities, general public, and others. There are many intriguing research questions about WOM in the pharmaceutical industry that await researcher attention. For example, how does the WOM among physicians and patients affect prescription decisions of drugs? How do peer effects change over a drug's product life cycle? Who in the physician and patient networks are opinion leaders and what are their characteristics? How can firms efficiently identify the connections among physicians and patients? How should firms allocate sales force resources by leveraging the social influence among physicians and patients? However, studies on WOM and social influence in the pharmaceutical industry are limited, mainly because of lack of adequate data to infer connections among physicians or patients.

Physician-to-physician connections are unobservable to researchers. Researchers have defined networks in terms of geographical proximity (Bell and Song 2007; Manchanda et al. 2008), and nominated opinion leader and physicians pairs (Iyengar et al. 2011b; Nair et al. 2010). In the former approach, researchers use the zip codes of physicians' primary practices to identify physicians' locations, compute the distance between each pair of physicians, and define physicians located within a specified mileage to be in each other's reference group. In the latter approach, researchers conduct surveys to ask physicians to nominate a few other physicians who are their opinion leaders or with whom they discuss medical questions. However, both methods have limitations. Using geographic proximity based on limited radius around the location of a physician's primary practice to identify reference group assumes all physicians within the location have equal influences on the focal physician.

Caution needs to be taken to rule out other factors that could cause physicians in the same area to act similarly. Conducting a large scale survey to ask physicians to nominate opinion leaders is expensive for many firms. Such an exercise may also elicit low response rates and small sample sizes (Iyengar et al. 2011b). Researchers need to look for new techniques to identify the connections among doctors. A promising avenue is the use of data on shared patients that can define the connections among physicians. Such a method would also allow us to measure the strength of connection through the total number of patients that any two doctors share, enabling us to generate weighted networks (Barnett et al. 2011; Christakis and Fowler 2011; Li and Shankar 2011).

The limited number of studies on WOM and social influence in the pharmaceutical industry offer contradictory results. In an analysis of the diffusion of tetracycline by doctors in four Midwestern communities in the 1950s, Coleman et al. (1966) document the existence of social contagion in physician networks. Van den Bulte and Lilien (2001) reanalyze the same medical innovation data supplemented with journal advertising data and show that contagion effects disappear when journal advertising effort was controlled for, although a critical component, physician detailing, was omitted. In contrast, Manchanda et al. (2008) document the existence and magnitude of contagion effects even after controlling for physician level detailing, sampling, as well as aggregate DTCA expenditures. The contagious peer effects among physicians are supported by Nair et al. (2010) and Iyengar et al. (2011b). More studies are needed to extend our knowledge in this area and guide pharmaceutical firms' marketing decisions.

16.3.2 Methodologies

The methodologies adopted by researchers to study WOM and social influence in the pharmaceutical industry can be categorized into two main types: hazard models and linear models.

WOM and social contagion studies involving new drugs focus on the social influence on the adoption timing of a new drug. The hazard model is commonly used for this purpose (Van den Bulte and Lilien 2001; Manchanda et al. 2008; Iyengar et al. 2011c) and is estimated using the maximum likelihood estimation method. The hazard function is specified as follows:

$$h_i(t|X_i) = \lim_{\Delta t \to 0} \frac{\Pr_i[t < T_i \le t + \Delta t | T_i > t, X_i]}{\Delta t}$$

where h_i is the hazard of physician i prescribing the drug at time t. X_i is a vector of covariates that includes marketing and social contagion measures, T_i is time elapsed until t, and Δt is a small change time. Furthermore, a proportional hazard model is typically used as follows:

$$h_i(t \mid X_i) = h_o(t)\exp(X_i\beta)$$

where $h_o(t)$ is the baseline hazard function and β is a parameter vector. Researchers have tested different forms of social contagion measures such as adoption, usage, and volume of usage of the new drug by peer physicians.

Nair et al. (2010) use a linear response model to study the impact of nominated opinion leaders' prescriptions on the nominating physicians' prescriptions of an established drug. The linear model is in the form below:

$$y_{it} = \beta D_{it} + \delta x_{j(i),t} + \gamma_{it}$$

where y_{it} and $X_{j(i),t}$ denote the new prescriptions written by physician i and physician i's opinion leaders at time t. D_{it} denotes the number of details on physician i at time t. Prescriptions of opinion leaders serve as a proxy for the opinions held by the opinion leaders toward the prescribed drug. The parameter δ measures the influence of opinion leaders' prescriptions on physicians' prescribing decisions. The linear model is a reduced form of the prescription behavior process. It serves as an approximation of a nonlinear model and is appropriate for a wide range of situations (Hartmann et al. 2008).

There are significant methodological challenges for researchers to infer social influence from physician prescription behavior. Correlation in physician prescription behaviors can arise from three possible sources other than social contagion effects: endogenous group formation, correlated unobservables, and simultaneity. These sources pose significant challenges for detecting the existence and measure the magnitudes of social contagion (Manski 1993; Nair et al. 2010).

Endogenous group formation often referred to as "homophily," occurs when people with similar "tastes" tend to come together. Their inherit similarities may cause them to take similar actions independently even without social contagion. Thus, such a phenomenon could impede the identification of true social contagion. This identification problem can be overcome by including individual-specific fixed effects when panel data is available (Aral et al. 2009). Analysis based on cross-sectional data alone may lead to spurious contagion effects.

Simultaneity happens when product sales or diffusion changes the amount of WOM while WOM also affects the level of sales or diffusion process. Moreover, WOM is dynamic; it is an autocorrelated time series with carryover across time. Researchers have used vector auto regression (VAR) models to capture the dynamics and simultaneity aspects of WOM analysis (Rui et al. 2011; Trusov et al. 2009).

Social contagion can occur via verbal communications (WOM) and observational learning. The concept of observational learning stems from social learning studies in psychology (Bandura 1977). Chen et al. (2011) attempt to disentangle the impact of WOM and observational learning on the sales of digital cameras using a field experiment. An intriguing finding of their study is that while negative WOM is more influential than is positive WOM, positive observational learning information significantly increases sales, while negative observational learning information has no effect on sales.

16.3.3 Unresolved Research Questions

Whether pharmaceutical marketers should leverage social media is not an issue anymore. The question is how to strategically plan and execute social media campaigns. Both researchers and practitioners seek better understanding of how online and offline word of mouth operates in the context of pharmaceutical industry. There is a long list of unresolved research questions in this field as summarized below.

When: When to enter social media? Are there pioneering advantages and/or follower advantages (Varadarajan et al. 2008)? During which stage of a product's life cycle, should a product be promoted most through social media marketing?

Where: Where should firms start a social media marketing campaign? Blogs, Facebook, Twitter, Youtube, or across all social media outlets? Should firms sponsor an existing community or create their own?

Whom: Who should firms target? Who are the opinion leaders and influencers? Should drug companies use their existing call plans as a social media target list? Should firms target loyal patients and heavy prescribers? How should they optimize sales force resource allocation so that it leverages the power of WOM?

What: What should be the contents of social media campaigns? Should they be branded or nonbranded? How should firms respond to negative effects or adverse attacks? How should they leverage social media to mitigate the impact of negative events such as recalls and competitive launches? Should they take proactive actions to communicate with patient, physician, and regulatory communities prior to the outbreak of negative events?

How: How does WOM affect a drug and how does the effect change over a product's life cycle? Which therapeutic category should be promoted, using which social media outlet? Can a new media strategy that proved successful for one brand resonate with another brand's target audience?

Table 16.2 summarizes selected studies on WOM in social media and social contagion in the pharmaceutical industry.

In the coming years, we expect to see more research on online WOM and social media to address above questions. To facilitate researchers to conduct research on social media in the pharmaceutical industry, Table 16.3 summarizes datasets that are either publically available and those that can be purchased from various sources.

16.4 How to Leverage Social Media Effects

The rapid growth of social media is fundamentally changing how pharmaceutical brands can communicate with target audiences. Brands not only talk to customers, customers talk back to brands. The monologue has transformed into a dialog with millions of people potentially listening and participating in the conversation.

Table 16.2 Summary of selected research on word of mouth in social media and social contagion in the pharmaceutical industry

Article/work	Model type	Data	Key findings/guidelines	Key limitations
Online word of mouth				
Godes and Mayzlin (2004)	Linear panel data model with fixed effect	Online posts on 44 TV shows from Usenet newsgroups	Dispersion of WOM rather than volume of WOM is a significant explanatory factor of TV rating	Ignores marketing mix variables. Dispersion and volume of WOM are moderately correlated. Results may not be generalizable to purchase decisions of products with financial costs
Bart et al. (2005)	Structural equation analysis	6,831 consumers across 25 websites from 8 website categories	The drivers and role of online trust are different across site categories and consumers	Does not include spillover effects of online trust over time
Chevalier and Mayzlin (2006)	Log-log cross-sectional model	Sales ranks and reviews of 2,387 book titles from Amazon.com and bn.com	Number of reviews, length of reviews, and review stars are significant predictors of sales ranks	Treats reviews as exogenous to sales ranks. Ignores carryover effects of reviews and sales ranks
Mayzlin (2006)	Game theoretic model	Not available	Firms with lower quality products spend more resources on promotional chat on the Internet than firms with higher quality products	No empirical evidence
Liu (2006)	Log-log cross-sectional model for each week	12,136 messages that discuss 40 movies on Yahoo.com message board	Volume of WOM rather than valence of WOM is a significant predictor of box office revenues	Assumes WOM can only affect box office revenues in the subsequent week
Godes and Mayzlin (2009)	Aggregate market-level model	A field test involving 1,000 agents across 15 markets in the United States and an experiment with 96 responses	Firm generated WOM is more impactful if the WOM was spread from a less loyal customer than from a loyal customer and to an acquaintance than to a friend or a relative	Assumes all WOM is positive. Analysis relies on self-reported WOM
Trusov et al. (2009)	VAR model	E-mail invitations and sign-ups to a social networking site. Media mentions of the site and promotional events	WOM referrals have substantially longer carryover effects than traditional marketing actions and produce substantially higher response elasticities	Ignores valence of WOM. Cannot account for heterogeneity using aggregate data. Sign-up time-series data are stationary, suggesting none of the studied covariates have permanent effects on sign-ups

(continued)

Table 16.2 (continued)

Article/work	Model type	Data	Key findings/guidelines	Key limitations
Berger et al. (2010)	Time-series model and ANOVA	Sales and *New York Times* reviews of 244 titles and two experiments	Negative publicity may increase the sales of products with low existing awareness, by increasing awareness or accessibility	Does not control for extremes of reviews
Van der Lans et al. (2010)	Viral branching model	A viral campaign to promote financial services to 228,351 participants	The reach of eWOM can be accurately predicted by a viral branching model that also accounts for marketing activities	Reach of WOM may not be a significant predictor of sales. Does not include quality of reach
Nam et al. (2010)	Hazard model	3,650 adopters of Video-on-Demand (VOD) movie rental service. Individual-level activation, usage, distance to retail and rental stores data and aggregate demographic data	The effect of negative word of mouth on the adoption of VOD service is more than twice as large as the effect of positive word of mouth	The truncated hazard model is based on only adopters, potentially leading to spurious evidence of contagion
Schmitt et al. (2011)	Linear panel data model with fixed effects. Hazard model.	Panel data on 9,814 customers acquired by a leading German bank through its referral program and other methods	Customers generated through referral programs have a higher contribution margin and a higher retention rate, and are more valuable in both the short and the long run than those acquired from non-referral methods	Customer lifetime value and effectiveness of referral programs could be a function of product complexity and incentives
Rui et al. (2011)	Multivariate VAR model and Dynamic panel data model	Movie revenues and Twitter tweets on 63 movies	WOM on Twitter is a significant determinant of box office revenues	Omits movie characteristics in the models
Sonnier et al. (2011)	Bayesian dynamic linear model (DLM)	Daily sales revenue data and daily counts of positive, negative, and neutral online comments for the firm	Positive, negative, and neutral communications have significant effects on daily sales performance after controlling for dynamics and endogeneity	Omits marketing efforts and seasonality

Zhang et al. (2011)	VAR model	Weekly number of new and returning sellers and buyers and total weekly commission from a C2C website in Europe	Contributor (seller) acquisition has the largest financial value because of the strong network effects on content consumers (buyers) and other contributors	Does not disentangle the difference sources of network effects such as word of mouth, observational learning, product assortment enrichment, direct social interaction, etc.
Ansari et al. (2011)	Hierarchical Bayesian model	A sequential network of communications among managers involved in new product development activities and online collaborative social network of musicians	Multiple relationships (e.g., friendship, communications, and music downloads) share common antecedents and exhibit homophily and reciprocity. Offline proximity is relevant for all online relationships. Artists exhibit similar roles across relationships	Does not incorporate the dynamic formation of network connections over time
Word of mouth and social contagion in the pharmaceutical industry				
Van den Bulte and Lilien (2001)	Hazard model	Medical innovation data and journal advertising data	Contagion effects disappear when marketing efforts are controlled for	Omits detailing efforts
Manchanda et al. (2008)	Binary choice model with duration dependence (equivalent to a discrete-time hazard model)	Physician level prescriptions, details and samples, aggregate DTCA expenditures, and addresses of 466 physicians in Manhattan and Indianapolis markets	The social multiplier of marketing is about 11 %	Uses geographic proximity (20-mile radius) to infer physician-to-physician contacts. Geographical proximity can reflect other unobservables that affect the actions of all the agents in the location similarly
Nair et al. (2010)	Linear panel data model with fixed effects	Physician level prescriptions, details and samples. 290 surveys of opinion leader–physician pairs	Peer effects are statistically significant and responses to marketing activity across nominators and opinion leaders are asymmetric	Relies on survey data conducted by a third party. It is unclear whether data collected are from a representative sample or whether it is subject to selection bias. Self-reported opinion leader–physician relationship may not capture actual physician-to-physician communications

(continued)

Table 16.2 (continued)

Article/work	Model type	Data	Key findings/guidelines	Key limitations
Iyengar et al. (2011a)	Hazard model	185 doctors in three cities with individual level data for adoption, calls, demographic, self-reported leadership, network data on discussion, and patient referral ties among physicians supplemented with co-location measures	The pattern of network ties is only weakly associated with co-location of physicians. Contagion operates through social networks, likely driven by social learning mitigating functional and physical risks, as well as through co-location, likely driven by social-normative pressures	Unable to distinguish co-location contagion from heterogeneity in time-invariant workplace characteristics
Iyengar et al. (2011b)	Hazard model	185 doctors in three cities with individual-level data for adoption, calls, demographic, self-reported leadership, network data on discussion, and patient referral ties among physicians	Social contagion exists in new product adoption after controlling for marketing efforts and system-wide changes. Opinion leadership and sources' volume of product usage moderates social contagion effects on new product adoption	Low response rates from surveyed doctors. Small sample size
Van den Bulte and Iyengar (2011)	Hazard model	Simulated data, medical innovation data, and zip code-level adoption data from Netgrocer.com	Hazard models built on right-truncated data can induce spurious positive duration dependence that suggests social contagion exists when it doesn't	Assume positive duration dependence implies social contagion, but it could reflect other constructs

Table 16.3 Datasets relevant for research on social media in the pharmaceutical industry

Database name, provider	Types of data
Sales, financial and market data	
SDI (Surveillance Data, Inc.)	Pharmacy audits, physician prescription behavior, dispensing of generics
Medi-Span (Wolters Kluwer)	Drug sales and price data
IMS LifeLink	Longitudinal prescription information, patient-level metrics
IMS National Prescription Audit	National prescription activity and payment modes
IMS National Sales Perspectives	Pharmaceutical product sales to pharmacies, clinics, hospitals at actual transaction prices
IMS NPA Market Dynamics	Patient-level prescription data
IMS Rx Benefit Design	Drug sales volume and market share by patients' insurance benefits
IMS Therapy Forecaster	Ten-year therapy-level forecasts in key international markets
CRSP/Compustat	Financial and market data on public firms
Datastream (Thomson Financial)	Financial and market data on public firms
Delphi Pharma's Product Trends and Company Trends Databases	Historical and forecast data for top drugs and leading pharma firms
Factiva (Dow Jones)	Business news and articles on pharma, stock quotes
PHIND (Informa)	Business news and articles on pharma
Lexis-Nexis	Business news and articles on pharma
URCH Publishing	Reports and insights related to pharma
OECD, WHO, CIA World Factbook, World Bank	Economic, demographic data by country
Media data	
AC Nielsen	Data on DTC Advertising
Media Vest Global	Data on DTC Advertising
Radian 6	Monitor mentions, sentiments, and chatters on social media platforms
GNIP	Real-time social media data and analysis.
Sermo	Allow drug companies to "listen" in to physician discussions on Sermo.com
Twitter Developers	Twitter API resources
Youtube Direct	Youtube API resources
ComScore	Internet usage data

Source: Adapted from Petrova (2011)

With social media, marketers gain firsthand insight into the topics that interest customers and the language they use. Pharmaceutical marketers have the opportunity to move beyond speaking at customers to engaging with them. Fundamentally, incorporating social media into communications strategies means a cultural change. It is a shift from a culture of speaking to a culture of listening as well as speaking, from individual consumption to group experience sharing, from personal sales marketing to transparency and authenticity. Social media offer competitive advantage to firms that develop authenticity of the message earlier than their competitors.

Fig. 16.2 How WOM helps in the sales funnel

Social media also help in the sales funnel through WOM as shown in Fig. 16.2. Social media can enhance effectiveness of the sales funnel's different stages such as lead generation, lead qualification, persuasion, customer relationship management, and support.

As discussed earlier, social media are both a challenge as well as opportunity for pharmaceutical firms. Building a social media strategy can be an overwhelming task. Firms can follow the LEADS strategy to effectively implement social media marketing (Hoffman 2009). The strategy comprises the following steps.

- *Listen*: In this first stage, firms listen in on the conversations in the social media that relate to their industry, market, and brands. As the reporting implications of patient experiences are better clarified by the FDA, pharmaceutical firms can learn from monitoring the dialogs among doctors in the Sermo network.
- *Experiment*: Once firms have a good understanding of the key issues learned from listening to conversations, they can identify key communication initiatives to adopt through the social media. They can set up trials or experiments to examine the effectiveness of such initiatives.
- *Apply/adapt*: Based on the learning from the experiments, firms can decide whether to apply the initiatives on a large scale across the gamut of social media for a wider range of products or brands. Many times, they may need to adapt their initiatives before rolling it out across platforms and brands.
- *Develop*: Once a firm applies its initiatives, it may need to develop its expertise further in that method.
- *Strengthen*: In this phase, firms consolidate their social media capabilities. Based on the results of their development initiatives, firms choose to enhance their competencies in the use of social media.

As firms follow the LEADS strategy for social media strategy, they should also integrate it with their overall marketing strategy. Pharmaceutical firms can follow a six-step plan to integrate social media marketing with their overall marketing.

Track brand. This step involves monitoring the brand in all forms of media, including social media. Third-party vendors such as Radian 6 provide measures of brand mentions and enable firms to track their brands.

Identify and communicate with patient and physician opinion leaders (e.g., Six Until Me diabetes blog, Brass and Ivory blog). Pharmaceutical firms need to first identify opinion leaders among physicians and patients by monitoring relevant blogs. They should provide timely unbiased information relating to their brands to these opinion leaders.

Support social network(*s*) (e.g., Ning, MySpace, WebMD, CureTogether, PatientsLikeMe). Pharmaceutical firms can be proactive by supporting relevant social networks of physicians and patients through relevant content and financial sponsorship. However, they may need to weigh the pros and cons of explicitly advertising their sponsorship because it could detract from the authenticity of the site and messages.

Hangout with physicians and experts in their networks (e.g., EyeSpaceMD for ophthalmologists, SpineConnect, MedTrust). In the relevant social networks, firms need to engage physicians and patients by discussing relevant issues and ideas.

Use video. Because the visual medium is powerful for memorability, firms should actively seek opportunities to use video. Posting, sharing, and distributing relevant information videos will enhance the authenticity of the brand.

Go mobile. Firms should use the rapidly growing mobile media to engage physicians first. Once they start engaging physicians, they can continually experiment to figure out the best way to engage them. They should establish partnerships with mobile operators, applications providers, and other technology providers. Because speed is of essence, firms are better served by forming relationships early and not waiting for the perfect partner.

16.5 Implications

The allocation of marketing resources while leveraging unmeasured and new media is becoming a challenging task for practitioners (Shankar 2008; Shankar and Hollinger 2007). Metrics that quantify social media activities are needed to measure social media efforts and their impact on brand performance. The most prominent and obvious metric of social media activities is engagement, but engagement is not an easy metric to capture.

16.5.1 Measuring Success (Returns)

Commonly used measures of engagement can be summarized as three Cs and three Ss.

C1: Content measures: Analyzing how content is consumed, shared, adapted, and amplified

- S1. Site measures: Analyzing Web site metrics including visitors, time, downloads, and feedback.
- S2. Search measures: Assessing paid and organic search for company content and keywords.
- S3. Syndication measures: Assessing engagement with brand-related content beyond own Web site, including video views, links, etc.

C2. Conversation measures: Analyzing volume, content, and sentiment of relevant conversations, including share of voice, message penetration, favorability, or intensity of opinion.

C3. Campaign measures: assessing ROI against defined campaign objectives

Some popular metrics for measuring social media impact are:

- Percentage increase in outcomes as measured by increase in downloads, registrations, qualified leads, or online sales
- Percentage increase in engagement as measured by the number of repeat visitors, time on site, comments, re-tweets, links, and references from blog posts or tweets
- Percentage improvement in Google page rank
- Percentage increase in share of desirable conversations or recommendations vs. die competition
- Percentage increase in share of desirable positioning on key issues vs. competitors
- Percentage increase in posts containing one or more key messages
- Percentage increase in share of visibility for your thought leaders

Many third-party vendors provide measurement and tracking software that include eventlog analysis. These vendors include: SAS on-demand, Idolstats.com, Biz360, Sentimentmetrics, TrendRR.com, technocrati.com, and twitteratti.com.

Firms can measure the success of their Twitter presence and tweets in a number of ways.

- ROT: A rough measure of a brand's effectiveness on Twitter. It measures how much the conversation flows around and toward the firm's posts.
- The Retweet (RT) quotient is becoming an increasingly important measure of popularity. Third-party social media metrics firms are starting to offer services that track a brand's presence on Twitter and other networks.
- A number of novel tools available to gauge a firm's Twitter feed's sociability and influence relative to other feeds. Twitalyzer (www.twitalyzer.com) analyzes influence, the relevance and information value of posts. TwitterGrader

(www.twittergrader.com) ranks the tweets on influence based on a proprietary algorithm. Twinfluence (www.twinfluence.com) purports to measure the clout on the service.
- Twitter's own search engine offers one of the indispensable monitoring tools. Firms can enter their brand's name or your Twitterfeed's name both with and without the "@" command. Each search delivers different results on how the feed is being mentioned and retweeted around the Web.

In communicating with patient audiences through social media, the first question firms need to ask is not what message they want to see penetrate in a given blog or forum, but how they can contribute to an ongoing two-way dialog with the community and meet people seeking health information.

16.5.2 Dos and Don'ts of Social Media

Our preceding discussion on social media and networks offers some prescriptions for pharmaceutical firms.

- *View social media over long term*. Social media and networks are here to stay. Therefore, pharmaceutical firms need to develop a long-term social media strategy. Although they can experiment in the short-term and improve their strategies, firms should approach social media from a long-term perspective.
- *Facilitate dialogs and conversations*. Sponsoring a Twitter chat that invites experts to discuss with patients about a health condition or health story in the news is a good way of starting useful conversations. Firms could allow consumers to submit questions to experts about health conditions and other questions around medications.
- *Offer content valued by stakeholders*. The importance of contents in digital era cannot be emphasized enough. When information is flooding online, only the most valuable contents can attract users and drive repeated visits.
- *Update content frequently*. Firms need to constantly update their sites and online initiatives. They can continually improve their digital and social media presence by sponsoring a weekly chat or support a group on social media.
- *Don't plug in/push propaganda/ads*. Social media are channels to reach new customers and build loyalty of existing customers through building digital communities and providing valuable contents, which can be ultimately translated into higher sales. Firms should educate their e-customers and don't hard sell using plug in/push propaganda or popping out ads, which can only annoy your e-customers and drive them away.
- *Customize content to communities*. Given that their competitors constantly improve their digital and social media initiatives, firms need to offer added value to the communities they sponsor. One way they can provide the incremental value is to customize content to the community members.

- *Experiment even if it means failures*. As social media is constantly evolving, firms should be prepared to learn continually. Successful pharmaceutical firms will be those that are bold to experiment with social media initiatives and learn from them.

16.6 Conclusions

A growing reliance on online communication, facilitated by advances in telecommunication devices, has enabled social media to become a vital channel for information exchange. This chapter reviewed how social media are redefining marketing, particularly in the context of the healthcare and pharmaceutical industries. It assessed the stream of literature on word of mouth and analyzed examples from pharmaceutical companies such as Johnson & Johnson, GSK, and Pfizer. It provides an actionable framework and strategy for marketers to think about and develop an integrated social media marketing strategy. Finally, it highlights fruitful avenues for future research.

Social networking is not a fad. It is a global phenomenon happening in all markets and infiltrating economic, social, and cultural borders. As the communication landscape continues to evolve, only companies that are proactive by engaging in online communities early and by innovating continuously through social media will experience significant success.

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Chapter 17
Understanding Sample Usage and Sampling as a Promotion Tool: State of Industry Practice and Current Research

Xiaojing Dong, Michael Li, and Ying Xie

Abstract In the United States, drug sampling has been one of the most important marketing practices adopted in the pharmaceutical industry. The U.S. pharmaceutical industry delivered an estimated $18.4 billion worth (in retail value) of free drug samples to doctors in year 2005 alone – more than all other marketing expenses combined. Although sampling, as a marketing tool, has been studied in the marketing literature, especially for consumer package goods; sampling in the pharmaceutical industry is very special due to the constraints that drug samples cannot be legally dispensed directly from the manufacturers to consumers. This creates a unique environment in which doctors play "gatekeeper and decision maker" role in dispensing samples to patients.

In this chapter, we first discuss the current industry practice of pharmaceutical sampling in detail, focusing on the following seven topics: (1) why samples are used; (2) the regulations governing pharmaceutical sampling; (3) sample decision support practice in pharmaceutical industry; (4) how drug samples are delivered to physicians; (5) how samples are consumed or dispensing pathway; (6) how samples are used in treating patients; and (7) the concept of "Source of Business" and how it is related to sample usage. We then discuss various sources of data that can be used

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for research on pharmaceutical sampling. After that, we review the academic research as well as industry studies on the effects of samples on pharmaceutical sales. Lastly, we close the chapter with directions for future research for both practitioners and academic researchers.

17.1 Introduction

In the USA, the practice of dispensing drug samples is one of the most important tools adopted by the pharmaceutical industry. Industry studies have shown that sampling as a marketing practice accounts for a significant proportion of company marketing budgets. Drug sampling is effective in reaching physicians as evidenced in a survey by Henry J. Kaiser Family Foundation (2002) which showed that 92 % of all doctors had accepted drug samples from pharmaceutical sales representatives. The US pharmaceutical industry delivered an estimated $18.4 billion worth (in retail value) of free drug samples to doctors in 2005—more than all other marketing expenses combined (Donohue et al. 2007). Therefore, it is important for pharmaceutical companies to understand how to distribute most efficiently these resources to targeted physicians.

Sampling is claimed to be "the most effective but most expensive way to introduce a new product or to create new excitement for an existing one" (Armstrong and Kotler 2009, p. 433). Beyond the pharmaceutical industry, the practice of distributing free product samples has been adopted by companies in a wide range of industries such as consumer packaged goods and newspapers (Schultz et al. 1998). Compared to sample distribution practices in these other industries, pharmaceutical sampling is limited because drug samples cannot be legally dispensed directly from the manufacturers (the pharmaceutical companies) to consumers. This creates an environment in which doctors have ultimate control over what drug samples a patient can try. During this process, doctors play a "gatekeeper and decision maker" role in dispensing the billions of dollars' worth of free samples to patients. As a result, in order to assess the effectiveness of pharmaceutical sampling it is essential to understand what drives doctors' free sample dispensing decisions.

Pharmaceutical sampling has become one of the frequently debated topics in mass media due to the recent increase in public scrutiny regarding the soaring healthcare cost in the USA (e.g., Rabin 2007). In particular, the somewhat unexpected finding that poor, uninsured Americans are less likely than wealthy, insured Americans to receive free drug samples in Cutrona et al. (2008) stirred a heated public discussion about whether free samples indeed play a "subsidy" role as claimed by the US pharmaceutical industry and backed up by many doctors. Also, there is evidence showing that patients receiving free samples had higher out-of-pocket costs than those who did not, which may lead to discontinuity of treatment, especially for low-income patients (Chimonas and Kassirer 2009). Responding to these criticisms, some US institutions, such as the University of Michigan Health

System, have completely banned their doctors from dispensing free drug samples to patients, while others including the University of Pennsylvania and Stanford University medical schools have prohibited staff members from accepting free drug samples[1] (Rabin 2007). Therefore, understanding the motivation for sampling in a physician's prescription decision is of interest to pharmaceutical companies in designing an effective sampling strategy while maintaining healthy public relations. Results could also help policy makers decide whether sampling should be encouraged to the benefit of patient welfare.

Unlike other promotional tools employed in pharmaceutical marketing, the effects of sampling are not always one-sided. On the one hand, free drug samples can stimulate trial and improve sales. On the other hand, sampling might cannibalize sales from regular prescriptions. The extent of cannibalization could be severe, considering the over $18 billion retail value of drug samples distributed in 2005 alone. Therefore, it is important to consider both the positive and negative influences of pharmaceutical sampling when evaluating the profit impact on sales.

In this chapter, we first provide an overview of common practices in pharmaceutical sampling in the USA. Then we discuss various sources of data that can be used for drug sampling research. After that, we provide a literature review on the effects of samples on pharmaceutical sales from both the academic literature and the empirical studies in the industry. We close the chapter with suggestions for future research, for both practitioners and academic researchers.

17.2 Current Industry Practice of Pharmaceutical Sampling

In this section, we discuss industry practice of pharmaceutical sampling in the USA. Specifically, we focus on the following topics: (1) why samples are used; (2) the regulations governing pharmaceutical sampling; (3) sample decision support practice in pharmaceutical industry; (4) how drug samples are delivered to physicians; (5) how samples are consumed or dispensing pathway; (6) how samples are used in treating patients; and (7) the concept of "source of business" (SOB) and how it is related to sample usage.

17.2.1 Why Samples Are Used?

Pharmaceutical samples are delivered by manufacturers or by third party distributors, dispensed by physicians, and consumed by patients. These three parties share certain views on the roles of samples, while each member has its own reasons for using samples. Patients as consumers perceive samples as a quick access to

[1]Free drug samples can be provided to Stanford's pharmacy to be used in free clinics.

Table 17.1 Reasons for using samples

To start therapy immediately
To convince a patient to start therapy or to increase patient compliance
To encourage a patient to come back for a follow-up visit
To treat a medical problem that is of a limited nature (for short-term use)
To test efficacy before filling a prescription
To assess tolerability before filling a prescription
To help in switching a patient to a new medication
To gain first-hand experience with a drug
For dosage titration (increasing dosage temporarily)
On patient request or to increase patient satisfaction
For patient convenience (e.g., if the drug store is closed)
To preserve patient confidentiality
Because they are there
If samples are about to reach the expiration date
Because "it's common policy"
To teach and to demonstrate
To taste-test the drug (this is mentioned quite often by pediatricians)
For personal use, for family use, and for staff use

treatment and a way to reduce their medication expense. Physicians use samples to provide better service for patients and improve their relationship with patients. Pharmaceutical companies use samples to promote drugs and to gain access to customers.

The key decision maker regarding sample usage is the physician. Physicians use samples differently depending on the medical condition of the patient. Sawaya (2002) summarized the reasons why physicians use samples (Table 17.1) based on the result of a physician survey. These reasons reflect clinical, logistical, as well as social issues faced by physicians on a daily basis.

As there are many different reasons for physicians to dispense samples to patients, it would be a challenge to separately identify and quantify the factors that drive sample dispensation of a brand.

17.2.2 Government Regulations

In the USA, the practice of pharmaceutical sampling is subject to detailed government regulations. According to "Prescription Drug Market Act" (PDMA) passed by the U.S. Federal Government in 1987, drug samples cannot be sold, traded, donated, or supplied at a reduced price to a third party, including charitable organizations. Drug samples can only be distributed to practitioners who are licensed to prescribe such drugs. PDMA requires distribution of drug samples only upon written request (called "sample signature" in the industry) by physicians with proper

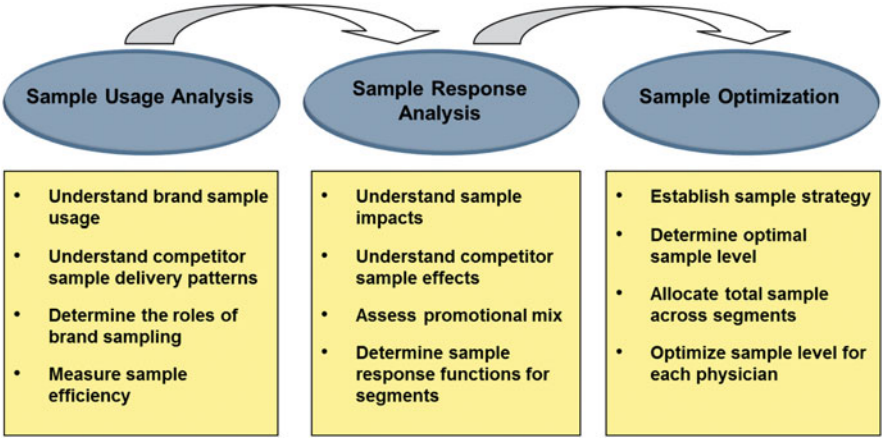

Fig. 17.1 Core sample-related analyses in the pharmaceutical industry

documentation. Sample distribution by mail or by sales representatives (sales reps) also requires a written receipt designated by the manufacturer or distributor acknowledging delivery and indicating name, address, and signature of practitioner or designee as well as the name, strength, and quantity of drug samples received. According to PDMA, free drug samples must have a label that clearly denotes its status as a drug sample, such as "sample," "not for sale," and "professional courtesy package." Manufacturers are required to keep detailed tracking data of sample distribution.

17.2.3 Sample Decision Support Practice in Pharmaceutical Industry

As one of the most important promotion instruments, sampling has been studied extensively by pharmaceutical companies in order to gain competitive advantages in the market. The focus has been centered on understanding (a) how the sample is used, (b) prescription responses to sampling, and (c) how to deploy samples effectively. The analytical process is illustrated in Fig. 17.1. The foundation for fact-based decision making is to have good measurement of actual activities. The optimal sample strategy or decision needs to be based on an empirical sample response pattern, which depends on sample usage information. However, different from prescription dispensing that has been tracked by many different data sources, the record of sample dispensation is only available from limited data sources in the industry.

Sampling decision remains to be a challenge for brand managers in practice because of data availability and the unique nature of sampling as a promotion tool. How many samples should be allocated to each brand, segment, and physician? This question is one of the most critical and difficult marketing decisions faced by

a pharmaceutical company. On the one hand, if a physician does not have enough samples for a particular drug, he may not start a new therapy or continue an existing therapy with that drug. Instead, he may start a new therapy using a competitor's drug for which samples are available. On the other hand, if the physician has too many samples available, the samples could cannibalize either new prescriptions or renewal prescriptions of the same brand.

Sample response models are difficult to build for several reasons. First, samples are frequently delivered during detailing encounters. In fact, on many occasions samples are physician access enablers. Without sample drops, many detailing encounters with physicians may not happen. This concurrency of sample drops and detailing creates a challenge to disentangle the effect of sampling from the effect of detailing. Second, a sample drop is recorded for delivery to a specific physician yet the delivered samples may be shared among several physicians from the same office. Therefore, the physicians who acknowledge the receipt of samples may be identified as oversampled while other physicians within the same group practice may be identified as under-sampled. Third, unlike regular prescriptions that are tracked by standard pharmacy-based prescription audits such as IMS or NDC audits, prescriptions consisting of samples (except vouchers) do not go through a pharmacy and there is no good physician level audit on sample usage for each physician (with the exception of ImpactRx data for a limited size panel). All these factors make it difficult to build accurate sample response models. Consequently, the sampling–prescription response is more of a black box than a detailing–prescription response relationship.

Many pharmaceutical companies have personnel dedicated to sample analysis, planning, and operation management. Table 17.2 provides a list of sample-related marketing research questions that frequently come up in the daily operation of pharmaceutical companies. Some of these questions may not be effectively addressed due to lack of data or methodology.

17.2.4 How Samples Are Delivered to Physicians

Traditionally, the majority of drug samples are physically delivered by sales reps either during detailing visits or on sample only visits. Some companies send the samples via mail and have sales reps obtain signatures from physicians. Some pharmaceutical companies use independent sample distributors because of regulation compliance or cost and efficiency concerns. In addition to direct delivery to physicians, a voucher is another way of distributing samples, which has become more popular in recent years, especially for generic drugs. Vouchers can be provided by pharmaceutical company sales reps or mailed by generic companies that intend to encourage the prescription of lower priced drugs. Vouchers are redeemable in pharmacies with the physician's approval. The pharmacies will get reimbursed for the vouchers they fill. Voucher activities are generally recorded by pharmacies as regular prescription scripts without co-payment by patients.

Recently, e-Sampling (i.e., electronic sampling) has emerged as a new trend in distributing samples to physicians. e-Sampling allows physicians to request samples

Table 17.2 Selected sampling-related measurement issues faced by pharmaceutical companies

Category	Selected sampling-related questions/issues
Description of sampling activity	Are sales reps breaking up the boxes of samples into 1, 2, 3, or 4 SDOT (sample days of therapy)?
	How many SDOT are the physicians giving away?
	What is the competition's sample configuration?
	How many of the competition's samples were given away?
	What are my competitors' sampling strategies?
	Are samples provided as treatment for the same patient diagnoses as scripts (i.e., contrast off-label usage for samples vs. scripts)?
	Do reps' sampling activities conform to the company's sample plan?
	To what extent does "counter sampling" occur (i.e., does the rep oversample physicians who have more competitor samples in their inventory)?
	Which products are physicians requesting samples for and are they receiving a sufficient amount of requested samples?
	How are samples used by different types of patients and by different sources of business?
Roles of sampling	What are the roles of sampling?
	How do physicians see the value of samples?
	Are there any proper physician segmentations in terms of sample valuation or perception?
	Identify physicians who should not be sampled; i.e., are there physician, practice, third party, or patient characteristics that make sampling unproductive?
Mechanism between sample drop and usage	What is the linkage between sample drop and sample usage?
	What are my reps doing in the sample closet?
	What channels are used to distribute samples for my brand?
Sampling effect on prescribing	What are the effects of my brand's sampling promotion?
	What are the effects of my competitors' sampling promotion?
	Does sampling increase physicians' prescribing activity or replace (reduce) prescribing activity?
	Is my brand oversampling?
	What are the sample effects on different types of source of business or different types of patients?
	What is the ROI of my brand's sample promotion?
	What is the long-term effect of my brand's sampling promotion on physician prescribing?
Sampling strategy and tactics	What is the optimal sampling strategy?
	Give away more or reduce samples
	Optimal sample packaging size or the ideal SDOT per box/unit
	Identify and design optimal sampling strategies according to product lifecycle (launch/growth/mature/decline)
	What is the optimal sample level for a targeted physician group practice?
	What sampling distribution strategy is actually implemented by the reps: e.g., random, opportunistic, to favored physicians, in proportion to prescribing to appropriate patient populations, and to physicians most responsive to sampling?
	How is measuring effectiveness of sampling package designs used to induce "pull" by physician?
	How is measuring effectiveness of patient promotion and patient education materials integrated into the sample packaging to induce conversion to new prescription or to induce improved patient compliance and persistency (for refills)?

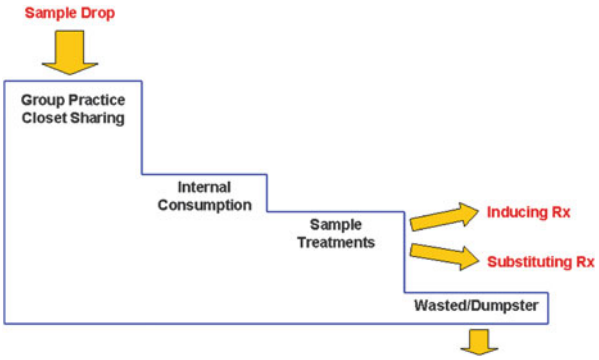

Fig. 17.2 Illustrations of physical sample dispensation pathways

through the internet and have the samples delivered by mail. The combination of e-Sampling with promotional websites has become a cost-effective way for pharmaceutical companies to reach "white space," i.e., non-detailed and "no-see" physicians. This new sample delivery method increases the importance of sampling due to its wide and easy access. However, it also raises new challenges in management of marketing channel integration between off-line and on-line channels for pharmaceutical companies.

17.2.5 Sample Dispensation Pathway

The pathway starting from the time when samples were dropped off by sales reps to samples being dispensed by physicians can be complicated and nontransparent. Samples dropped off by sales reps are normally only provided to a specific physician yet can be shared among physicians within the same group practice. This is because samples are typically stored in a sample closet which is accessible to all physicians in the same group. Although samples are typically dispensed to patients, surveys have shown that they can sometimes be consumed by physicians, their families, and friends. For example, Westfall et al. (1997) conducted a physician and staff survey in a family practice residency, and they found that 66 % of all respondents reported samples being used for personal use and 34 % reported samples being used for their own family use. In addition, over supplied samples can expire and be thrown away.

Figure 17.2 provides a graphical illustration of the dispensation pathway for a typical drug sample. Samples delivered to a physician belonging to a group practice will be shared, internally consumed, and possibly discarded. The physician who receives the samples typically only dispenses a small portion of the samples delivered to her and she also dispenses other drug samples received by other physicians in the same group practice. Because of these organizational reasons, sample delivery does not correspond to sample dispensing at the physician level. This unobserved step in the pathway makes sample planning and allocation even more challenging.

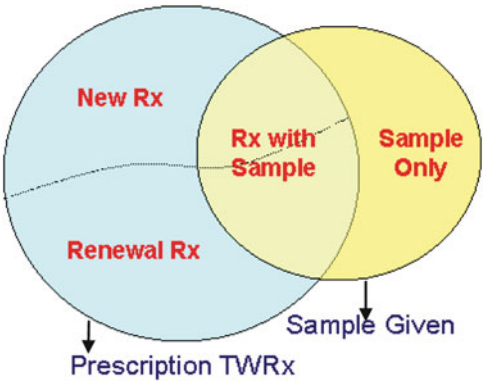

Fig. 17.3 Illustration of sample dispensation

Table 17.3 Summary statistics of selected sample usage measures for top 150 brands

Descriptive statistics	Sample given/ TWRx	SO/ TWRx	NWRx with sample/ NWRx (%)	RWRx with sample/ RWRx (%)	Sample only/sample given (%)	Sample only/ NWRx
Mean	0.28	0.14	22	7	42	0.31
Median	0.19	0.08	22	6	45	0.28
Standard deviation	0.24	0.15	12	6	17	0.24
Maximum	1.31	0.84	55	42	76	1.26
Minimum	0.00	0.00	0	0	0	0.00

17.2.6 Sample Dispensing Patterns

Typically, a physician has three options when prescribing a drug to a patient, as illustrated in Fig. 17.3: prescription treatment (either new or renewal), sample only treatment, or prescription treatment with sample.

As a concrete illustration of sample dispensation patterns, we provide a descriptive analysis of the top 150 most promoted (based on detailing volume) brands that primary care physicians prescribed in the USA. The data comes from the ImpactRx sample treatment audit and was for the year 2010. There are several basic data notions to be explained here. TWRx stands for total written prescriptions, which is the sum of new prescriptions and renewal prescriptions written[2] by physicians. Similarly, NWRx stands for newly written prescriptions, which are new prescriptions written by physicians. We constructed the following metrics at brand level to measure sample usage and provided the summary statistics of these metrics for 150 brands in Table 17.3.

[2]The ImpactRx data is collected from its physician panel; therefore, the prescriptions are "written" by physicians but may not be "dispensed" through pharmacies which have certain degree of prescription switching power. To distinguish from the normally used "dispensed" prescription data obtained from pharmacy audit, ImpactRx uses "written" prescription measure.

- *Sample given/TWRx*: This ratio measures the number of treatments with free samples relative to the number of total written prescription treatments for each brand. Sample given (SG) includes both sample only (SO) treatment and prescription treatment with samples.
- *Sample only/TWRx*: This ratio measures the number of sample only treatments relative to the number of total written prescription treatments for each brand.
- *NWRx with sample/NWRx*: This ratio measures the percentage of newly written prescriptions which are prescribed with samples out of the total number of newly written prescription treatments for each brand.
- *RWRx with sample/RWRx*: This ratio measures the percentage of renewal written prescription treatments which are prescribed together with samples out of the total number of renewal written prescription treatments for each brand.
- *Sample only/sample given*: This ratio measures the percentage of free sample treatments without prescription out of the total number of treatments with free samples for each brand.
- *Sample only/NWRx*: This ratio measures the number of the percentage of free sample only treatments relative to the number of newly written prescription treatments for each brand.

Note that above statistics are based on a sample of 150 brands. They provide some insights regarding how samples are used in the most promoted products among primary care physicians. Here are some observations based on these statistics. First of all, samples are widely used among primary care physicians. Of all the 150 brands considered, 137 brands (91.3 %) have instances where NWRx were prescribed with samples at the same time and 143 (95.3 %) have sample only treatments.

Secondly, sample usage intensity varies widely across brands, as indicated by the standard deviation of the ratio of sample given/TWRx. The average of this ratio across all brands is 0.28 and the median value is 0.19. The brands having the lowest "sample given/TWRx" ratio are OXYCONTIN, VYVANSE, ANDROGEL, NUCYNTA, and RECLAST. The brands having the highest "sample given/TWRx" ratio are PENNSAID and DULERA, both of which are at their launch phases in the data period. Overall, about 73 % of the 150 brands have "sample given/TWRx" ratio at 10 % or higher. This indicates that sample promotion is commonly used by a majority of the most promoted products in the United States.

Thirdly, the average percentage of new prescription treatments prescribed with samples is 22 %, and this ratio is only 7 % for renewal prescription treatments. In other words, sample usage with new therapies is more than 3 times of sample usage with continued therapies. This indicates that samples are used more frequently by primary care physicians to initiate new therapies than to ensure continuation of existing therapies.

Lastly, sample only treatment without prescription is a common practice and accounts for a majority of how samples were dispensed to patients. On average, the ratio of "sample only" to "sample given" for all 150 brands is 42 %, and the median is 45 %. Fifteen brands have two-thirds of their sample treatments dispensed without any written prescriptions.

Table 17.4 Definition of SOB

Source of business	Diagnosis type	Prescription type
New diagnosis	Newly diagnosed	NWRx
Switched from nondrug treatment	Previously diagnosed	
Switched to new medication		
Add-on therapy		
Ongoing diagnosis		RWRx
Titration of current medication		

17.2.7 Sample Dispensing and Source of Business

NWRx measures new prescriptions of a drug. When a patient switches pharmacy or changes his family doctor, or visits a specialist for the first time, the prescriptions are generally recorded as NWRx. To avoid such ambiguity, the concept of SOB is used to further define types of prescription treatments by incorporating patient prescription history information. Starting in the year 2000 as patient longitudinal prescription data became widely available, SOB has been gradually adopted in pharmaceutical market research and promotion analysis practice.

The definition of SOB is described in Table 17.4. A written prescription script can be classified into one of the six categories of SOB which are (1) new diagnosis, (2) switched from nondrug treatment, (3) add-on therapy, (4) switched to new medication, (5) ongoing diagnosis, and (6) titration of current medication. Among all these six categories, except for the first one which is used for a newly diagnosed condition, all the others are for a condition that was previously diagnosed. (1)–(4) correspond to NWRx, and (5) and (6) correspond to RWRx. Using SOB, different types of NWRx prescriptions can be distinguished by considering patients' treatment histories, which was missing in the NWRx/RWRx categorization. In particular, (1) in SOB refers to a condition that is newly diagnosed. (2) and (3) correspond to a situation in which a patient was previously diagnosed with a particular disease but just switched to the prescription from either nondrug treatment or some other medical/drug treatment. (4) "Add-on therapy" refers to a situation that a patient is prescribed with additional and different prescription treatment given existing prescription treatment. For example, diabetes patients who have Actos may get Januvia as an "add-on" therapy. Based on the SOB classification, renewal prescription consists of two types of treatments: (5) ongoing diagnosis, which refers to a continued prescription of the same brand for a patient with a previously diagnosed condition and (6) titration of current medication, which refers to a continuing prescription of the same brand at a different dosage. For example, a physician may prescribe a 20 mg Lipitor to a patient who is currently getting 10 mg Lipitor because she decides the current dosing is not sufficient. By incorporating the information regarding patients' treatment histories, the SOB concept offers a deeper and more precise understanding of brand usage comparing to the traditional NWRx and RWRx concepts. For example, some brands are considered by doctors as first line therapies so

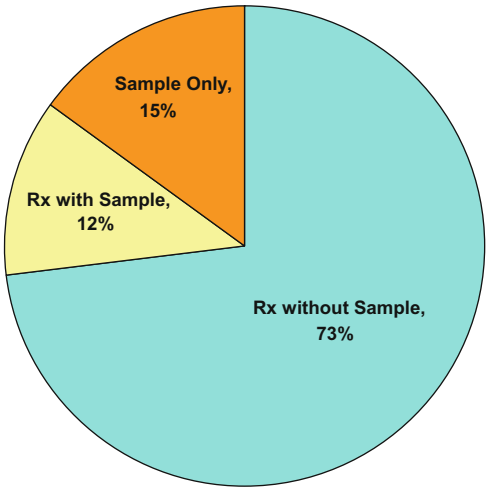

Fig. 17.4 Treatment volume distribution: antidepressant class

they are better measured by using market share among new patients. Other brands are considered as second line treatments and are used more often as add-on therapy. The SOB concept helps to distinguish these two situations. Since longitudinal patient level data became available in early 2000s, SOB has become a popular data measure for physician segmentation and targeting, as well as promotion response analysis in the pharmaceutical industry.

Similarly, further breaking down of the sample treatments by SOB can provide more insight into how samples are used by physicians. To demonstrate the SOB patterns for sample and prescription treatments, we conducted an analysis using data from the antidepressant class. The data records prescriptions and samples dispensed from primary care physicians in a 6-month period from January to June of 2008. In this analysis, only three heavily detailed brands are considered (LEXAPRO, EFFEXOR/XR, and PRISTIQ). Generic drugs and nondrug treatments are excluded from this analysis. As plotted in Fig. 17.4, the majority of antidepressant prescription treatments (73 %) were given without samples at all. "Sample only" treatments account for 15 % of the total prescription treatments and "prescription treatments with samples" account for the remaining 12 %.

Figure 17.5 provides a breakdown of SOB distribution by treatment types in the antidepressant class. We notice the following three patterns in sample dispensation from this analysis. First, in the antidepressant class, samples were most frequently used to initiate new patient therapy among all of the SOB measures. Fifty-four percent of "sample only" treatments and 51 % of "prescription with sample" treatments were prescribed to patients with a new diagnosis, while only 20 % of "prescription without sample" treatments were prescribed for newly diagnosed patients. In addition, 10 % of "sample only" prescription treatments and 7 % of

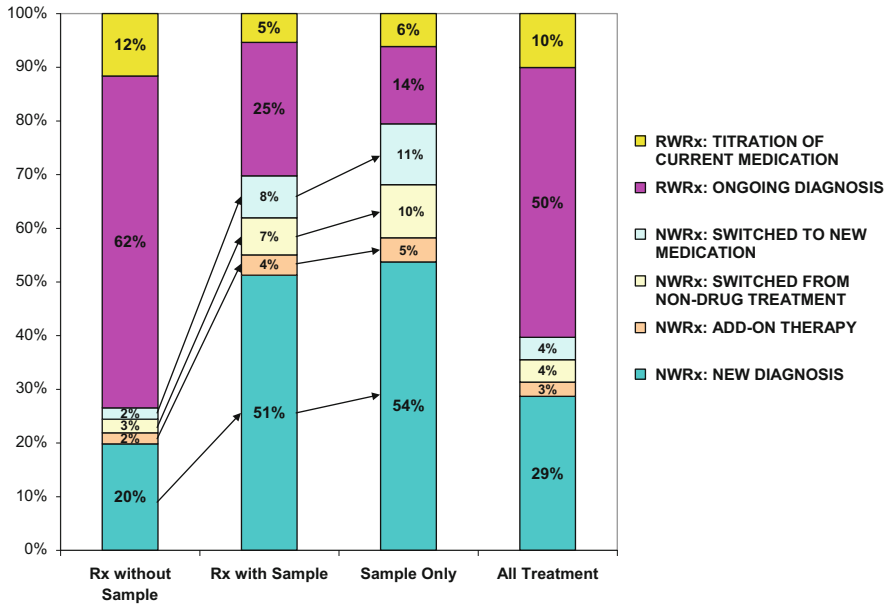

Fig. 17.5 Source of business (SOB) distribution by treatment type: antidepressant class

"prescription with sample" treatments were prescribed to patients who switched from nondrug therapy, while only 3 % of "prescription without sample" treatments were prescribed to these patients. Second, samples also play an important role in competitive treatment switching; 11 % of "sample only" treatments and 8 % of "prescription with sample" treatments were prescribed to patients who switched to new drug therapy, whereas only 2 % of "prescription without sample" treatments were prescribed for the same purpose. Third, samples are also used for renewal treatments, including titration and continuing current treatment, but at a relatively lower percentage than prescription treatment without sample category. In summary, samples are important in getting new patients to start on a particular brand rather than ensuring renewal prescription.

Examining the data from a different angle, we plot the treatment type distribution by SOB in Fig. 17.6. This plot allows us to examine how different types of sample treatments were used across different types of patients. The graph shows that "sample only" treatments had the highest share among patients who "switched to new medication," which is also referred to as competitive switches. "Sample only" treatments account for a higher share in "switched from nondrug treatment" and "new diagnosis" patients relative to other categories in SOB. Finally, samples are used more often in starting new treatments than in preserving renewal treatments. These results indicate that sampling is important in helping drug manufacturers gain access to patients that are new to the brand.

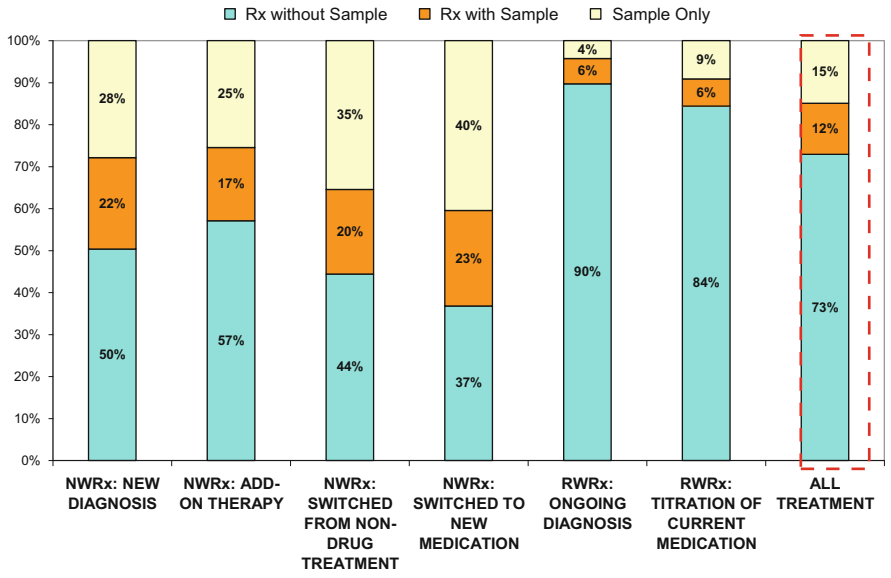

Fig. 17.6 Treatment type distribution by SOB: antidepressant class

17.3 Sample Data Sources for Marketing Research

In this section, we provide an overview of three major data sources that are available for marketing research on pharmaceutical sampling.

17.3.1 IMS Health Data

In the pharmaceutical industry, the most widely used drug sample data comes from the Integrated Promotional Services™ (IPS) by IMS Health. The database started in 1992, while its predecessor the National Detailing Audit™ collected data from 1958 to 1992. IPS is a physician detailing activity audit that tracks office-based pharmaceutical promotion in the continental USA. Each brand's promotion volume is projected to national level. The IPS physician panel sample consists of 3,800 physicians in 25 specialty groups (100 specialties) from 43 states across the USA. Physicians are asked to participate for at least a year. Some physicians may choose to stay on the panel for multiple years.

The IMS sampling data is collected from one third of its members (i.e., 1,265 physicians) of the IPS physician panel. The nurses or office administrators from those physician offices report sample drops by sales reps from manufacturers as well as samples mailed to the panel physicians. All sampling measures are projected

to the national level for each specialty. The data report three main sample drop measures for each brand:

1. Number of extended sample units[3] for each product form and strength.
2. The mode of sample size for each product form and strength.
3. The average number of tablets, capsules, or grams.

In addition, the data also record three delivery types, including in-person detailing, service visit, and mail delivery. Most market research applications using these data are based on projected sample volume and market share for each brand within a market. One major limitation of the IMS sample audit is that the projection error can be significant for some small brands or brands with fewer sample drops. To the best of our knowledge, no physician level modeling analysis has been conducted using IPS sample data.

17.3.2 Scott-Levin/Verispan/SDI Health Data

As one of the main competitors to IMS' IPS, Scott-Levin Associates started Personal Selling Audit (PSA) in 1993. Physicians reported similar sales rep activities over time, which normally takes them about 10–15 min per month. PSA has a panel of about 4,300 physicians from 32 specialty groups. Scott-Levin was acquired by Quintiles in March 1999 and became a part of Verispan in March 2002. Verispan was bought out by SDI Health LLC in July 2008.

These data are provided at monthly level and report the following information by product, company, and physician specialty:

1. Number of details
2. Duration of each detailing call
3. Detailing sequences
4. Number of samples dropped

Similar to IPS, only a portion of PSA panel (about 1,600 physicians) report sample information.

17.3.3 ImpactRx Panel

ImpactRx started collecting data from its physician panel in 2002. By 2011, they had a panel of more than 4,100 physicians from 14 specialties. Similar to IMS IPS audits, ImpactRx panel records a complete audit on promotion details; in addition, it also collects information on patient treatment, diagnosis, and demographic data

[3]Extended sample unit represents basic unit of a sample package such as tablets, capsules, grams, tubes, and bottles. Since extended units for any products can represent a variety of forms, these data cannot be logically summed up beyond product/form/strength level.

from the same physician panel. ImpactRx data are not projected to national level. These data are ideal for measuring treatment responses to various promotional tools at the individual physician level.

ImpactRx collects sample usage data as a part of physician treatment activities. The data reports the type of sample treatment prescribed by physicians (i.e., whether it is new prescription treatment with samples, renewal prescription treatment with samples, or sample only treatment), as well as the amount of samples dispensed on each prescription occasion measured by sample counts and sample days of therapy. Each sample or prescription treatment has a unique diagnosis code (ICD-9) so that a treatment can be identified for a specific medical condition.

As a measure of sales reps' detailing activities, ImpactRx data recorded sample signature data starting in October of 2010. Physicians reported sample signature signed as well as vouchers and coupons distributed to each doctor during each product detailing.

17.4 Literature Review of Academic Research on Pharmaceutical Sampling

In this section we review existing academic studies on prescription sampling from both the marketing and medical literature. We first summarize prior literature on the effects of free drug samples on physicians' prescription choices and prescription drug sales. We then discuss previous studies that examine the drivers of physicians' free drug sample dispensing behavior and explore the roles free samples play in physician's prescription decisions.

17.4.1 The Effects of Free Drug Samples on Prescription Choice

The vast majority of the existing marketing studies on the effects of free drug samples have focused on evaluating the impact of free samples on prescription drug sales or physician's prescription choice.

Gönül et al. (2001) studied the effects of detailing and sampling on an individual physician's prescription decision. They found that sampling had a positive effect on physician's prescription decisions, but this effect had diminishing returns. Using a large pooled time series of cross-sectional data involving three drugs and 74,075 individual physicians, Mizik and Jacobson (2004) also find that detailing and free drug samples have statistically significant positive effects on the number of monthly new prescriptions issued by a physician. However, the magnitudes of these effects are modest compared to the findings in previous studies.

Using individual level panel data, Manchanda et al. (2004) analyzed physician's prescription decisions with a hierarchical Bayesian framework. They suggest there

is a significant and positive influence of drug sampling on an individual physician's prescription decisions. The influence affects both the physician's base prescription rate and the physician's responses to detailing. This concept is furthered by Manchanda et al. (2008). They found that sampling stock positively affects the probability of a physician's adoption of a new drug. Finally, Montoya et al. (2010) use a nonhomogeneous hidden Markov model and find that while detailing may be more useful as an acquisition tool, sampling is more useful as a retention tool.

The effect of drug samples on prescription decisions is also a topic that is frequently discussed in the medical literature; yet the findings are mixed. Some studies suggest free samples may cannibalize regular prescriptions in the short term. For example, Boltri, Gordon, and Vogel (2002) reported that usage of recommended antihypertensive drugs increased when samples were removed from one clinic. In another study, Brewer (1998) found that residents in two programs with restrictions on samples prescribed more recommended nonsteroidal anti-inflammatory drugs (NSAIDS) than residents in a comparable program but without restrictions on samples. However, other studies suggest the opposite effect that free samples help to enhance the sales of the promoted drugs. For example, the findings by Symm et al. (2006) and Adair and Holmgren (2005) suggest that physicians who distribute free samples are more likely to prescribe those medications than their counterparts. One obvious limitation of such studies is that free sample dispensing was the only determinant considered, while a wide range of other factors that would impact a physician's prescription decision, such as other marketing mix and patient characteristics, were left out of the studies.

17.4.2 Drivers of Physician's Free Sample Dispensing Decision

Most research that examines the determinants of a physician's drug sample dispensing decision exists in the medical literature. Two main motives suggested by the literature are an *experimentation* role and a *subsidy* role. The experimentation role of free drug samples hinges on the belief that free samples are a cost-effective way for a physician to test for the match between a new drug and a particular patient. The subsidy role relates to the cost saving to indigent patients through supply of free drug samples. For example, Chew et al. (2000) conducted a physician survey to investigate the purpose of dispensing drug samples. They found avoiding cost to the patient is the primary reason for dispensing drug samples and evaluating treatment effectiveness is the secondary reason when the diagnosed condition is complicated. In addition, Backer et al. (2000) conducted a field study that found individual physicians vary in their intent when dispensing samples. In particular, physicians use samples to test for efficacy, as a temporary relief for convenience of their patients, or to save cost for their patients.

If an "experimentation" role of free drug samples exists, we would expect that a patient is more likely to receive free samples (rather than a full prescription) of a drug from her physician if she has not been prescribed the drug before. Furthermore, it usually only takes a few trials to find out whether a drug is working for a patient. Thus, if the physician's main motive is to experiment when she gives free samples to a new patient, we would expect that the sample dosage will be lower in this case. On the other hand, if free drug samples play a "subsidy" role in physician's prescription decision, we would expect that an indigent patient (e.g., one with low income or with inadequate insurance coverage) is more likely to receive free samples from her physician. In fact, a number of studies in the medical literature provide empirical evidence for this view. Taira et al. (2003) showed that among elderly patients, those with financial problems are more likely to receive free drug samples. Through a patient survey, Stevens et al. (2003) found that self-pay/uninsured patients more frequently report receiving free drug samples than patients with public aid. Morgan et al. (2006) find that giving out free samples to help patients with financial difficulties was a common practice among the 397 obstetricians and gynecologists who participated in the study. However, a more recent study by Cutrona et al. (2008) reported a somewhat unexpected finding that poor and uninsured Americans are less likely than wealthy or insured Americans to receive free drug samples. As the authors speculate, this finding could be partly due to the cofounding facts that the poor and uninsured might be less likely to visit physicians. Thus, their access to free samples is more limited compared to other patients. Nevertheless, the question of whether the indigent patients are more likely to receive free drug samples conditional on their visits to the doctors remains unanswered and warrants further investigation.

As mentioned before, the majority of marketing studies have focused on evaluating the impact of samples dropped by pharmaceutical firms on physician's prescription choice, but have not investigated individual physician's decision on free drug sample dispensing. One noticeable exception is Venkataraman and Stremersch (2007), in which the authors find that both detailing and physician meetings have a positive effect on the number of samples dispensed by physicians. However, the authors do not explore further the underlying drivers of physicians' sample dispensing behavior (i.e., whether it is due to the "experimentation" role, the "subsidy" role, or both). Dong and Xie (2011) took one step further to provide deeper insights into physician's sample dispensing behavior by incorporating patient characteristics that relate to physicians' two fundamental motives in free sample dispensing in both the sample dispensing model and the sample quantity model. Using a physician panel dataset of sample dispensing and prescription choices in both the PPI and the ED categories provided by ImpactRx, Dong and Xie (2011) jointly estimate a multinomial logit model of joint brand and treatment mode (i.e., whether to dispense free samples or to write a prescription) choice and a count model of quantity decision at individual physician level in a hierarchical Bayesian framework. They propose that the long-term effect of free samples on brand choice might depend on the underlying motivation of the dispensing physician. On the one hand, if the purpose is to stimulate trials through "experimenting," a physician's free sample dispensing

would have a positive effect on her future prescription, as demonstrated in existing studies on the effect of sampling in the pharmaceutical industry. On the other hand, if the main objective is to provide financial assistance or subsidy to an indigent patient, a null effect of free sample dispensing on a physician's future prescription of the same brand should be observed. This is similar to the cannibalization effect as shown in Bawa and Shoemaker (2004). They find that in general physicians are more likely to dispense samples to patients who are newly diagnosed, have an ongoing diagnosis but were prescribed a different drug on the previous visit, or do not have any insurance coverage. However, the tendency to dispense samples to each of the above-mentioned types of patients differs considerably across physicians. As for the long run effects, they find that free sample dispensing will induce future prescriptions if the samples are dispensed to new patients. In addition, they do not find a significant effect of free samples on future prescription decisions if dispensed to patients without any insurance coverage.

17.5 Industry Research in Practice

The above section reviewed academic research on pharmaceutical sampling. In practice, to gain competitive advantages, pharmaceutical companies also conduct extensive studies on sampling. In general, these studies can be grouped into three categories: (1) sample modeling at aggregate level; (2) sampling modeling at disaggregate level; and (3) sample allocation models. In this section, we provide an overview of these three types of studies.

17.5.1 Sample Modeling at Aggregate Level

Aggregate modeling using brand level data is one common way of conducting sample analysis in industry practices. The objective is to understand and assess adequacy and effectiveness of sample resource allocation at brand level from a strategic perspective. One approach is to evaluate how a brand's TWRx/NWRx volume or market share is influenced by sample volume in addition to detailing volume. Normally a multivariate time series model approach is employed for such analysis using a brand's own promotion and sales data. This type of analysis is usually constrained by the length of the time series. Another aggregate model approach utilizes competitor promotion and sales data to build a representative brand model by pooling brand level data from all competitors. This approach requires a cross-sectional time series model by using detailing and sample audit data such as IMS Health IPS data. Since the mid-1970s, some practitioners started using the seeming unrelated regressions (SUR) approach to build a brand level promotion response model, which allows analysis across multiple therapeutic classes. A similar approach is also

used in the ROI Analysis of Pharmaceutical Promotion (RAPP) by Neslin (2001) and Wittink (2002). Pooling multi-brand data increases sample size and expands the range of hypotheses to be tested. This type of analysis can provide directional views to a particular company, because it is based on cross-brand experience.

From the practice perspective, the advantages of aggregate sample modeling include:

- Sample effectiveness can be compared with both personal promotion, such as detailing and nonpersonal promotion, and other marketing instruments, such as journal spending and direct to consumer spending (DTC).
- Easier to evaluate competitive sample drop effects.
- Can provide life cycle perspective because of historical and cross-brand perspective.
- Dynamic effect and seasonality can be easily specified and estimated.
- ROI assessment at brand level can be easily conducted.

Limitations of aggregate sample modeling are:

- Longer historical data is needed for modeling so the result can be useful for long-term strategic planning but may not be accurate for short-term implementation.
- May be subjected to aggregation errors.
- Limited by sample size or data period.
- Multi-collinearity between detailing and sample drop.
- Not tactical for field implementation and action, for example, at segment level.

17.5.2 Physician Level Modeling

Test–control study is a commonly used approach in the industry to evaluate impacts of promotion such as detailing, new messaging, DTC, direct mail, and sampling at individual physician level. Typically, the response measure is prescription shares by a physician. The test and control groups are selected in such a way that across groups the physicians are similar in prescribing patterns (in terms of volume) and external factors. ANOVA or ANCOVA model is applied to test prescribing share or volume difference between test (sample exposed) and control (no sample exposure) groups while other factors are controlled through either covariates or data selection. The same approach is also used for pre- and post-analysis, which requires longer duration of the data. The ROI can be easily calculated based on test and control analysis.

Normally, this type of approach is used on secondary data, such as physician prescription data or longitudinal patient data. A large sample size can ensure that a sufficient sample can be obtained with more factors controlled. Different companies used different matching methods to form test and control groups that are comparable. One of the main limitations of the test and control analysis is that it is difficult to eliminate all confounding factors so that physicians in test and control groups are exactly comparable except for differences in sample or other promotion stimuli.

Recently, panel model at the physician level has become a standard analytical practice for most pharmaceutical brands where physician level sales data are available. Pharmaceutical companies started to adopt this approach in late 1990s, just a few years after physician level data (such as IMS Xponent) became available. Every large pharmaceutical company by now has developed an enterprise level modeling system that can produce promotion response analysis at brand and segment level on a regular basis to support call planning, physician targeting, and resource allocation. Typically, physicians' NWRx, TWRx, or share measures from IMS or NDC are used as a dependent or response variable, and independent variables include number of calls, samples left to physicians, meetings and events, and other promotion and marketing variables such as DTC. The modeling methods are drawn from econometrics and marketing science literature, including dynamic panel models, generalized linear models, mixed models (random effect models), count models (Poisson and NBD), and hierarchic Bayesian models.

Most of the panel models as described above utilize internal promotion data and prescription records from data vendor such as IMS. There are some well-known limitations of using this internal promotion data. First, the promotion information is subject to self-reporting errors (which may be caused by the company's incentive structure). Second, no competitive promotion measures exist at the physician level. Thus, the estimated promotion effectiveness can be significantly biased especially in a competitive market. Third, sample drop measure to any doctor may not be an accurate measure of sample promotion due to sample sharing within a group practice, sample signature practice, and the existence of other sample distribution channels.

In the past 5 years, panel modeling approach using patient transactional level data, instead of monthly physician level data, has become a popular way to evaluate the effectiveness of detailing, message, and promotion tactics. There are several advantages of such an approach. First, it models stimuli and response relationship at a more granular level; second, it considers timing between promotion and response explicitly; third, it reduces multi-collinearity and data aggregation; and lastly, more transactional level factors can be considered in the model. As nonpersonal or alternative channel promotion targeting of patients has gained a more important status in recent years, many pharmaceutical companies also used this platform to evaluate the effectiveness of nonpersonal promotion such as direct mail, voucher, and co-pay card.

17.5.3 Sample Allocation Model

The ultimate question for every sales team is how many samples should be distributed to a targeted physician so that paid prescriptions can be maximized in the long run. One approach adopted in the industry is the method of "one-period inventory problem," also called the "newsvendor problem." The objective of this approach is to find the optimal number of samples to distribute that will maximize the expected profit. The expected profit is the sum of expected profit under the uncertainty of

demand. Under certain distribution assumptions, such as normal or Poisson distribution, optimal sample decisions can be obtained with a closed form solution. The implementation of this approach requires some observational measures on physician sample usage. This inventory approach of optimal sample allocation has the following shortcomings. First, it treats sample use the same way as merchandise inventory decision, while ignoring the possible impact from promotional efforts. Second, the implementation of this approach requires the information on physician sample usage rate and sample closet stock level, which may not be observable. Third, the calculation of opportunity cost and revenue potential can be tricky due to the short-term and long-term trade-off. Lastly, competitive sample drops and stock levels are not considered in this model, which can present significant influences in physician sample usage and prescription behavior.

17.6 Future Research

In the above, we summarized the current research in both academia and industry regarding pharmaceutical sampling. Comparing to other promotional tools (such as detailing and direct to consumer advertising), pharmaceutical sampling is still an understudied topic. Next, we provide a non-exhaustive list of topics for future research.

First, how to determine the right sample quantity for different physician segments and how to target specific physicians remain to be important questions and call for more future research. The inventory approach of optimal sample allocation is a passive service model based on several assumptions related to unobserved conditions. Designing a better sampling decision model for group practice physicians that models physician prescribing with unobserved variables such as physician sample usage rate and sample closet stock level continues to be a challenge in the pharmaceutical industry practice.

Second, the dynamic effects of sampling on prescription writing are not well understood. Most business practices focus on the short-term effect. However, sampling can have negative short-term and positive long-term effects on prescriptions. Understanding the dynamics of sampling on future prescriptions and the effects of detailing on sample usage can be valuable to guide marketers in planning sample strategies.

Third, it is important for marketers to have a better understanding regarding how patient level information influences a doctor's decision on sample usage. In such research, how to address unobserved behavior such as sample closet sharing is a challenging question to researchers.

Fourth, it is important for marketers to understand how sampling strategy should be adjusted based on the drug's product life cycle stage. Historical analogue approach is currently used in new product launch planning practices. In this approach, researchers should evaluate all aspects of historical launches, including both successful and unsuccessful launches, to understand what strategies worked

and what did not. This market research intelligence can provide guidance on all major new product launch planning. In addition, more rigorous statistical empirical research on launch strategies as well as on other stages in the life cycle (growth, mature, and decline) will be valuable.

Finally, as the role of physical sample drop declines and alternative sample distribution channels expand, pharmaceutical companies need to understand the relative effectiveness of different sample delivery channels such as sample signature, vouchers, e-sampling, and patient assistance program. This new sampling mix optimization is an important issue in the new era of multiple-channel sample distribution.

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Chapter 18
Pharmaceutical Detailing Elasticities: A Meta-Analysis

Shrihari Sridhar, Murali K. Mantrala, and Sönke Albers

Abstract Facing maturing product portfolios and growing physician resistance to their promotion by medical sales representatives (i.e., detailing) in developed markets, the pharma industry is struggling to develop more effective selling strategies and appropriately size and deploy its sales forces. In this process, having benchmark answers to the following questions can be helpful: (1) How effective is personal selling or detailing to physicians? (2) What is a generalizable quantitative estimate of detailing effectiveness? (3) How does detailing effectiveness vary by product life cycle stage and geographic region? To provide these answers, the authors present a meta-analysis of 373 econometric estimates of pharma detailing *elasticities* appearing in 48 previous papers. They find the mean estimate of current-period detailing elasticity is 0.21. Further, elasticity estimates are higher for products that are offered in early life cycle stages and Europe compared to the USA. Also, product life cycle stage and geographic location have a significant interaction effect on detailing elasticity estimates. Specifically, the mean detailing elasticities of late stage products in Europe and the USA are 0.17 and 0.14 respectively; while the mean detailing elasticities of early stage products in Europe and the USA are 0.41 and 0.23 respectively. Also, year of data collection and stage in life cycle have a significant interaction effect on elasticity estimates. Specifically, elasticities from more recent studies of early stage products are lower than those from earlier studies. This comports with

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reported trends that pharmaceutical detailing effectiveness in new product launches is declining over time. The meta-analysis also revealed a number of methodology-related factors as significant determinants of the detailing elasticity compiled from previous studies. After correcting for these methods-related biases, the mean detailing elasticity reduces to 0.18. Using this method bias-corrected estimate of mean detailing elasticity in conjunction with plausible product margins, the authors demonstrate that optimal detailing spending to sales ratios today (1) should be in the region of 6–7 % over pharma product life cycles; (2) should involve judicious shifts from higher to lower detailing emphasis as products age; (3) should be larger in Europe than in the USA.

18.1 Introduction

In pharmaceutical marketing, detailing, i.e., personal selling to physicians has been the key component of pharma promotion in the developed markets for decades. Most recently, Cegedim-SK&A (2011) reports that in 2009–2010, US Pharma Companies spent about $28 billion promoting drugs to prescribers, with detailing accounting for about $15.3 billion, or about 54 % of total annual promotion spending.[1] The corresponding numbers for the top five European markets (France, Germany, Italy, Spain, and the UK) were about $18.5 billion for total pharmaceutical promotion spending with detailing to healthcare professionals accounting for $11.8 billion or 60 % of total promotion spending (Derrick 2011). Interestingly, however, total pharma promotion spending in the USA declined by 10 % from 2009 to 2010, continuing a trend that has been evident for the past few years. US pharmaceutical companies are cutting back mostly in detailing and sampling, while spending in mailings and print advertising grew from the previous year (Cegedim-SK&A 2011). Indeed, there has been a 25 % reduction in the US pharmaceutical sales force since 2005. In 2005, the US pharmaceutical sales industry employed 102,000 reps. It is estimated there will be just 75,000 in 2012 (Baldwin 2011). In contrast, overall pharma promotion expenditure in the top five European markets has exhibited small 0.5–3 % annual increases over the last few years. However, like the USA, total detailing spend has decreased in recent years, albeit at a much slower rate than in the USA, e.g., it was down 2.5 % from 2009 to 2010 (Derrick 2011).

[1] Based on Gagnon and Lexchin (2008), we believe Cegedim's (CAM Group's) estimate of total spending on detailing includes not only the average "cost to field the rep" (salary and benefits of the representative and the transportation cost) but also the costs for the area and regional managers, the cost of the training, and the cost of detail aids such as brochures and advertising material. In contrast, IMS Health estimates of detailing spending only consider the "cost to field the rep." Thus, Cegedim CAM Group's estimate of US pharma detailing spending in 2005 was nearly 2.8 times IMS' estimate of $7.3B for that year (Donohue et al. 2007; Gagnon and Lexchin 2008). Data from a third source, SDI Promotional Audits (recently acquired by IMS Health), utilized in a 2009 Congressional Budget Office (CBO) report by Campbell (2009) indicates that US pharma companies' detailing spending was roughly $11.25B in 2005, or about 55 % of the CAM estimate for that year.

There has been much commentary focused on the trends in pharma promotion spending in general, and detailing in particular. The decreases in detailing headcounts in the USA have been attributed to causes that include considerable merger & acquisition activity, a reduction in blockbuster drug launches, growing influence of managed care organizations, pricing regulation pressures on physician prescriptions, and growing resistance of physicians to seeing reps due to increasing time constraints (e.g., Baldwin 2011). According to one study by Cegedim-SK&A, now one in four physicians refuses to see reps. In the past, pharmaceutical companies could draw a direct correlation between share of market and share of voice. So they kept ratcheting up the volume by way of throwing more reps at physicians (popularly labeled the *detailing arms race*, e.g., Elling et al. 2002). The evidence suggests that this approach actually worked in an era of frequent waves of blockbuster launches. However, today, that is no longer true as new blockbuster product development has slowed down. As a consequence, sales forces have taken a hit as they have been downsized and redeployed for more effective as well as efficient promotion (Baldwin 2011).

In this era of massive changes in the healthcare sales environment, especially in the USA, whether or not traditional pharma sales forces have a future is being seriously debated in many quarters. Some commentators have asserted that due to online technology advances that can inform and respond adequately to buyers' questions, outside sales forces will disappear. For example, *Selling Power* (Gschwandtner 2011) suggests that it is likely that of the 18 million salespeople in the USA today, there will be only about four million left by year 2020! Realistically speaking, however, due to the important role face-to-face selling plays at different stages in most industries' sales cycles, outside sales forces of significant sizes are likely to remain in place in the foreseeable future (e.g., Mantrala and Albers 2010). However, sales force structure and deployment are likely to significantly change as new selling models are devised. In particular in the pharma industry, aided by advances in technologies such as new smartphone apps and e-Detailing (e.g., Alkhateeb and Doucette 2008), pharmaceutical detailing style, deployment, and messaging are likely to significantly change, e.g., moving from a one-size-fits-all approach to scientific matching of messages to individual physicians (Baldwin 2011).

As the pharma industry struggles in the face of maturing product portfolios to develop and implement new effective selling strategies, and appropriately size and deploy its medical sales forces in the USA and Europe, it would certainly help to have answers to the following core questions: (1) How effective is personal selling or detailing to physicians? (2) What is a generalizable quantitative estimate of detailing effectiveness? (3) How does detailing effectiveness vary by product life cycle stage and geographic region? Our objective in this chapter is to answer these questions and shed light on their implications for pharma companies' optimal detailing spending to sales ratios. The methodological approach we follow is to draw empirical generalizations from a meta-analysis of the accumulated quantitative knowledge to date with respect to pharma detailing effectiveness. Given its prominence, numerous individual quantitative studies of pharma detailing effectiveness in various market settings and therapeutic categories have been conducted

over the past decades (e.g., Manchanda and Honka 2005; Fischer and Albers 2010). In this chapter, we compile and analyze these relevant econometric studies over past decades to provide up-to-date empirical generalizations about the magnitude and determinants of detailing elasticity, a valuable quantitative measure of detailing effectiveness.

The value of meta-analyses of the type we propose to theory development and management is well established in the marketing literature (e.g., Farley et al. 1995; Hanssens 2009; Henningsen et al. 2011). The usefulness of deriving a meta-analytic estimate of the *elasticity*, i.e., the ratio of the percentage change in output (say, dollar or unit sales) to the corresponding percentage change in selling effort (e.g., dollar expenditures), as the metric of selling effectiveness is also well established. Specifically, the elasticity measure is favored in such meta-analyses because it is dimensionless and easily interpretable (Sethuraman et al. 2011; Tellis 1988, p. 332). So far, however, research on drawing out generalized quantitative estimates of the effectiveness of detailing from the body of past-related individual econometric studies is limited. In a recent paper Albers et al. (AMS) (2010) conducted a meta-analysis of personal selling elasticities from numerous econometric studies across multiple industries including pharmaceuticals. Based on an analysis of their data, they provide a rough estimate of mean detailing elasticity, uncorrected for methods bias, of 0.245 in the pharma industry compared to a mean of 0.34 for personal selling elasticities from all-industry settings. The AMS (2010) work, however, was not focused on the pharma industry and does not include several important studies of pharma detailing effectiveness that have appeared since it was completed (e.g., Bhatia and Le 2011; Dave and Saffer 2010; Fischer et al. 2011; Gönül and Carter 2010; Kolsarici and Vakratsas 2010; Nair et al. 2010; Osinga et al. 2010). Another meta-analysis paper by Kremer et al. (2008) is focused on the pharma industry but is concerned with several types of pharma promotions including detailing. Furthermore, their meta-analytic estimates of detailing elasticity suffer from several shortcomings that have been discussed by AMS (2010). Thus, there remains a need for a comprehensive, up-to-date meta-analysis focused on pharma detailing elasticities to develop empirical generalizations that can guide pharma industry sales executives as they rethink their promotion strategies today. In this chapter, we specifically concentrate on empirical generalizations with respect to *current period* (or short-term) detailing elasticity that can guide pharma executives' detailing investments in different market settings.

The total number of current-period detailing elasticity estimates from past econometric research compiled and analyzed in this chapter is 373, significantly larger than the number of 284 detailing elasticities included in the AMS (2010) analysis. The major qualitative findings from the focused meta-analysis in this chapter are fairly consistent with the findings of AMS (2010), but there are some exceptions and significant quantitative differences. In particular, the raw mean estimate of detailing elasticity that we find is about 0.21, perceptibly lower in magnitude than the raw mean of 0.245 for personal selling in pharma settings reported by AMS (2010). The seemingly small difference implies significant differences in optimal levels of detailing efforts—as shown later in this paper.

Additionally, we obtain some new insights with respect to the determinants of detailing elasticity. In particular, unlike AMS (2010), we find a significant interaction effect between geographic region and product life cycle (PLC) stage on detailing elasticity. Specifically, detailing elasticities are highest for products which were in their *early* life cycle stage in Europe, and lowest for products in their late life cycle stage in the USA.[2] After adjusting for the significant methodology-induced biases found in our meta-analysis, we determine that the mean estimate of current-period detailing elasticity is about 0.178. This value can be used as a benchmark to guide researchers and practitioners assessing detailing effectiveness spending levels in various circumstances (geographic and life cycle stage).

The rest of this chapter is organized as follows: First, we describe the scope of our database and meta-analysis; and the selected determinants or independent variables that could affect detailing elasticities that we investigate. Then we present our meta-analytic model and methodology; describe our results and ensuing empirical generalizations; and discuss their managerial implications.

The determinants or drivers of detailing elasticity that we investigate include variables falling in three classes: (a) *market type characteristics*, (b) *dataset characteristics*, and (c) *researcher's choices with respect to model specifications*. Additionally, we investigate the interactive effects of these covariates and two market-type factors, geographic region and PLC stage. Subsequently, we obtain the methodology bias-corrected distribution of detailing elasticities. We then discuss the implications of our results for pharma sales force managers and researchers. We conclude with some suggestions for further research.

18.2 Database Scope

We restrict detailing elasticity measurements from past studies included in this meta-analysis to those that are (1) based on *ratio-scaled objective* (e.g., Rich et al. 1999) measures of selling *output* (e.g., sales volume in units or dollars, number of prescriptions), and input *effort*, e.g., "size" measures such as the total number of salespeople or dollar expenditures on detailing, "frequency" measures such as the number of sales calls or details, and "time" measures such as number of selling hours; (2) derived from objective, econometric data and not subjective decision calculus data (e.g., Lodish et al. 1988); (3) firm-level rather than industry-level response function parameter estimates; (4) current-period measures, either directly provided or derivable using author-reported lagged effects; and (5) unambiguously reported or derivable from the estimated coefficients and/or other relevant data reported in the study.

[2] According to Grabowski (2002), the representative new drug introduction in the United States during the mid-1990s, had an average effective (post-launch) patent life (EPL) of approximately 12 years, similar to reported average EPL of drugs launched in Europe (e.g., Andersson and Hertzman 1993). Based on these average EPLs, we consider "early" lifecycle stage as 5 years or less since launch of a product on the market.

18.2.1 Database Description

Our database spans the last 5 decades, and the USA and Europe (Belgium, France, Germany, Italy, Netherlands, Portugal, United Kingdom) regions, encompassing a wide range of sales-environments. The database (see Table 18.1) includes relevant *papers from* multiple disciplines (marketing, management, operations research, economics, and health economics) as well as industry- and government-based studies. A *paper* is a distinct document offering some *original analysis* finding/s by its author/s—this rules out duplications or redundant papers in the database (see, e.g., Wood 2008). Collectively, these papers provide analyses of many *distinct datasets*, each containing information about sales response to detailing effort in some specific market setting. If a *different estimation technique/model is applied to the same dataset* in either the same paper (e.g., Berndt et al. 1995) or different papers (e.g., Berndt et al. 2003), we treat the resulting elasticity observations as multiple *distinct measurements from one dataset*. Conversely, one paper may provide analyses of multiple *distinct datasets*, contributing one (or more) distinct detailing elasticity estimates from each dataset (e.g., Narayanan et al. 2004). Applying these definitions, our database includes 48 *research papers* that use 44 *distinct datasets*, providing a total of 373 detailing elasticity *measurements* (see Table 18.1).

18.3 Methodology

18.3.1 Database Compilation

We compiled our database using a variety of sources as in AMS (2010). These include: (1) All *relevant sales force models review articles*, e.g., Albers and Mantrala (2008), Vandenbosch and Weinberg (1993) and references they cite; (2) a number of *computerized publication search* services such as *Proquest from ABI/Inform*, *Business Source Premier from EBSCO*, *Kluwer Online*); (3) all relevant *working papers* posted on the Web, e.g., those on *Social Science Research Network*; (4) reports of relevant *consulting engagements* from prominent scholars; (5) archives of technical reports and/or working papers of the *Marketing Science Institute*, the *Institute for the Study of Business Markets*, and leading business schools; and (6) responses to a request for unpublished works posted on the marketing network ELMAR@ama.org. Inclusion of unpublished works helps avoid publication bias that would reduce measurement variability in the meta-analysis (e.g., Assmus et al. 1984, p. 66; Andrews and Franke 1991, p. 83; Tellis 1988, p. 340; Rust et al. 1990).

Table 18.1 Detailing elasticities included in the analysis

Paper no.	Authors	Year	Publication outlet	Volume (issue), pages
1	Albers Report 1	2001	Research Report (Unpublished Paper)	NA
2	Albers Report 2	1998	Research Report (Unpublished Paper)	NA
3	Albers Report 3	2004	Research Report (Unpublished Paper)	NA
4	Albers Report 4	2006	Research Report (Unpublished Paper)	NA
5	Albers Report 5	2006	Research Report (Unpublished Paper)	NA
6	Albers Report 6	2006	Research Report (Unpublished Paper)	NA
7	Albers Report 7	2005	Research Report (Unpublished Paper)	NA
8	Arora	1979	Journal of Advertising Research	19(3), 57–62
9	Azoulay	2002	Journal of Economics & Management Strategy	11(4), 551–594
10	Berndt, Bui, Lucking and Urban	2001	The Economics of New Products	58, 277–322
11	Berndt, Bui, Reiley, and Urban	1995	American Economic Review Papers and Proceedings	85(2), 100–105
12	Berndt, Pindyck, and Azoulay	2003	Journal of Industrial Economics	51(2), 243–270
13	Bhatia and Wang	2011	International Journal of Research in Marketing	28(1), 51–61
14	Bhatia, Hansen, and Krishnamurthi	2006	Technical Report (ISBM Report)	6-May
15	Ching and Ishihara	2008	Working Paper	NA
16	Chintagunta and Desiraju	2005	Marketing Science	24(1), 67–80
17	Dhaval Dave, Henry Saffer	2010	NBER Working Paper	NA
18	Dong, Chintagunta and Manchanda	2010	Working Paper	NA
19	Dong, Manchanda, and Chintagunta	2009	Journal of Marketing Research	46(2), 207–221
20	Donohue and Berndt	2004	Journal of Public Policy & Marketing	23(2), 115–127
21	Fischer and Albers	2010	Journal of Marketing Research	47(1), 103–114
22	Gonul, Carter	2010	Health Care Management Science	13, 101–111
23	Gonul, Carter, Petrova and Srinivasan	2001	Journal of Marketing	65(3), 79–90
24	Gonzalez, Sismeiro, Dutta, and Stern	2008	Working Paper	NA

(continued)

Table 18.1 (continued)

Paper no.	Authors	Year	Publication outlet	Volume (issue), pages
25	Iizuka and Jin	2007	Journal of Industrial Economics	45(4), 771–780
26	Janakiraman, Dutta, Siesmeiro, and Stern	2008	Management Science	54(6), 1080–1093
27	Janakiraman, Siesmeiro, and Dutta	2009	Journal of Marketing Research	46(4), 467–481
28	King	2002	Working Paper	NA
29	Kolsarici, Vakratsas	2010	Journal of Marketing Research	47(4), 1078–1089
30	Lim, Kirikoshi, Okano	2008	International Journal of Pharmaceutical and Healthcare Marketing	2(3), 195–215
31	Manchanda and Chintagunta	2004	Marketing Letters	15(2–3), 129–145
32	Manchanda, Xie, and Youn	2008	Marketing Science	27(6), 961–976.
33	Mizik and Jacobson	2004	Management Science	50(12), 1704–1715
34	Montoya, Netzer, and Jedidi	2008	Working Paper	NA
35	Montoya, Netzer, and Jedidi	2010	Marketing Science	29(5), 909–924
36	Nair, Manchanda, and Bhatia	2006	Working Paper	NA
37	Narayanan, Desiraju, and Chintagunta	2004	Journal of Marketing	68(3), 90–105
38	Narayanan, Manchanda, and Chintagunta	2005	Journal of Marketing Research	42(3), 278–290
39	Neslin	2001	Working Paper	NA
40	Osinga, Leeflang, Wieringa	2010	Journal of Marketing Research	46, 173–185
41	Richard and Van Horn	2004	International Journal o f Industrial Organization	22, 523–540
42	Rizzo	1999	Journal of Law and Economics	42(1), 89–116
43	Rosenthal, Berndt, Donohue, Epstein, and Frank	2003	Frontiers in Health Policy Research	6(1), 1–26
44	Shankar	1997	Marketing Science	16(3), 271–293
45	Skiera and Albers	1998	Journal of Personal Selling and Sales Management	28(2), 145–154
46	Venkataraman and Stremersch	2008	Management Science	53(11), 1688–1701
47	Wittink	2002	Working Paper	NA
48	Wosinska	2002	Working Paper	NA

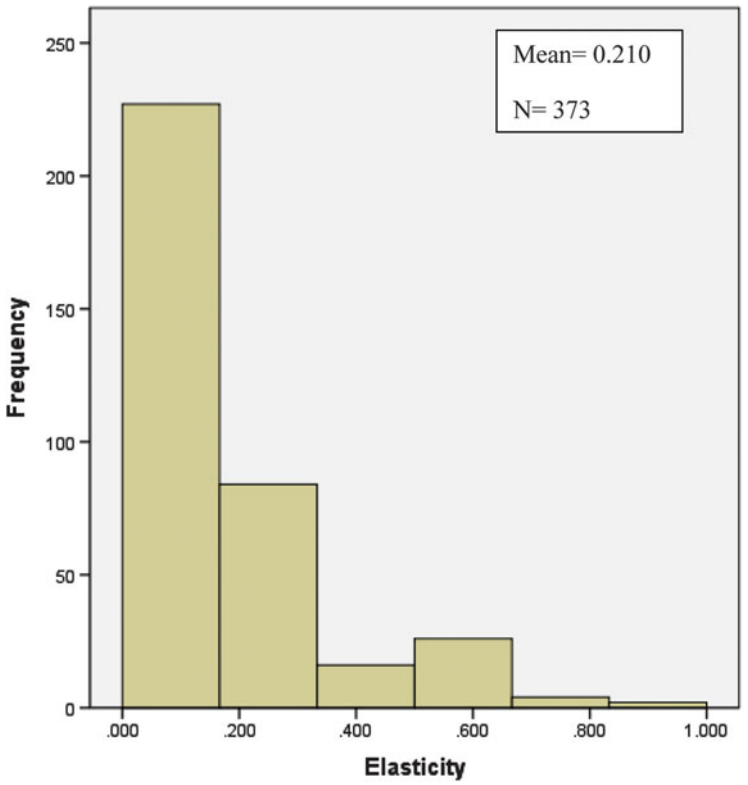

Fig. 18.1 Histogram

18.3.2 Data Coding

Two judges who were not members of the meta-analysis research team separately coded all the observations in our database on the selected independent variables. Agreement between the two judges was greater than 90 % and a third judge amicably resolved inconsistencies.

18.3.3 Frequency Distribution of Observed Detailing Elasticities

Figure 18.1 displays the overall frequency distribution of the 373 current-period personal selling elasticity estimates in our database. As expected, we see that 99 %

Table 18.2 List of results

		Geographic setting	
		Europe	USA
Panel A: Sample size by cell			
Stage in product life cycle	Late	32	206
	Early	74	61
Panel B: Detailing elasticity means unadjusted for biases (grand mean = 0.210)			
Stage in product life cycle	Late	0.169	0.140
	Early	0.410	0.230

of these estimates are positive. We find the "raw" mean in our database (unadjusted for any methodology-induced biases) to be 0.21, compared to 0.245 in AMS (2010).

In keeping with our research questions, we also present the means of the elasticities by PLC stage and geographic setting. Panels A and B of Table 18.2 list some key descriptive data of the subsamples. We have 32 elasticities from the late stages of the PLC from Europe, and 206 from the late stage of the PLC from USA.[3] These elasticities have a mean of 0.17 and 0.14 respectively. Also, we have 74 elasticities from the early stages of the PLC from Europe, and 61 from the early stage of the PLC from USA. These elasticities have means of 0.41 and 0.23 respectively.

Note that the means presented in Panel B of Table 18.2 are unadjusted for any methodology-induced biases (e.g., the elasticities could have stemmed from a model that omitted other marketing-mix variables, thereby biasing the estimate). Therefore, to obtain a better understanding of the means by each category, we first need to identify any systematic biases that might be driving these means. For this purpose, we build a meta-analytic model that can help identify the factors that systematically explain upward or downward movement in the elasticities. Next, we present the independent variables considered in our analysis.

18.3.4 Independent Variables (Determinants) and Coding

We group our independent variables into three categories: (1) variables capturing *market characteristics* (stage in the product life cycle, geographic setting), (2) variables capturing *dataset characteristics* (years spanned by a dataset, absolute or relative form of sales output measure, and temporal aggregation of the data) and (3) variables capturing *researcher choices with respect to response model specification & estimation* (consideration of dynamics, capturing endogeneity and heterogeneity in sales response, including other marketing-mix instruments such as promotions

[3] Se Footnote 2 for our definition of "early" vs. "late" PLC stages; the coding of elasticity measurements into early or late PLC stage categories is described below.

and advertising in the response model, and inclusion of interactions between the marketing-mix instruments in the response model). For brevity, we will explain the operationalization of the variables along with their effect on the detailing elasticity in the next section. The selection of these variables was guided by AMS (2010) and earlier meta-analyses in marketing.

18.3.5 Estimation Model and Procedure

We model detailing elasticity as a linear function of the selected independent variables (determinants) like AMS (2010). We note there are two levels of variation in our database, i.e., the 373 personal selling elasticity measurements come from different datasets, and the number of elasticity measurements per dataset varies. Measurements within a dataset share values on several determinants while they may differ on other determinants. Since determinants at the measurement level (lower level) and dataset level (higher level) contribute to variation in personal selling elasticity, but some measurements are not independent within a study, there is a nested error structure that must be accounted for. Similar to AMS, we use hierarchical linear model (HLM) estimation (e.g., Bijmolt and Pieters (2001, p. 159) and Raudenbush and Bryk (1992, p. 440)) in our study. Interested readers are referred to Bijmolt and Pieters (2001) for more details about HLM.

We performed several checks to ensure the robustness of our results. First, as there is no direct diagnostic for multicollinearity in hierarchical linear modeling, we checked the regression condition index that has a value of 5 which indicates low multicollinearity. Second, we tested for various plausible interaction effects amongst all our independent variables and the two focal market characteristics, i.e., stage in the PLC and geographic setting. Since introducing two interaction effects (one with stage in the PLC, and one with geographic setting) along with the main effect of each of the independent variables would introduce severe multicollinearity, we tested the interaction effects one at a time and retained only the significant ones. Third, we tested for the effects of several other covariates namely, *number of observations in the dataset*, *whether or not competitive marketing efforts were explicitly modeled*, *interactions between temporal aggregation and the inclusion of lagged effects*, and whether *inputs and outputs were measured in monetary* (vs. *physical*) *units*. We did not find any of these effects to be significant and hence excluded these from our final model.

18.4 Estimation Results

The HLM model estimates are reported in Table 18.3. As highlighted here as well as in the last column of Table 18.3, we found 12 significant effects. The overall fit of our model to the data ($R^2 = 0.308$) is satisfactory considering that we are using our model for descriptive purposes, and also higher than the model fits obtained in

Table 18.3 Estimation results

Variable	Estimate	Std. error	*p*-Value
(A) Market type			
Stage in product life cycle			
Late			
Early	0.742	0.123	<0.0001
Geographic setting			
Europe			
USA	0.019	0.074	0.795
Early stage X USA	–0.285	0.086	0.001
(B) Dataset characteristics			
Trend			
Year of data collection (mean-centered)	0.002	0.004	0.567
Early stage X year of data collection	–0.023	0.008	0.003
Sales output measure			
Absolute			
Relative	0.073	0.063	0.251
Temporal aggregation			
Monthly			
Quarterly	0.373	0.138	0.010
USA X quarterly	–0.344	0.145	0.018
Yearly	–0.071	0.175	0.685
(C) Researcher choices			
Consideration of dynamics			
No lagged effects			
Independent variable lagged	–0.155	0.055	0.008
Dependent variable lagged	–0.118	0.063	0.069
Endogeneity in sales response			
Not accounted for			
Accounted for	0.047	0.056	0.399
Early stage X accounted for	–0.193	0.101	0.057
Heterogeneity in sales response			
Not accounted for			
Accounted for	–0.062	0.064	0.343
Promotions variable			
Omitted			
Included	0.097	0.060	0.105
Early stage X included	–0.315	0.086	0.001
Advertising variable			
Omitted			
Included	–0.106	0.059	0.073
Interaction effects			
Omitted			
Included	0.196	0.056	0.001

earlier meta-analyses (e.g., 0.16 in Bijmolt et al. 2005, and 0.29 in Tellis 1988). These results are summarized and discussed below.

The results with respect to the two market-type characteristics are as follows.

Product life cycle (*PLC*) *stage*. A key advantage of detailing is face-to-face exchange between physician and sales rep that can address the former's questions and objections. This advantage tends to be more pronounced in the case of newer pharma products. For example, Narayanan et al. (2005) found that sales calls for new pharmaceuticals are more *informative and persuasive*, resulting in higher average personal selling elasticity values in the launch phase than those in the later stages of the life cycle.

In our analysis, we dummy code the PLC stage variable as being 1 if the product is in the early stage of the PLC and 0 if it is in the late stage of the PLC. Coders were instructed to look for explicit statements in the paper about whether a product was in the early or late stage of the PLC. If such statements were not provided, the coders used a rubric where they inferred the stage of the PLC based on the date of launch of the drug. If detailing elasticities were estimated using data which were predominantly generated over a time horizon less than 5 years after date of launch of the product (the date of launch is generally provided in the paper), the PLC stage was coded as early; otherwise coded as late (see also Footnote 2). Table 18.3 indicates a shift in setting from late to early stage has a significant main effect ($b = 0.742$, $p < 0.01$) as well as interaction effects with several other variables on estimated detailing elasticity. Therefore, all of these effects must be interpreted together to assess the overall effect of a shift in the market setting from late to early stage. We accomplish this by calculating the difference in detailing elasticities between early and late stages of the product life cycle, holding all other moderators at their mean value. We find that, holding all moderators at their average level, detailing elasticities at the early stage are higher than those in the late stage by *0.125*.

Geographic setting—USA vs. *Europe*. In pharma promotion, Europe is more heavily reliant on information provided through sales forces than in the USA where direct-to-consumer *advertising* is allowed (Fischer and Albers 2010). There is also more saturated sales force coverage in the US pharmaceutical market, e.g., Chintagunta and Desiraju (2005). Therefore, we expected that detailing elasticities will be lower in US settings than in European settings.

Accordingly, we dummy code the geographic setting variable as being 1 if the elasticity stemmed from the USA and 0 if the elasticity pertained to Europe. As we see in Table 18.3, we found no main effect for geographic setting, i.e., detailing elasticities between Europe and USA do not appear to be different ($b = 0.019$, not significant (ns)). However, we found a *significant interaction* between stage of the PLC and geographic setting. Since we found other interaction effects, we calculated the difference in detailing elasticities between the USA and Europe, holding all other moderators at their mean value. We find that detailing elasticities in Europe are higher than those in the USA by *0.21*.

One possible reason for this is the difference in the regulatory profiles of countries in Europe vs. the USA. According to a classification based on five regulatory

dimensions offered by Stremersch and Lemmens (2009), European pharma markets, especially France, Italy, Spain, and UK are far more regulated than the USA. Greater regulation implies that persuading physicians to prescribe a new drug is a much more complex or difficult sale in Europe than in the USA. Buyers will need more answers and convincing to try something new when their actions are restricted by regulation. In such circumstances requiring more information provision, personal selling tends to be the most effective marketing instrument. An indicator of this is the relative length of detailing calls in the USA vs. Europe. In the USA, detailing visits last on average between 3 and 4 min; in Europe (UK) around 9 min (Heutschi et al. 2003), suggesting that European physicians find detailing visits to be relatively more valuable than US physicians.

The next three findings pertain to *dataset characteristics*.

Year of data collection. As stated in the introduction, there appears to be a trend of growing resistance of physicians to detailing as pharma product lines mature and there is more oversight of prescription decisions by managed care organizations. Therefore, we expect that within the span of our database, detailing elasticities will decrease over the years of data collection. Towards this end, we operationalized year of data collection as mean year in the panel from which elasticities were estimated. Again, we found no main effect for this argument ($b = 0.002$, ns).

However, we found a significant interaction effect between the year of data collection and stage in the PLC. Specifically, we found that detailing elasticities in the early stage of the PLC significantly decline over the years of data collection ($b = -0.023$, $p < 0.01$). One possible reason is that since it became permissible in 1997, DTC advertising has been frequently used in addition to detailing in early phases of product life cycles in the USA (e.g., Donohue et al. 2007; Liang and Mackey 2011) and recent econometric models that include DTC advertising in addition to detailing have found such advertising has a significant positive effect on total class sales (e.g., Donohue and Berndt 2004), as well as a main effect on brand share (Narayanan et al. 2004). We reason that in the presence of such significant effects of DTC advertising, more recent econometric models involving newer products that include DTC advertising will yield lower detailing elasticities than older models from the pre-DTC era.

Relative vs. *absolute output measure*. Elasticities based on absolute sales measures capture changes in sales due to both primary (market expansion) and secondary (share expansion) changes resulting from varying selling effort (see, e.g., Hagerty et al. 1988). In contrast, share-based elasticities classify only a portion of the market expansion as primary demand (Steenburgh 2007). Accordingly, we expected that detailing elasticities from models using relative (share) output measures will be smaller than those from models using absolute output measures.

In our analysis, we dummy coded the output measure variable as 1 if measured in relative terms and 0 if measured in absolute terms. From the main effect in Table 18.3, we found no evidence that detailing elasticities are higher in settings that use relative output measures than those that use absolute measures ($b = 0.073$, ns).

Temporal aggregation of data. Previous meta-analyses (e.g., Tellis 1988; Assmus et al. 1984; Bijmolt et al. 2005) have suggested that estimates of marketing

elasticities can vary due to differences in data measurement intervals. In the detailing context, sales cycles are fairly short. In such settings, short-term temporal variations in both selling effort and resulting sales can occur in part due to the prevalent use of nonlinear incentive mechanisms with periodic (monthly or quarterly) incentive payouts (e.g., Zoltners et al. 2006, p. 222; Mantrala et al. 1994). Similar to Tellis (1988), we expected that short-term temporal variation will not be picked up in annual data as much as by shorter interval data.

We dummy coded two variables to capture temporal aggregation. We coded one variable to be 1 when the temporal aggregation was quarterly and 0 otherwise, and a second dummy variable to be 1 when the temporal aggregation was yearly and 0 otherwise. We found a main effect for the quarterly dummy as reported in Table 18.3 ($b = 0.373$, $p < 0.01$). Also, we found a weak significant two-way interaction between the quarterly dummy variable and the geographic setting variable ($b = -0.344$, $p < 0.10$). Since we found other interaction effects, we calculated the difference in detailing elasticities between monthly and quarterly data, holding all other moderators at their mean value. We find that, holding all moderators at their average level, quarterly detailing elasticities are lower than monthly detailing elasticities by *0.34*. Also, we found no significant difference between elasticities estimated with yearly data and monthly data ($b = 0.071$, ns).

The next six findings are with respect to *researcher's model specification choices*.

Inclusion or not of lagged output effects and lagged input effects. Detailing effort has significant carryover effects. For example, based on sales force studies at 50 pharmaceutical companies, Sinha and Zoltners (2001) report that the aggregate sales carryover from selling effort in 1 year is 75, 80 % the next year, 62–78 % the year after, and 52–70 % in the fourth year. Thus, the effectiveness of current-period detailing would be overstated if lagged leads (lagged output effects) or past effort (lagged input effects) are omitted.

Accordingly, we employ two dummy variables for capturing the inclusion of lagged input and output effects in a past study's model specification: the first of these has a value 1 if lagged input was included, 0 otherwise; the second has a value 1 if lagged output was included, 0 otherwise. As can be seen in Table 18.3, we found that detailing elasticities from response models that include lagged input and/or lagged output effects were smaller than those from response models that exclude these effects by 0.155 ($p < 0.05$) and 0.118 ($p < 0.05$) respectively.

Accounting for endogeneity of detailing effort. Endogeneity refers to a correlation between the input variable and the error term of the estimated response model which, for example, arises if management allocates sales effort strategically or uses rules such as effort allocations proportional to past sales. Some researchers have accounted for endogeneity in model estimation, e.g., via the use of instrumental variables (e.g., Chintagunta and Desiraju 2005), while many have not. If an input such as detailing is treated as exogenous when it is indeed endogenous, then both theoretical analyses and empirical evidence show its elasticity may be overestimated (e.g., Manchanda et al. 2004, p. 472). Therefore, we expected that detailing elasticities from models that account for endogeneity will be lower than those from models that do not account for endogeneity.

We use a dummy coded variable to capture the inclusion or not of endogeneity in response models (1 if included, 0 if not) and investigated its effects in our meta-analytic model. The results shown in Table 18.3 indicate that while the main effect is not significant ($b = 0.047$, ns), the effect of the interaction between stage of PLC and the inclusion of endogeneity was negative and significant ($b = -0.193$, $p < 0.10$). Since we found other interaction effects, we calculated the difference in detailing elasticities between models which account for endogeneity vs. those that do not. We find that, holding all moderators at their average level, models that account for endogeneity report detailing elasticities to be lower by 0.045. That is, when endogeneity is accounted for in response models involving products in the early stage of the PLC, detailing elasticities tend to be significantly lower.

18.4.1 Accounting for Heterogeneity in Response to Detailing

As several studies have shown over the last decade, physician response to detailing is likely to be heterogeneous due to both observable and unobservable factors (e.g., Manchanda and Chintagunta 2004; Skiera and Albers 1998). However, a number of past studies do not allow for heterogeneity in detailing response parameter estimates. To assess the effect of not accounting for heterogeneity in response among past studies in our database, we dummy coded a variable for the inclusion of heterogeneity in response to detailing effort in the model (1 if included, 0 if not) and incorporated this in our meta-analysis. The result shown in Table 18.2 indicates no significant differences in elasticity parameter estimates from models that account for heterogeneity in sales response vs. those that do not ($b = -0.062$, ns).

18.4.2 Variables Whose Omission Could Bias Detailing Elasticity Estimates

If the response model specification in a particular study setting omits a *relevant and plausible influencer* of sales (e.g., advertising, promotions) then the resultant personal selling elasticity estimate can be biased, although any predictions with respect to the direction of the bias may be unfounded (e.g., Clarke 2005). Therefore, we examined if there are any systematic biases in detailing elasticity observations due to omissions of promotions or advertising (either journal or DTC) from the original models.

Accordingly, we dummy coded two variables for the inclusion of promotions (1 if included, 0 if not) and advertising (1 if included, 0 if not) in the response model. For promotions, the main effect in Table 18.2 shows no significant difference in detailing elasticities for models that include promotions in the response model vs. those that do not ($b = 0.097$, ns). However, we find a significant interaction between the promotions variable and the stage of the PLC ($b = 0.315$, $p < 0.01$). Since we found other interaction effects, we calculated the difference in detailing

elasticities between models which account for promotions vs. those that do not. We find that, holding all moderators and interaction effects at their average level, model that include promotions report detailing elasticities to be lower by *0.16*. This could be because the most common form of promotion, namely, free drug samples, are heavily used in the introductory and early stages of prescription drug life cycles (e.g., Joseph and Mantrala 2009), and once the drug has been launched, reps' detailing may be adding little value beyond (increasing) sample drop-offs in the eyes of physicians especially when they are in the "trying out" mode (see also Manchanda and Chintagunta 2004, p. 139).

As regards detailing elasticity estimates after accounting for advertising, the result shown in Table 18.2 indicates pharma sales response models that include advertising result in detailing elasticities that are on average lower by 0.106 than those from models that exclude advertising ($b = -0.106$, $p < 0.05$).

Inclusion of interactions of detailing with other marketing communication variables: Physician prescriptions can be affected by interactions of detailing and other marketing communication variables such as journal advertising (e.g., Narayanan et al. 2004). Since such interactions usually have positive effects, excluding them from a model could result in a deflated estimate of detailing elasticity. This is because the marginal effect of detailing on sales will be underestimated as it will not include the coefficient pertaining to the interaction term. Thus we expect that detailing elasticities from response models that include interactions between detailing and other marketing communication variables will be higher than those from response models that exclude such interaction effects.

We dummy coded a variable for the interactions of detailing with other marketing communication variables (1 if included, 0 if not). The result shown in Table 18.3 indicates models that include such interactions result in detailing elasticities that are higher than models that do not ($b = -0.196$, $p < 0.01$).

18.4.3 Research Methodology Bias-Corrected Benchmark Elasticity

Following the lead of AMS (2010) and Tellis (1988, p. 337), a practically useful generalized estimate to draw from this meta-analysis is the mean of detailing elasticities *after correcting each for the statistically significant biases introduced by researchers' methodology choices*. Specifically, we consider that the "unbiased" reference response model is one that includes promotions, involves a product in the early stage of the PLC, includes advertising, corrects for endogeneity especially if the geographic setting is USA, and includes lagged effects. Correcting each of the 373 observed elasticities for their deviations from the above reference values of the significant independent variables, and taking the average of the corrected estimates, we obtain the mean corrected elasticity of *0.178*, *compared to 0.227 in AMS* (2010). As we discuss in the next section, this market-based benchmark value of detailing elasticity can serve as a useful input for managers, and sales researchers.

Table 18.4 Adjusted elasticity and optimal detailing spend

		Geographic setting	
		Europe	USA
Panel A: Detailing elasticity means adjusted for biases (grand mean = 0.178)			
Stage in product life cycle	Late	0.155	0.101
	Early	0.403	0.188
Panel B: Optimal detailing spend as percentage of sales for different values of detailing elasticity			
Stage in product life cycle	Late	11.2 %	7.2 %
	Early	29.0 %	13.5 %

Towards this end, we separated the bias-corrected elasticities estimated in an early stage of the PLC from those estimated in the late stage of the PLC and also separated elasticities estimated based on data in the USA vs. Europe. Panel A of Table 18.4 lists some key descriptive data of the subsamples. For the 32 elasticities from the late stage of the PLC from Europe, and the 206 elasticities from the late stage of the PLC from USA, we find bias-corrected mean elasticities of 0.155 and 0.101 respectively. Also, for the 74 elasticities from the early stages of the PLC from Europe and 61 from the early stage of the PLC from USA, we find bias-corrected mean elasticities of 0.403 and 0.188 respectively. Thus, the *drop* in detailing elasticity as a drug ages is significantly larger in Europe than in the USA (even though the magnitude of this elasticity remains higher than in the USA over both stages of the drug's patent-protected life.) It appears that European physicians are more responsive to information provided by detailing in the drug's introductory phase than US physicians—perhaps due to more onerous regulations on other forms of new product promotion and the ban on DTC advertising. From this relatively higher level, the falloff in detailing elasticity as the product matures appears much sharper in Europe than in the USA as the perceived information value of continued detailing declines in both regions.

18.5 Discussion and Conclusions

18.5.1 Normative Implications of Meta-analysis

In this section, we illustrate and discuss the implications of our meta-analytic findings for optimal detailing to sales ratios on average, by PLC stage and geographic region, and relative to other elements of the pharma promotion mix. For this purpose, we recall the Dorfman-Steiner (D-S) (1954) theorem that states the profit-maximizing level of detailing effort (assuming other marketing efforts such as advertising are held constant) for a monopoly is that at which the marginal revenue product of personal selling spending is equal to the price elasticity. The D-S theorem also establishes the condition that when price and detailing are set optimally, the absolute value of the demand elasticity is equal to the inverse of the monopoly markup (see, e.g., Leeflang et al. 2000, p. 154). Thus, the D-S theorem implies the following conditions hold at optimality:

$$(D_S / R) = -(D_E / P_E) = mD_E, \tag{18.1}$$

where D_S denotes personal selling (detailing) spending; D_E is the detailing elasticity; R *d*enotes sales revenues; P_E represents the price elasticity, and m is the gross margin (price less cost of goods sold expressed as a fraction of price). We apply this condition to obtain some normative implications.

What is the benchmark optimal detailing spend to sales ratio? Following (18.1), the meta-analytic estimate of detailing elasticity can be employed to answer this question given some estimate of the mean price elasticity or the average gross margin percentage. Over the years, various reports have indicated that makers of patent-protected, or single-source brand-name drugs typically enjoy gross margins greater than 60 % (e.g., Scherer 2007). In *Pharmaceutical Executive*'*s* Tenth Annual Audit, Trombetta (2011) reports that the average gross margin of the top 23 publicly traded drug companies (by sales revenue) for 2010 was about 72 % which is down from the mean gross margin estimate of about 78 % for the top 20 pharma and biotech companies in 2008 offered by analysts of Zacks Investment Group in March 2009.[4]

Consider a typical monopoly drug today priced at a gross margin of 72 %. If the maker of this drug is pricing optimally then (18.1) implies the corresponding price elasticity is about −1.39. Employing this illustrative mean price elasticity estimate of −1.39, and our overall bias-corrected estimate of 0.178 for detailing elasticity, the D-S theorem condition implies the optimal percentage of detailing expenditures to total revenues is about 13 %. In contrast, assuming the same price elasticity, the bias-corrected estimate of short-term pharma detailing elasticity of about 0.227 derived from AMS (2010) implies a higher optimal detailing to sales percentage of about 16 %. Thus, the difference of about 0.05 between the current and AMS (2010) studies' meta-analytic estimates of detailing elasticity is significant in that it implies a significant difference in the corresponding optimal detailing to sales percentages. Naturally, the magnitude of this optimal ratio decreases as the detailing elasticity decreases. Thus, given the fixed estimate of price elasticity, our meta-analytic mean estimate of detailing elasticity provides a benchmark detailing to sales ratio for companies to assess the optimality of their overall detailing expenditure, i.e., it serves as a "starting point for optimization" (Farley and Lehmann 1994).[5]

However, as stated at the outset, the industry has been significantly cutting back on detailing since 2007 (e.g., Berenson 2006; Hensley 2007). For example, the

[4] http://www.zacks.com/stock/news/17942/Pharma+Wary+of+Healthcare+Reform

[5] In this elasticity-based analysis, "detailing spending" properly includes all costs that vary as the units of detailing effort vary, e.g., reps' compensation, cost of transportation, preparation time, and expenses but not necessarily the costs of area and regional managers, training etc. as in the CAM Group measure (see Footnote 1). Thus, we expect the detailing spending measure will include a few more cost items than the IMS measure but not as many as the CAM measure. A reasonable compromise appears to be to use the SDI Promotional Audits measure of detailing spending as utilized by the Congressional Budget Office (Campbell 2009). Unfortunately, we have been unsuccessful so far in finding the precise definition of the SDI detailing spending metric and if and how it differs from the metric used by IMS now that the latter has acquired SDI.

December 2009 Congressional Budget Office Report (Campbell 2009) indicates that overall spending on detailing by US companies was about 12 billion dollars or about 6.3 % of 2008 sales of about $189 billion in the USA. This contrasts with previous research by Novartis cited by the Eularis consulting company (www.Eularis.com) that found the average detailing to sales percentage in 2006 was about 10 %, implying a significant reduction in detailing emphasis by US companies between 2006 and 2009. Further, according to *MM&M*'s 2011 Pharma Report (Iskowitz and Arnold 2011) the average detailing spending to sales ratio of the top six US pharma companies' in 2010 was less than 5 %. As illustrated below, our detailing elasticity meta-analysis suggests this trend of detailing cutbacks in the USA is consistent with the aging of product portfolios, i.e., increasing preponderance of late stage pharmaceutical products with reduced detailing effectiveness.

Optimal detailing emphasis by PLC stage (*early* vs. *late*) *and geographic region* (*US* vs. *Europe*). As already noted, Table 18.4 panel A displays our bias-corrected estimates of mean detailing elasticity for Early and Late Stage patent-protected pharmaceuticals in the USA and Europe. Continuing with the assumption of a mean price elasticity of −1.39 over the entire patent-protected life of the drug, Table 18.4 panel B indicates the corresponding optimal detailing spending to sales percentages in the four geographic region x PLC stage settings.

Interestingly, in the USA, the optimal detailing to sales ratio *for late stage products* is only *about 54 % of the optimal ratio for early stage products*. The difference is even starker in Europe where the optimal detailing to sales ratio for late stage products is only about 38.5 % of that for early stage products. Thus, in both regions, based on our meta-analysis finding of a lower mean detailing elasticity for late life cycle stage products, we see that the detailing emphasis in the pharmaceutical promotion mix should decrease as products mature. (For more insights into dynamically optimal resource allocation strategies in the presence of time-varying marketing effectiveness parameters see Fischer et al. 2011; Raman et al. 2011).

Next, comparing the US and European ratios with each other, we see that the optimal detailing to sales ratio in Europe for early stage products is more than twice the corresponding ratio in the US; while the optimal ratio in Europe for late stage products is about 35 % higher than that in the USA. This implies that multinational pharma companies should place a higher emphasis on detailing in promoting products in Europe than in the USA over their product life cycles, especially in the early stage of the product's life. More specifically, if gross margins and current sales are equal across both territories, deployment of more selling efforts in European than in US markets would be desirable, e.g., Skiera and Albers (1998, p. 213). However, as products age, a more drastic reduction in the emphasis on detailing is called for in Europe than in the USA, although the emphasis level (detailing to sales ratio) should remain higher than in the USA. As we have argued earlier, the ban on the use of DTC advertising as well as tighter regulations and restrictions on pharma promotion tactics in Europe are likely reasons underlying the differences in US and Europe optimal detailing to sales ratios shown in Table 18.4 panel B.

Lastly, Table 18.4 panel B indicates the optimal detailing to sales percentage for late stage products in the USA is about 7.3 % based on their mean bias-corrected detailing elasticity of 0.101 from our meta-analysis, and the assumed price elasticity of about −1.39 derived from Trombetta's (2011) audit of the top 23 publicly traded companies. Now suppose the average price elasticity magnitude were actually higher, say 1.67 instead of 1.4 across all companies. This implies a gross margin of about 60 % which is quite common (e.g., Scherer 2007) and a likely scenario for a majority of "me-too" products in an era of greater insurer pressure on prices. Then, the optimal detailing spending to sales ratio for late stage products in the USA would be as low as 6 %. Notably, the observed industry-wide detailing to sales percentage of 6.3 % in the Campbell (2009) report falls within this range of plausible optimal detailing to sales ratios for late stage products derived from their mean detailing elasticity provided by our meta-analysis. We conclude that reported cutbacks in US pharma companies' detailing spending are very consistent with the goal of optimizing detailing spend in the face of aging product portfolios.

Next, we illustrate the implications of our detailing meta-analysis results for pharma promotion mix spending allocations—specifically allocations between detailing, journal and other direct-to-physician (DTP) advertising, and DTC advertising.

Optimal detailing vs. *journal and DTC advertising*: The D-S (1954) theorem for marketing-mix optimization states that allocations of a given budget B to different promotion vehicles should be made proportionate to their elasticities. Considering, e.g., three vehicles, namely, detailing, journal advertising, and DTC advertising, the D-S theorem implies $D_S = (D_E/(D_E + A_E + C_E))B$; $A_S = (A_E/(D_E + A_E + C_E))B$; $C_S = B - (D_S + A_S)$ where D_S, A_S, and C_S denote detailing, journal advertising, and DTC advertising expenditures respectively, and D_E, A_E, *and* C_E are the respective elasticities. In a recent meta-analysis of pharma promotion elasticities, Kremer et al. (2008, p. 243) report an average DTP (journal advertising) elasticity of 0.123 (which is consistent with the finding of a mean short-term advertising elasticity of 0.12 for all products categories by Sethuraman et al. 2011). Kremer et al. (2008, p. 243) also report a mean DTC advertising elasticity of 0.073. Taking then A_E=0.*123*; C_E=0.073, and our estimate of pharma detailing elasticity D_E=0.178, the optimal allocations of a given budget to detailing, journal advertising, and DTC advertising should be in the ratio of 0.47:0.33:0.2, i.e., detailing spending should be about 2.35 times total spending on DTC advertising; and about 1.42 times other DTP (journal) advertising. According to Campbell (2009), detailing spending was in fact about 2.5 times as much as DTC advertising spending in 2008 so the industry in the USA was close to the optimal detailing to DTC advertising ratio that year. However, the industry has never spent as much on journal advertising as the optimal ratio of detailing to journal advertising expenditures suggests. Indeed journal advertising spending in the US context has been less than $0.5B over the last few years. This may, however, change as new technology-enabled forms of DTP advertising emerge even as traditional detailing effectiveness declines. Investigating the effectiveness of DTP advertising via new media and the implications for pharma promotion mix allocations is undoubtedly a rich and important arena for future research. We speculate that these studies will point to a much more balanced allocation between

detailing and other forms of DTP promotion in the future. Indeed, our results in Table 18.4 panel A indicate a mean current-period detailing elasticity for late stage pharma products in the USA of 0.101 that is already much lower than the mean advertising elasticity benchmark of 0.12 for all products reported by Sethuraman et al. (2011). Correspondingly, we determine that the optimal detailing spending to sales ratio for late stage pharmaceutical products in the USA is only about 3.6 % compared to the Sethuraman et al. (2011) estimate of 4.6 % for the optimal ad spend to sales ratio across all product categories.

Summary of key takeaways. The key managerial takeaways from the above analyses are:

1. As detailing elasticity has drastically diminished compared to personal selling effectiveness in general, pharma marketing managers are well-advised to aim for average detailing spending to sales ratios in the region of 6–7 % over pharma product life cycles.
2. However, average detailing elasticity is time-varying, noticeably higher for early stage than late stage products, implying that managers have to be more adept at formulating dynamically optimal detailing strategies involving judicious shifts from higher to lower detailing emphasis as products age (see, e.g., Fischer et al. 2011; Raman et al. 2011).
3. Moreover, average detailing elasticity in Europe over PLCs is higher than in the USA but drops much more sharply as products age. This implies that companies operating in both regions should allocate more resources to detailing (as a percentage of their sales) over a product's life cycle in Europe than in the USA. However, considering the differences in detailing elasticity in the early and late stages between the two regions, the shape of the dynamically optimal detailing policy over the PLC in Europe will not be the same as that in the USA.
4. As detailing loses its effectiveness, especially for late stage products in the USA, pharma marketing managers should find a more balanced allocation between detailing and other forms of DTP advertising, perhaps enabled by new technologies, more rewarding than in the past.

18.5.2 Conclusion

Despite the apparently "gloomy for traditional detailing" takeaways from our research, we are far from suggesting that the end of detailing in the pharma industry is near. Consider that advertising as a marketing variable has thrived despite empirical generalizations of the mean advertising elasticity falling between 0.1 and 0.2 since the first study by Assmus et al. (1984) nearly 30 years ago. In comparison, our finding is that average detailing elasticity is only about 0.178 today (compared to the all-industry mean personal selling elasticity of 0.304 reported by AMS 2101) but is still significantly high for early stage products and in Europe. Thus, while we expect lower albeit more optimal detailing spending (sales force sizes) than the levels around 2005, detailing remains the most potent marketing instrument for

new products, especially in Europe. That is, we see that detailing still has a critical role to play—perhaps somewhat downsized but, more critically, deployed more effectively over product life cycles and across geographic regions. Moreover, as the potential for discovering and marketing big blockbuster products like Lipitor is much lower today than in the past, big pharma's attention is increasingly shifting to the discovery of higher-margin, niche or specialty-driven drugs, e.g., in the disease areas of oncology, multiple sclerosis. that fill an unmet medical need and provide a more personalized approach toward treatment (LaMotta 2010a). The promotion of such products in the future will certainly require more sophisticated communication to specialist physicians and hospital buying centers than in the past—and face-to-face personal selling is likely to remain the best way to provide these communications (see, e.g., Mantrala and Albers 2010).

Additionally, as pharma market potentials of developed markets shrink with thinning new product pipelines, more aggressive generic producer entries, and stiffer managed care oversight, big pharma's attention is increasingly turning to the potential of emerging markets, e.g., the BRICS (Brazil, Russia, India, China, South Africa). The emerging markets are forecast to contribute around 70 % of pharmaceutical industry growth in the next 5 years with branded generics representing approximately 50 % by value in these emerging markets (LaMotta 2010b). Again, this is a "made for detailing" push scenario implying that pharma sales forces are likely to remain key marketing instruments in these markets. In fact, they are likely to grow. For example, Pfizer has been growing its sales forces and manufacturing capabilities in India and China over the last 2 years. The company announced in 2009 that it had entered into licensing agreements with two Indian pharmaceutical companies for off-patent medicines and branded generics. Our findings and insights from this pharma detailing meta-analysis are restricted by the quantity and quality of the detailing response models in our database. They can be enhanced and improved if more studies in more diverse market settings, along with more detailed descriptions of the selling-task, are conducted in the future. Considering the strategic moves being made by the industry summarized above, the need for econometric studies from more diverse settings is urgent to understand how detailing effectiveness will evolve in the new markets being chased by the industry. For the sake of having maximum impact (e.g., Farley et al. 1998) we hope more of these future studies are (a) from European, South American, or Asian settings, (b) use different levels of temporal aggregation, (c) include the critical omitted variables and (d) account for endogeneity in sales response.

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Chapter 19
Marketing Spending Models

Marc Fischer

Abstract To the surprise of many, pharmaceutical firms belong to the biggest spenders on marketing. The marketing spend-to-sales ratio may be as high as 30 %. Expenditures in the USA alone were $10.9 billion in 2009. Hence, there is a strong interest in understanding how effectively this industry spends its marketing money.

The objective of this chapter is to review and synthesize the literature on marketing spending in the pharmaceutical industry. It reviews recent trends in pharmaceutical marketing. It looks at how marketing managers in the pharmaceutical industry actually arrive at spending decisions. The author further discusses models that describe how pharmaceutical demand responds to marketing expenditures. He summarizes findings on the responsiveness and profitability (ROI) of various spending categories.

Another focus of the chapter is on normative applications of marketing spending models. Normative models help finding the right budget across spending categories, customer groups, and products. The discussion covers static and dynamic optimization approaches. The author identifies fields of promising future research from this synthesis of the extant literature.

19.1 Introduction

The pharmaceutical industry is one of the largest and most profitable industries worldwide. Healthcare expenditures represent about 8–15 % of the GDP of most developed countries (see OECD 2011). Expenditures on drugs are an important component of healthcare expenditures. For example, 10 cents of each healthcare

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dollar spent in the USA are on drugs. US prescription drug sales reached a value of US $ 300 billion in 2009. IMS Health predicts these expenditures to grow to US $ 360–390 billion by 2014 (Lundy 2010).

From 1995 to 2002, the pharmaceutical industry was the leading industry in the USA in terms of return on sales. Pharmaceutical firms still ranked third, realizing a return on sales of 19.3 % in 2008 (Lundy 2010). Due to the long, complex, and highly regulated development process, firms needed to invest ca. US $ 1,318 million into a new drug in 2005 (EFPIA 2011). The market success of the new product, however, is uncertain. It depends on several factors, among them the entry order position (e.g., Berndt et al. 1995), perceived drug effectiveness (Venkataraman and Stremersch 2007), etc. As a consequence, marketing becomes crucial in order to maximize revenues over the life cycle of the new product. Since product development, distribution, and pricing are highly regulated across the world, pharmaceutical firms are not as flexible as firms in other industries in using these elements of the marketing mix. A special focus therefore is on communication activities, which spans visits by sales representatives at physicians and pharmacists, advertisements in medical journals, advertisements directed at consumers on TV, radio, and other channels, etc.

Marketing expenditures are high. Pharmaceutical firms spent US $ 10.9 billion detailing and advertising in the USA in 2009 (see Fig. 19.1). Of these expenditures, US $ 4.3 billion was directed at consumers (DTC expenditures) and US $ 6.6 billion at physicians (IMS Health 2010). Given the high level and the importance of pharmaceutical marketing expenditures, managers have a natural interest in understanding and improving the effectiveness of their spending.

19.1.1 Recent Trends in Pharmaceutical Marketing

The practice of pharmaceutical marketing changes over time. The dominant approach during the 1990s and early 2000 was to extend the sales force and intensify detailing activities. As Fig. 19.1 demonstrates detailing expenditures are declining. This evolution reflects a recent trend that pharmaceutical firms turn away from the sales force centric commercial model. Pharmaceutical communication has become more complex today. It uses more channels and addresses more stakeholders than just physicians, e.g., patients, payers, healthcare professionals and authorities, pharmacists, practice nurses, and other medical support staff. The proliferation of channels and potential receivers of pharmaceutical messages appears to be an important trend.

Another trend is the systematic integration of product requirements, market needs, and firm capabilities to develop and implement a holistic brand concept. Pharmaceutical firms gradually understand that it needs more than an effective drug that can be explained in classical media. A successful drug today requires a careful brand positioning that is relevant to customers and differentiated from competitors. For example, the pioneer drug Viagra identified women as suffering from men's erectile dysfunction (ED) and repositioned ED as an issue of couples' quality of life.

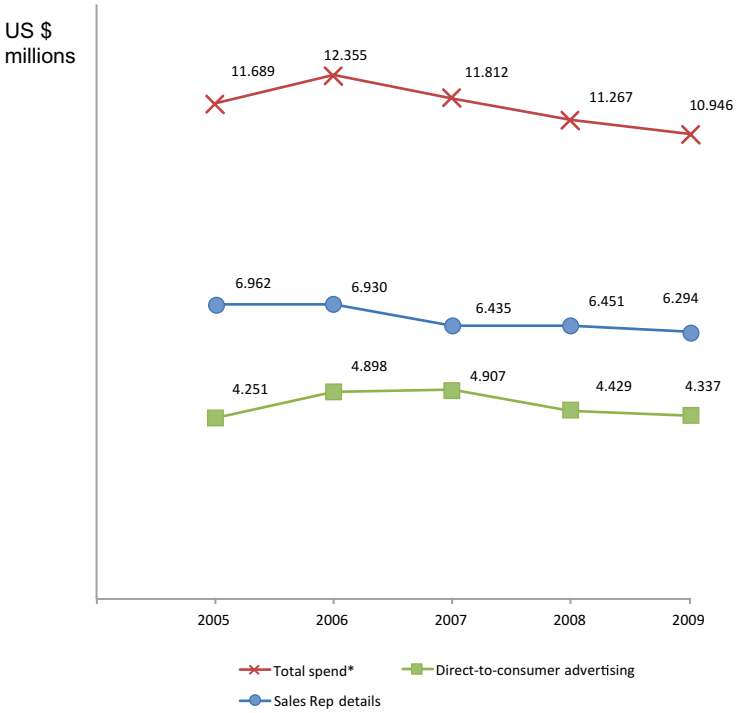

Fig. 19.1 US marketing spend by type, 2005–2009

Finally, the penetration of the Internet and other new digital media challenges the traditional communication model of pharmaceutical firms. Findings from the "Taking the Pulse® Europe" survey of physician's Internet behavior (Manhattan Research 2008) suggest that the Internet is becoming an increasingly relevant channel to multiply physician touch points. Across the major European countries, 95 % of physicians indicated that they use the Internet for professional purposes. 91 % agreed that the "Internet improves [their] clinical capabilities" and 84 % stated that the "Internet is essential to [their] professional practice." At least 49 % confirmed that they "frequently change [their] prescribing behavior as a result of information about products or treatment option [they] retrieved online." Pharmaceutical firms seem to respond to this development with basic E-strategies having similar tools and functionalities. However, there is an increasing level of experimentation with more elaborate E-marketing concepts, e.g., the use of third-party platforms as for Boehringer Ingelheim's Asasantin or the use of user-generated content as in Hospira's key opinion leader communities. Boeringer Ingelheim collaborated with Doctors.net.uk to promote its antithrombotic agent Asasantin. Doctors.net.uk developed a multiwave e-marketing campaign consisting of product, environmental, and educational information that was targeted at U.K.-based general practitioners, cardiologists, and

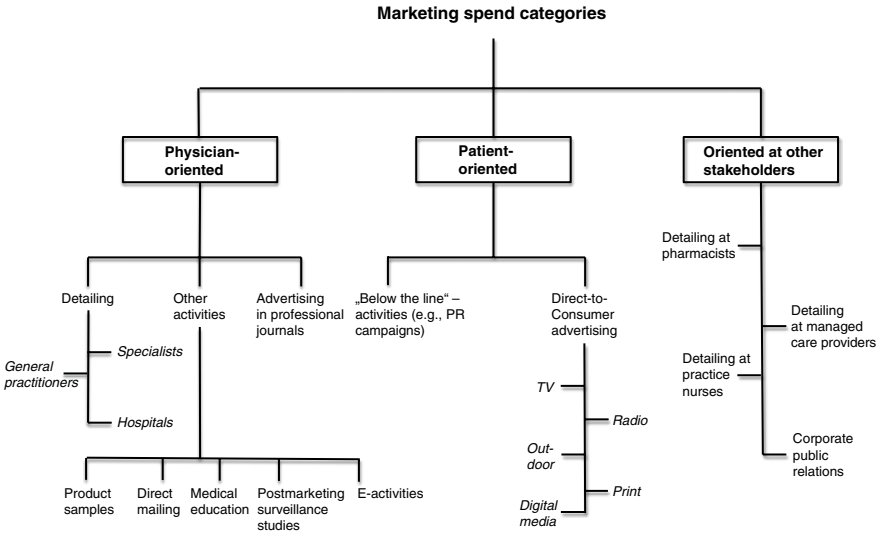

Fig. 19.2 Pharmaceutical spend categories

neurologists. Hospira sponsors the global online community of hematologists. The platform allows internationally scattered key opinion leaders to connect, share insights and questions.

19.1.2 Pharmaceutical Spending Categories

Because of the high degree of industry regulation it might appear that promotion activities are not very differentiated. The opposite, however, is true as Fig. 19.2 shows. Communication and promotion activities comprise tactics focused at physicians, patients, and other stakeholders such as pharmacists, healthcare insurers, regulators, etc. Communication efforts directed at physicians still account for the lion's share of the marketing budget in the pharmaceutical industry (Manchanda and Honka 2005; Neslin 2001; Wittink 2002). These efforts include personal selling activities by sales representatives (detailing) that target different groups of physicians: general practitioners, specialty physicians, and hospital-based physicians. Sales representatives discuss 1–3 products during a typical visit and often leave drug samples. Advertisement in professional journals is another physician-oriented communication activity. In addition to these traditional activities, a number of other activities have developed. Medical education encompasses invitations of physicians to conferences, symposia, and other professional events that allow strengthening the relationship with target physicians. Similar relationship-oriented motives are associated with postmarketing surveillance studies. Pharmaceutical companies

provide financial support to selected physicians who are willing to report on their observations of a promoted drug within a patient sample. Since such studies are not considered independent medical studies, this type of marketing activity may be criticized under ethical norms. Finally, pharmaceutical companies use direct mailings to inform physicians about new drugs, therapies, etc.

Marketing activities that are directed at the patient/consumer are only allowed in a few countries such as New Zealand and the USA that relaxed its restrictive policy in 1997. DTC advertising covers the classical media, e.g., print media, TV and broadcasting, and the new digital media. In countries where DTC advertising is not allowed, companies use below-the-line activities such as general PR campaigns on disease programs and therapies to reach the patient. Generally, mentioning the drug's name is not allowed in such campaigns.

Finally, I note that promotion tactics that are directed at stakeholders other than physicians and patients have emerged over the last years. Among those tactics are detailing directed at pharmacists, practice nurses, and managed care providers. Depending on the drug category and the structure of the healthcare system in a country, these groups gain influence through their role as gatekeeper. In the diabetes care business, for example, a large share of the detailing budget is invested into practice nurses and pharmacists because these groups often recommend the blood sugar meter to the patient. Finally, pharmaceutical companies spend money on corporate public relations.

Today, several commercial vendors collect information on pharmaceutical expenditures in high quality and with a broad coverage of categories and countries. Well-established databases are the CAM database by CEGEDIM, S.A. (http://www.cegedim.com), the Verispan database by SDI Health LLC (http://www.sdihealth.com), and the MIDAS database by IMS Health Inc. (http://www.imshealth.com).

19.1.3 Industry Facts on Marketing Spending

Table 19.1 displays an excerpt from the Ad Age's list of top marketing spenders in 2009. Unsurprisingly, consumer packaged goods companies such as Procter & Gamble, Unilever, and L'Oréal lead this list. Interestingly, we find 11 pharmaceutical companies or 11 %, respectively, among the top 100 global marketers. Pfizer and GlaxoSmithKline spent US $ 1.83 billion and 1.63 billion, respectively, on advertising alone. The other firms in this list spent at least several hundred millions of US dollars.

Advertising expenditures are important but by far not the leading marketing spend category for pharmaceutical firms. Figure 19.1 shows the development of detailing expenditures, DTC expenditures, and expenditures on professional journal advertising in the USA. The lion's share of the marketing budget is spent on physician-oriented activities, whereas detailing covers more than 90 % of these expenditures. It should be noted that this statistic does not include the value of distributed free drug samples and expenditures on other activities such as postmarketing surveillance

Table 19.1 Top global advertising spenders in 2009 (US $ millions)

Rank 2009	Advertiser	Country of origin	Worldwide media spending
1	Procter & Gamble	USA	8,679
2	Unilever	UK/Netherlands	6,033
3	L'Oréal	France	4,560
…			…
14	Pfizer	USA	1,827
16	GlaxoSmithkline	UK	1,630
45	Merck & Co.	USA	774
46	Bayer	Germany	771
59	Novartis	Switzerland	561
72	Bristol-Myers Squibb	USA	440
76	Sanofi-Aventis	France	427
78	Boehringer Ingelheim	Germany	412
81	Eli Lilly & Co.	USA	394
84	AstraZeneca	UK	377
92	Abbott Laboratories	USA	307
…			…

Source: Advertising Age DataCenter's Global Marketers 2010 report

studies and medical education. The data from major European markets in Fischer et al. (2011a, b) show that these expenditures can be very substantial, as well.

If all marketing and sales-related expenditures are considered together the marketing-sales ratio appears to be quite high. A nonrepresentative analysis of the 2011 annual reports of six global pharmaceutical companies (Novartis, Bayer, Roche, Teva, Baxter, and Merck) reveals that marketing and sales expenditures correspond, on average, to 23 % of their total revenues in 2010. It should be noted that even Teva, the leading generics manufacturer, spent an impressive US $ 2.97 billion on marketing and selling, which represents 18.4 % of its revenues.

In their study of a major cardiovascular category in the 1980s and 1990s, Bauer and Fischer (2000) estimate that the average new drug receives US $ 414 millions in terms of marketing investment, which is 1.8 times higher than the average R&D investment at that time. Ca. US $ 330 millions are spent within the first 3 years around product launch. Industry experts estimate that a drug requires ca. US $ 600 millions marketing support within the 3-year period around product launch today. I shall later report on recent studies (Narayanan and Manchanda 2009; Osinga et al. 2010) that provide reasons for this high launch investment. To summarize, the marketing investment into a new drug is substantial. Together with the high investments into product development, it suggests that only a blockbuster drug offers the capacity to deliver a positive product NPV. A blockbuster drug is a drug that generates worldwide revenues of more than 1 billion US dollars per year. Empirical studies on the profitability of drugs suggest that less than 30 % achieve a positive NPV over their life cycle (Bauer and Fischer 2000; Grabowski and Vernon 1990).

19.1.4 Overview of the Chapter

Marketing scholars have been dealing with pharmaceutical spending issues for a long time (e.g., Caplow and Raymond 1954; Montgomery and Silk 1972). The interest, partly driven by broader availability of data, considerably increased over the last years producing a literature rich of modeling approaches and empirical findings. The objective of this chapter is to review and synthesize this literature. My focus is on spending models. Given that sales force expenditures represent the largest bulk of marketing expenditures, a host of decision problems is associated with finding the optimal structure and incentive system for the sales force. Firms have to determine the optimal size of its sales force, the optimal size of territories and effective compensation plans. At the level of the individual salesman, for example, decisions on the optimal trip length and sequence of trips have to be made. All these issues are well-known classical communication planning problems (Skiera and Albers 2008). Since the literature on pharmaceutical sales force models is very rich, it deserves a special attention, so that I will not discuss these approaches here.

In the following, I will first look at how marketing managers in the pharmaceutical industry actually arrive at spending decisions (Sect. 19.2). In Sect. 19.3, I discuss models that describe how pharmaceutical demand responds to marketing expenditures. This section also summarizes findings on the responsiveness and profitability (ROI) of various spending categories. Section 19.4 turns the focus on normative applications of marketing spending models. It covers static and dynamic optimization approaches. Finally, I will identify fields of promising future research from the synthesis of the extant literature in Sect. 19.5.

19.2 Rules and Patterns of Pharmaceutical Spending

Marketing budgeting issues are discussed in common textbooks of marketing (e.g., Kotler and Armstrong 2010). Theory suggests that marketing budgets should be set at a level where incremental profits equal the incremental budget increase (Mantrala 2002). Unfortunately, the required marginal effect of a budget change is not that easy to obtain. It depends on the type of market response and the structure of the optimization problem (dynamics in demand and supply, portfolio effects, budget restrictions, etc.). In addition, data availability is limited and model estimation introduces uncertainty just due to the sampling error. For these and other difficulties, firms use simplified, heuristic rules of budget setting, e.g., percentage-of-sales rule and competitive parity rule. There is, however, no guarantee that the application of these rules leads to optimal results. They are rather expected to result into suboptimal decisions and a significant waste of resources (Mantrala 2002). In Sect. 19.4, I shall discuss normative spending models, which try to overcome these severe limitations, in more detail.

Given the large gap between normative budgeting theory and practice, it is important to understand which rules pharmaceutical managers use to determine the marketing budget and which factors influence these decisions. The literature on actual budgeting behavior in general is scarce; it is almost nonexistent with respect to the healthcare industry. Most studies survey managers about their decision rules. Only a few studies try to infer budgeting practices and influential factors from real decisions.

19.2.1 Findings from Management Surveys

Managers have been surveyed for their budgeting behavior as early as in the 1960s (Hurwood 1968). Latest results are available from surveys in China (Prendergast et al. 2006) and Australia/New Zealand (West and Crouch 2007). Researchers have noticed a growing sophistication in the use of budgeting rules over the years (e.g., Blasko and Patti 1984; Mitchell 1993). Sophistication means that management moves away from simple heuristics such as percentage-of-sales towards the application of objective-and-task rules or even modeling approaches (Piercy 1987). The percentage-of-sales rule assumes a certain percentage of past or anticipated sales to be spent on marketing. Objective-and-task rules follow the idea to set the budget so that a specified target such as market share or profit contribution is achieved in the planning period. Modeling approaches do this in a more formalized way and usually employ marginal analysis to find the optimal budget. In addition, research suggests that the process of budget setting is highly complex and substantially influenced by norms, politics, and negotiation capabilities (e.g., Fischer 2011b; Piercy 1987).

Wagner and Fischer (2011) summarize the results of 26 survey studies on budgeting behavior. This summary reveals that the percentage-of-sales method is by far the most often used heuristic. The objective-and-task method also exhibits a high frequency followed by rules that are competitor-oriented (e.g., match competitors). The results are based on respondents from many industries including the pharmaceutical industry. Unfortunately, to the best of my knowledge, no survey study is available that investigates budgeting behavior in pharmaceutical firms only. Eight out of the 26 studies reviewed in Wagner and Fischer (2011) explicitly mention that they include respondents from the healthcare industry. On average, these studies report that 47 % of firms use the objective-and-task method, 38 % the percentage-of-sales method, and only 15 % the competitive parity rule.

Management surveys offer valuable insights into budgeting practices, but they are also limited. Findings are subject to the subjective perception and interpretation of budgeting practices by surveyed managers. Since often only one manager is asked for his/her evaluation the responses do not fully reflect a process that is in fact influenced by many more people. Econometric models that relate actual product budgets to potential influence factors can overcome these validity concerns.

19.2.2 Findings from Econometric Models

The literature on econometric studies of actual marketing budgeting behavior is very scarce. In an early attempt, Lilien (1979) and Lilien and Weinstein (1984) report on the ADVISOR project that investigates the determinants of industrial marketing budgeting practices in USA and European companies. The ADVISOR database is built on self-reported product budget levels and potential determinants such as product sales, customer concentration, etc. Regression results (Lilien 1979; Lilien and Weinstein 1984) show that the level of sales, the number of users, and the complexity of the industrial product lead to higher marketing budgets. Older products and those with a higher sales concentration of customers are associated with lower budgets. As the sample of firms includes pharmaceutical firms, these results should at least partly reflect their budgeting behavior.

A recent study by Wagner and Fischer (2011) provides insights into actual budgeting behavior of pharmaceutical firms across the five largest European markets. The authors use quarterly marketing and sales data provided by CEGEDIM and IMS Health over a period of 12 years. The dataset covers 79 companies that market 518 drugs in four large prescription drug categories and 5 countries. The econometric model formalizes the impact of decision rules on product budgets that derive from three common budgeting practices: percentage of anticipated sales, profit maximization (representative of objective-and-task rule), and competitive parity. The competitive parity rule, for example, assumes that a firm follows key competitors in their budget decisions to raise or decrease the budget. The model also incorporates moderating factors, such as the stage in the life cycle and competitive intensity, to explain under which condition which rule exerts a higher influence on the budgeting process outcome.

Overall, the results suggest that the percentage-of-sales rule is the most frequently used rule (>80 % of brand budgets influenced), followed by the competitor-oriented rule (>50 %), and the profit-oriented rule (ca. 40 %). However, none of the rules seems to impact the budgeting process exclusively. In addition, the results suggest that the influence of the percentage-of-sales rule is stronger after patent expiry and at later stages of the life cycle. Profit maximization has more relevance in less competitive markets where firms can exert a greater monopolistic power. Competitive parity seems to play a greater role for drugs that are still under patent protection, probably in order to keep the market share required for harvesting the product.

19.3 Modeling Demand for Pharmaceuticals

19.3.1 Overview of Model Approaches

Expenditure response models attempt to establish a relationship between a demand variable and a spending variable. Demand is usually measured in terms of brand unit sales or market share, but it may also refer to the demand of other stakeholders

such as shareholders. At the individual level (physician, patient, or pharmacist), we observe demand for ethical drugs in form of prescriptions. Aggregation across decision makers produces brand sales that may be further aggregated to reflect category sales. In the following, I shall focus on brand demand models because they are directly incorporated into the budgeting problem. For category demand effects of pharmaceutical spend categories, I refer the interested reader to a recent in-depth study of the US market by Fischer and Albers (2010).

Depending on the level of data analysis, different types of response models have been suggested (for a general overview, see Hanssens et al. 2001; Leeflang et al. 2000). At the individual level, conditional logit models are available to model drug choice. Double-log response models have been used to specify the impact of pharmaceutical spending on aggregate brand sales. It is not only the type of data that drives the choice of the model form, but also the marketing phenomenon the researcher wants to model. For example, Bass-type diffusion models describe the penetration of a new drug among a potential adopter population. All these model types have been used in research on pharmaceutical brand demand.

Table 19.2 provides an overview of the rich literature on marketing spending models for pharmaceuticals. While I do not claim this list to be complete, it should represent the diversity and significance of contributions. In addition to the type of demand model, the table classifies spending models according to their main focus of application, the included pharmaceutical spending categories, and the consideration of interactions and marketing dynamics. Spending models may be used for description, prediction, or normative application such as optimizing the marketing budget. They may include as many spending categories as are effectively used. It is also important to understand to what extent the spending models do capture interactions across decision variables, competitors, and countries. Because of the variety of communication channels, the integration of international markets and the intense competition, I suspect that such interactions do play a role.

The table is ordered chronologically. One of the first applications of a response model to pharmaceutical products is by Montgomery and Silk (1972) who specify a distributed lag model to capture the multiple dynamic effects of pharmaceutical marketing efforts. These dynamics and the prediction of new product sales are also the focus of diffusion models that have been suggested (e.g., Hahn et al. 1994; Lilien et al. 1981). A distinctive feature of all pharmaceutical diffusion models is that they model a complex diffusion process involving different segments of customers including repeat buyers. Note that repeat buying (i.e., refills) are often a multiple of first-time prescriptions. If marketing efforts successfully initiate trial prescriptions, these efforts also impact future sales via repeat prescriptions. Spending models thus need to account for these strong dynamic marketing effects. In fact, the vast majority of models in Table 19.2 (87 %) do include marketing dynamics, most often by specifying a marketing stock variable.

From Table 19.2, it is obvious that detailing is part of virtually every demand model reflecting the importance of this instrument. Since the abolishment of the ban on patient-oriented marketing in the USA in 1997, studies with US data have increasingly focused on this spending category. Models including expenditures on

Table 19.2 Summary of marketing spending models

Author/s	Marketing spending category	Main focus of application	Type of demand model	Consideration of interactions across			Marketing dynamics	Level of data analysis
				Decision variables	Competitors	Countries		
Montgomery and Silk (1972)	Samples, PJA, direct mailing	Descriptive	Log–log	–	–	–	✓	Aggregate
Parsons and Vanden Abeele (1981)	Detailing, samples, direct mailing	Descriptive	Log–log	✓	–	–	–	Aggregate
Lilien et al. (1981)	Detailing	Predictive/normative	Bass-type diffusion	–	–	–	✓	Aggregate
Rao and Yamada (1988)	Detailing	Predictive	Bass-type diffusion	–	–	–	✓	Aggregate
Hahn et al. (1994)	Total spend	Predictive	Bass-type diffusion	–	–	–	✓	Aggregate
Berndt et al. (1995)	Detailing, PJA, DTCA	Descriptive	Log–log	–	–	–	✓	Aggregate
Shankar (1997)	Detailing, PJA	Descriptive/normative	Log–log	–	✓	–	–	Aggregate
Shankar et al. (1998)	Total spend	Descriptive	Bass-type diffusion	–	✓	–	✓	Aggregate
Dekimpe and Hanssens (1999)	Detailing, PJA	Predictive	Vector error correction	✓	–	–	✓	Aggregate
Rizzo (1999)	Detailing	Descriptive	Log–log	✓	–	–	✓	Aggregate
Shankar et al. (1999)	Total spend	Descriptive	Log–log	–	–	–	–	Aggregate
Gönül et al. (2001)	Detailing, samples	Descriptive	Latent class logit	✓	–	–	✓	Individual
Neslin (2001)	Detailing, PJA, DTCA, PME	Descriptive	Log-linear	✓	–	–	✓	Aggregate
Wittink (2002)	Detailing, PJA, DTCA, PME	Descriptive	Log-linear	✓	–	–	✓	Aggregate

(continued)

Table 19.2 (continued)

Author/s	Marketing spending category	Main focus of application	Type of demand model	Consideration of interactions across				
				Decision variables	Competitors	Countries	Marketing dynamics	Level of data analysis
Azoulay (2002)	Detailing, PJA	Descriptive	Mixed logit	–	–	–	✓	Aggregate
Berndt et al. (2003)	Detailing	Descriptive	Logit and Bass-type diffusion	–	–	–	✓	Aggregate
Narayanan et al. (2004)	Detailing, DTCA, OME	Descriptive	Mixed logit	✓	–	–	✓	Aggregate
Mizik and Jacobson (2004)	Detailing, samples	Descriptive	Linear	–	–	–	✓	Individual
Donohue and Berndt (2004)	Detailing, DTCA	Descriptive	Nested logit	✓	–	–	✓	Individual
Manchanda et al. (2004)	Detailing	Descriptive/normative	NBD	–	–	–	✓	Individual
Manchanda and Chintagunta (2004)	Detailing, samples	Descriptive/normative	Poisson	✓	–	–	–	Individual
Chintagunta and Desiraju (2005)	Detailing, OME	Descriptive	Mixed logit	–	✓	✓	–	Aggregate
Narayanan et al. (2005)	Detailing, DTCA, OME	Descriptive/normative	Mixed logit	–	–	–	✓	Aggregate
Fischer, Shankar, and Clement (2005)	Total spend	Descriptive/normative	Log–log	✓	–	✓	✓	Aggregate
Venkataraman and Stremersch (2007)	Detailing, PME	Descriptive	NBD	✓	–	–	✓	Individual
Gonzalez et al. (2008)	Detailing	Descriptive/predictive	Mixed logit	–	–	–	✓	Individual

Narayanan and Manchanda (2009)	Detailing	Descriptive/normative	Mixed logit	–	–	–	✓	Individual
Chintagunta et al. (2009)	Total spend	Descriptive	Logit	–	–	–	✓	Individual
Ching and Ishihara (2010)	Detailing	Descriptive	Logit	–	–	–	✓	Individual
Montoya et al. (2010)	Detailing, samples	Descriptive/normative	Hidden Markov	–	–	–	✓	Individual
Fischer and Albers (2010)	Detailing, PJA, DTCA	Descriptive	Log–log	–	–	–	✓	Aggregate
Fischer et al. (2010)	Total spend	Descriptive	Log–log	✓	–	<✓>	✓	Aggregate
Colsarici and Vakratsas (2010)	DTCA, detailing, PJA	Descriptive/predictive	Bass-type diffusion	–	–	–	✓	Aggregate
Nair et al. (2010)	Detailing	Descriptive/normative	Linear	–	–	–	✓	Individual
Osinga et al. (2010)	Physician spend, DTCA	Descriptive	Log–log	✓	–	–	✓	Aggregate
Dong et al. (2011)	Detailing	Descriptive	Poisson-lognormal	–	–	–	✓	Individual
Osinga et al. (2011)	Physician spend, DTCA	Descriptive	Stock return response	–	–	–	✓	Aggregate
Fischer et al. (2011a)	Total spend	Descriptive/normative	Log–log	–	–	–	✓	Aggregate
Fischer et al. (2011b)	Detailing, PJA, PME, OME	Normative	Log–log	✓	–	–	✓	Aggregate

PJA Professional journal advertising, *DTCA* Direct-to-consumer advertising, *PME* Physician meeting expenditures, *OME* Other marketing expenditures

physician meetings or postmarketing surveillance studies, which are presumably subsumed among "other marketing expenditures," however, are still rare.

The vast majority of models are descriptive (85 %) and based on aggregate data (67 %). The frequent use of aggregate data is clearly driven by the greater access to this data. Note that in countries such as Germany, it is even not allowed for commercial vendors to collect and sell individual physician or patient data. Individual-level data, however, are necessary to study important questions such as the flow of information among a social network of physicians (Nair et al. 2010) or the allocation of resources across physicians (e.g., Montoya et al. 2010).

Table 19.2 reveals that several models (36 %) consider a possible interaction among decision variables, e.g., marketing spending categories (e.g., Wittink 2002), other mix variables such as price (e.g., Narayanan et al. 2004) and quality (e.g., Venkataraman and Stremersch 2007), and strategic decision variables such as time to market (Fischer et al. 2005). In contrast, interactions among competitors and across countries are each incorporated in only three studies out of 39 (8 %). Given the large product variety in many categories and the global nature of the business, these issues warrant greater attention in model building.

19.3.2 Generalizations About the Responsiveness of Pharmaceutical Demand

Given the rich empirical research on marketing spending models for pharmaceuticals, a natural question arises whether we can assert any generalizations about the responsiveness of drug demand to marketing efforts. Three recent meta-analyses approached this question. Kremer et al. (2008) summarize the findings of 58 studies that report 781 elasticities of various pharmaceutical spend categories. Sridhar et al. (2014, in this book) use 373 elasticities from 48 pharmaceutical studies. The meta-analysis by Albers et al. (2010) focuses on personal selling that includes other industries, as well. All three studies provide a strong generalized result that detailing is a very effective marketing element. Kremer et al. (2008) report an average elasticity of 0.326, which appears to be a bit higher than the average elasticity of 0.210 in Sridhar et al. (2012). An elasticity of 0.210 means that sales rises by 21 % if detailing expenditures increase by 100 %. As these authors note, the difference may be due to the fact that they only consider current-period brand-level elasticities whereas the finding in Kremer et al. (2008) also includes long-term and category-level elasticities.

The study by Kremer et al. also provides insights into the demand responsiveness with respect to other spend categories that are generally lower compared with detailing. These elasticities are 0.123 for professional journal advertising, 0.073 for DTCA, and 0.062 for other physician-oriented spending categories. Interestingly, the responsiveness of detailing is, on average, 4.5 times higher than that for DTCA. Expenditures in the USA, however, have been only 1.45 times larger, on average, over the last years (see Fig. 19.2 again). An easy explanation for this striking

discrepancy is not readily available and deserves more research. But, the benefits of DTCA seem to be broader than those captured in a brand sales model. For example, Osinga et al. (2011) recently showed that DTCA has a significant positive effect on stock return beyond and above its revenue effects. Hence, the addressee of DTCA is not only the patient (or physician), but also the investor. In addition, we know from brand research that ad expenditures show only a marginal sales effect but contribute significantly to brand equity which in turn is a driver of firm performance (Srinivasan and Hanssens 2009).

Another striking discrepancy of the Kremer et al. study refers to the fact that elasticities obtained from individual-level models are considerably smaller than from aggregate-level models (see also Manchanda and Honka 2005). Idiosyncrasies in data collection may be responsible for this difference. Another possible explanation is the type of response model. Individual-level models typically model brand choice in a logit framework (e.g., Gonzalez et al. 2008; Narayanan and Manchanda 2009) while aggregate-level models often resort to the double-log specification (e.g., Fischer and Albers 2010; Osinga et al. 2010). Both specifications have very different implications for the behavior of elasticity and consequently for optimal expenditure levels (see also Albers 2012). Future research may investigate this issue in more detail.

19.3.3 Recent Model Developments

As Table 19.2 shows, the literature on marketing spend response models for drug demand is very rich. It is beyond the scope of this article to review all these models in detail. I rather shall highlight a few recent trends in model development.

The role of quality. Drugs are highly complex products that result from a long and capital-intensive process of development and approval through national surveillance authorities. Prior to approval the drug needs to show sufficient evidence on its effectiveness and safety from clinical trials. Drug quality is a multidimensional construct. Relevant dimensions are, for example, the improvement of a medical condition, the bioavailability, and the number of indications, side effects and interactions with other drugs. Product management regularly uses results from clinical[1] and surveillance studies in sales folders and talks for physician visits and advertisements in medical journals.

Azoulay (2002) proposes new measures of scientific evidence and incorporates them into a drug demand model. Specifically, he develops flow and stock variables that measure the research output from clinical placebo and comparative studies. Analyzing aggregate brand sales data in a discrete choice modeling framework and

[1]Product management does not only refer to phase III studies that are required to obtain drug approval but also to phase IV studies. These studies are carried out after launch and may include comparative studies to show the superiority of the drug over competitive drugs.

controlling for various drug quality dimensions, he finds significant evidence for the impact of clinical results on prescription behavior. In addition to the demand model, he specifies a model of detailing supply. It turns out that the level of detailing increases with the level of useful clinical research output. Accounting for the mediating effect via detailing in the demand model, drug sales respond with a total elasticity of 0.3–0.5 to the level of scientific evidence.

Venkataraman and Stremersch (2007) use physician-level data to analyze the moderating effects of drug effectiveness and drug side effects with respect to marketing efforts on drug prescription and sample dispensing. Their prescription model is a truncated regression model that assumes a negative binomial distribution (NBD) of prescriptions and allows for heterogeneity in physician responsiveness. Specifically,

$$\Pr\left(RX_{pjt} = k \mid \lambda_{pjt}\right) = \frac{\Gamma(\alpha + k)}{\Gamma(\alpha)\Gamma(k+1)}\left(\frac{\alpha}{\alpha + \lambda_{pjt}}\right)^{\alpha}\left(\frac{\lambda_{pjt}}{\alpha + \lambda_{pjt}}\right)^{k} \tag{19.1}$$

with

$$\ln \lambda_{pjt} = \ln E\left[RX_{pjt} \mid Z_{pjt}, x_{pjt}\right] = \beta_p + \beta_{p1}\mathrm{SE}_{jt} + \beta_{p2}\mathrm{Eff}_j + \left(\beta_p + \beta_{p1}\mathrm{SE}_{jt} + \beta_{p2}\mathrm{Eff}_j\right)\mathrm{Det}_{pjt} + \left(\beta_p + \beta_{p1}\mathrm{SE}_{jt} + \beta_{p2}\mathrm{Eff}_j\right)\mathrm{Meet}_{pjt} + x_{pjt}\Theta + \xi_{pjt}$$

where $\Pr(RX_{pjt}=k)$ is the probability of k new prescriptions of brand j written by physician p in period t. λ measures the mean prescription rate and α the degree of overdispersion. The mean description rate depends on λ, the drug's number of side effects, SE, and its effectiveness, Eff, which both moderate the influence of details, Det, and physician meeting attendance, Meet, on prescription behavior. Other variables are summarized in the vector x; β and Θ are parameter vectors to be estimated and ξ represents an error term. The sample-dispensing model is specified in a similar fashion (p. 1694).

The study finds that marketing responsiveness in terms of new prescriptions and sample dispenses is higher for drugs that demonstrate a greater effectiveness. This suggests that sales reps may use scientific evidence to improve the impact of a sales call. The study also shows a positive moderating effect of the number of side effects with respect to marketing efforts. The authors explain this finding with the information effect that a detailing call helps reduce the physician's uncertainty about the side-effect profile of a drug. While estimation results inform about the moderating role of drug effectiveness for marketing responsiveness, Albers (2012) remarks that the exponential conditional mean function does not allow optimizing marketing expenditures. Hence, using this model to derive normative budget implications is not possible.

Competitive interaction. Many firms compete for market share and profits in the global pharmaceutical industry. It seems reasonable to assume that marketing activity levels and market outcomes are not independent of competitive activity. As

Table 19.2 shows, the vast majority of response models, however, do not account for competitive interaction. Among the few contributions that consider competitive interaction is a model suggested by Shankar (1997). His model describes a duopoly situation where the pioneer is challenged by a follower brand. Both firms may play a Nash game or a Stackelberg leader-follower game in two spend categories, detailing and advertising. Depending on the game, it is possible to predict the optimal behavior of the pioneer in reaction to the entry of the new competitor. Application of the model to a pharmaceutical category improved the prediction of the pioneer's reaction behavior compared to alternative models.

Chintagunta and Desiraju (2005) extend Shankar's (1997) framework by allowing a broader range of competitive interactions within the market. In addition, they acknowledge that pharmaceutical firms often compete with each other in several international markets. Following the theory of multimarket contact competition, their model approach also includes across-market contact effects. Assuming a firm wants to maximize profits Π_{jt} for brand j in period t across all countries c where the drug is marketed, the objective function is given by

$$\Pi_{jt} = \sum_{c=1}^{C} \left[\left(p_{jt}^{c} - c_{jt} \right) Q_{jt}^{c} - D_{jt}^{c} \right] \tag{19.2}$$

where p denotes price, c denotes marginal cost, Q is the demand for the brand, and D is the level of detailing expenditures. The authors decompose brand demand into a mixed logit share model and a category sales model that are estimated separately. From (19.2), the first-order condition can be obtained:

$$\frac{\partial \Pi_{jt}}{\partial D_{jt}^{c}} = \left(p_{jt}^{c} - c_{jt} \right) \left(Qd_{jt}^{cj} + \underbrace{\sum_{k=1}^{K} \theta_{kj}^{c} Qd_{jt}^{ck}}_{\text{Within-market interaction}} \right) + \underbrace{\sum_{z=1}^{C} \left(\left(p_{jt}^{z} - c_{jt} \right) \sum_{k=1}^{J} \theta_{kj}^{zc} Qd_{jt}^{zk} \right)}_{\text{Across-market contact effect}} - 1 = 0 \tag{19.3}$$

In the above equation, Qd_{jt}^{ck} represents the first derivative of the sales of brand j in country c with respect to the detailing level of brand k in that country. Under conditions of competitive substitution, $Qd_{jt}^{cj} > 0$ and $Qd_{jt}^{ck} < 0$. The term θ_{kj}^{c} is a competitive interaction parameter that measures to what extent the firm deviates from Nash behavior. If the firm plays Nash, θ_{kj}^{c} equals 1. For $\theta_{kj}^{c} > 0$ interaction is less competitive leading to lower detailing investments. The opposite is true for $\theta_{kj}^{c} < 0$. In addition, across-market interactions may also be present. The interaction parameter θ_{kj}^{zc} reflects the interaction between brands j and k across markets c and z. For $\theta_{kj}^{zc} > 0$, as an example, contact in markets c and z results in more cooperative behavior between brand j and k in market c.

Chintagunta and Desiraju (2005) take this model to data for a major drug category in the USA and two European markets. They find both within-market and across-market contact effects of competitive interaction. The effects are different across brands and markets. For example, European markets seem to have no impact on detailing levels in the USA, but the analysis reveals interaction effects in the

other direction. Interestingly, authors note that the across-market interaction leads to more homogenous price-cost margins across the international markets.

The relevance of launch investment. Another stream of work contributes to our understanding of the temporal variation of marketing expenditures across the life of a new drug. In an early paper, Lilien et al. (1981, p. 503) derive from their diffusion model a policy that the market share of the new product should be driven to some competitive level and then maintained at that level. In order to achieve that target, detailing expenditures should be high in the introductory phase until the target share is achieved.

Recently, Osinga et al. (2010) introduced a dynamic brand sales model that is to capture transient and persistent effects of marketing efforts. Let y_t measure brand sales in period t, x_t measure marketing expenditures, and β_{0t} denote a stochastic trend in sales:

$$y_t = \beta_{0t} + \beta_{1t} x_t + \varepsilon_t \tag{19.4}$$

The authors assume that the stochastic trend β_{0t} follows a random walk with drift $\beta_{2t\text{-}1} x_t$, which leads to the following transition equation

$$\beta_{0t} = \beta_{0t-1} + \beta_{2t-1} x_t + \eta_{0t} \tag{19.5}$$

where ε and η are uncorrelated and normally distributed error terms. The parameter β_{1t} measures the transient marketing effect and $\beta_{2t\text{-}1}$ captures the persistent marketing effect. Osinga et al. (2010) assume a double-log sales response function and estimate the model by means of Kalman filtering for 88 prescription drugs from 39 categories. Their findings show that both persistent and transient marketing effects are strongest at the beginning of the life cycle. They become smaller or even disappear in later periods. From these findings, the authors conclude that it pays off to invest in marketing early in the life cycle, which is consistent with the expenditure patterns in their data.

Another noteworthy brand sales model suggested by Narayanan et al. (2005) incorporates the changing role of communication over the life cycle of a new product category. Their model distinguishes between an early phase of a product's life cycle, where detailing helps physicians to reduce uncertainty about the true quality of the product by updating their prior beliefs via a Bayesian learning process, and a subsequent phase, where detailing has a reminder effect and directly influences goodwill accumulation. Based on the estimates for the magnitudes of the two types of effects, the authors can show via simulation analysis that detailing expenditures should follow a temporal pattern with an emphasis put on expenditures during the early phase.

To summarize, the observation of high marketing investments around product launch seems to be well justified. Various approaches of modeling drug sales response suggest such temporal differences in marketing expenditures.

19.3.4 Return on Investment of Spending Categories

Managers are usually highly interested in models that enable them to quantify the return of a marketing investment (marketing ROI). The ROI concept is simple and recommendations can be derived in an intuitive manner. If the ROI of an activity is negative, then managers should no longer spend money on this activity. The opposite is true for positive returns. In addition, we know that the optimum level of an instrument is achieved if the ROI is zero provided that there are no budget constraints.[2] Consider the following basic profit equation where $\prod$ denotes profit, $Q(p, X)$ represents the market response function of unit sales with respect to price p and the level of expenditures for a marketing instrument X, and c denotes the marginal cost of producing one unit:

$$\Pi = (p - c)Q(p, X) - X \tag{19.6}$$

The short-term ROI in percent may be obtained as follows (see also Narayanan et al. 2004):

$$\mathrm{ROI}[\mathrm{in}\%] = (p - c)\frac{\partial Q}{\partial X} - 1[\times 100] \tag{19.7}$$

The exact expression depends on the specification of the response model. In addition, the calculation of ROI changes if interactions are considered and dynamic effects are included culminating into a multi-period ROI.

Table 19.3 summarizes the ROI findings from several studies. Authors have used different functional forms to model brand sales, among them double-log functions, log-linear functions, and linear functions. The studies by Chintagunta and Desiraju (2005) and Narayanan et al. (2004) combine a mixed logit market share model with a category sales model to derive ROI estimates for expenditures on detailing and DTC advertising. Three studies are based on individual-level data (prescriptions issued by a physician), whereas the rest of the studies use aggregate brand sales data. Table 19.3 shows ROI figures in %, consistent with specification (19.3). For example, if 100 additional dollars spent on detailing generate 130 dollars additional profit contribution this is equivalent to an ROI of 30 % [(130 – 100)/100 × (100%)].

The studies in Table 19.3 show that detailing may provide substantial positive returns on investment at observed investment levels. The values are greater for drugs that generate higher baseline sales and that are in the early stages of their life (Neslin 2001; Wittink 2002). It seems that ROI figures obtained at the individual physician

[2] I want to emphasize that I use the term ROI from a marginal analysis perspective. Here, the objective is to find the profit maximizing spending level. The ROI measures the incremental profit gain from an incremental increase in spending level divided by that increase in spending. Practitioners sometimes refer to the ratio of total profit gain and total spending level. By definition, this ratio is maximized if incremental ROI is zero.

Table 19.3 Summary of return on investment estimates for pharmaceutical communication activities

Author/s	Response function	Data	ROI in %				ROI definition
			Detailing	DTC advertising	Journal advertising	OME	
Chintagunta and Desiraju (2005)	Mixed logit (share), Log–log (category)	Unit sales in one category and five countries, 1988–1999	-44–1,833				Short-term change in ex factory sales
Manchanda and Chintagunta (2004)	Poisson	Drug prescriptions at physician level for one drug in the USA, 1996-1998	23				Short-term change in retail sales
Montoya et al. (2010)	Hidden Markov	Drug prescription at physician level for one drug in the USA, 2 years	20–33[a]				Long-term change in profits
Mizik and Jacobson (2004)	Linear	Drug prescriptions at physician level for three drugs in the USA, 2 years	> 0 (1 drug) < 0 (2 drugs)				Long-term change in profits
Narayanan et al. (2004)	Mixed logit (share), Log–log (category)	Drug prescriptions at aggregate level in two US-categories, 1993–2002	665–1,664 – Positive interaction w/ DTCA – Negative interaction w/ price and OME	179–181 – Positive interaction w/ detailing – Negative interaction w/ OME			Long-term change in retail sales
Neslin (2001)	Log-linear	Drug prescriptions at aggregate level in the USA, 1995–1999	LB: 134–929 MB: 78–270 SB: 27–45	LB: -100–37 MB: -100–(-41) SB: -100–(-75)	LB: 442–579 MB: 347–429 SB: 122–250	256	Long-term change in retail sales
Wittink (2002)	Log-linear	Drug prescriptions at aggregate level in the USA, 1995–2000	LB: 210–1,060 MB: 20–110 SB: -10–0	LB: -60–30 MB: -90–(-80) SB: -100	LB: 210–1,120 MB: 130–320 SB: 520–620	LB: 210–1,070 MB: 100–260 SB: -90	Long-term change in retail sales

LB Large brands with sales > $200 m/$500 m, *MB* Medium brands with sales $50–200 m/$100–500 m, *SB* Small brands with sales $25–50 m/$25–100 m

[a]ROI is evaluated for optimal allocation policies with respect to detailing and sampling

level (Manchanda and Chintagunta 2004; Mizik and Jacobson 2004; Montoya et al. 2010) are smaller than those from studies using aggregate data. It should also be noted that in some cases,the authors encountered negative ROIs pointing to an overspending on detailing (Chintagunta and Desiraju 2005; Manchanda and Chintagunta 2004; Mizik and Jacobson 2004; Wittink 2002).

A few studies considered the ROI of other physician-oriented marketing efforts such as journal advertising or invitations to dinners and meetings (Neslin 2001; Wittink 2002). These studies conclude that ROIs of these activities are highly positive and firms therefore should consider raising or reallocating their budgets to them.

In contrast to physician-oriented efforts, negative ROIs are found with respect to DTC advertising unless the drug is classified as a recently introduced large brand (revenues > US$ 500 million). Narayanan et al. (2004) consider such brands in their sample and provide evidence that DTC advertising pays off at current spending levels. In addition, the authors analyze the interaction with other communication activities and price and find significant effects that alter ROIs for both DTC advertising and detailing efforts.

ROI-analysis provides important insights into the effectiveness of marketing activities in monetary terms. The analysis helps identify ineffective marketing policies that generate negative ROIs. Neslin (2001) and Wittink (2002) show that reallocating resources from DTC advertising to physician-oriented activities can substantially increase profits. However, an isolated ROI-analysis has its limitations. First, it does not inform how large the budget for a marketing variable should be to maximize total profits. Second, the growth potential of a product due to factors such as life cycle is not reflected. Third, in models where interactions across marketing instruments are specified, the ROI strongly depends on the level of investment of the other instruments. The negative ROI of a marginal DTC advertising dollar, for example, may turn into a positive ROI if the level of investment for other variables is optimized. Finally, single product ROI-analysis does not consider different profit improvement potentials across products or consumer groups. Optimal allocation decisions may not be derived from ROI-analysis, but have to consider additional parameters such as the scale of the revenue base and the profit contribution margin (Fischer et al. 2011b).

19.4 Setting Optimal Marketing Budgets

The key question in normative research on marketing spending models is how to determine the profit maximizing marketing budget. Structurally, this involves two further questions. What is the optimal total marketing budget? And how should that budget be optimally allocated across allocation units that may be countries, products, customers, activities, time periods, and combinations of these. In theory, both problems should be solved simultaneously yielding the optimal total budget that is allocated in an optimal manner. Apart from the technical challenges associated with a simultaneous solution, management practice usually solves these problems

separately. Moreover, in most cases, the total budget is set by top management and provides a financial restriction to all subsequent budgeting tasks. On the positive side, we know that profit gains from optimized allocation in the amount of 40–60 % by far outreach the gains from an optimized total budget that total only 3–5 % (Mantrala et al. 1992; Tull et al. 1986).

The literature on normative models of pharmaceutical marketing spending is emerging. We may broadly differentiate between static and dynamic models. Static models try to maximize short-term profits and obtain optimal spend levels for the current period. Dynamic models try to optimize the budget allocation over time and may consider maximizing discounted future profits. The suggested approaches are based on marginal analysis or simulation of market response functions that are part of the profit objective function. The main focus is on detailing as largest pharmaceutical spend category.

19.4.1 Static Optimization

Optimizing detailing expenditures across physicians. Manchanda and Chintagunta (2004) attempt to optimize the number of times a physician is detailed in a particular quarter. They model the number of prescriptions, y_{it}, written by physician i in quarter t to follow a Poisson distribution with a physician-specific mean λ_{it}:

$$\Pr\left(y_{it}=y_{it} \mid \lambda_{it}\right)=\frac{\lambda_{it}^{y_{it}} \exp(-\lambda_{it})}{y_{it}!} \tag{19.8}$$

where

$$\lambda_{it}=\exp\left(\beta_{0i}+\beta_{1i}\mathrm{NDET}_{it}+\beta_{2i}\mathrm{NDET}_{it}^{2}\right)$$

NDET_{it} denotes the number of times a physician is detailed in quarter t and β is a parameter vector to be estimated. Differentiating the mean prescription rate with respect to NDET and setting zero gives the optimal number of calls per quarter a physician should get. This point can be computed by $-\beta_{1i}/2\beta_{2i}$ (Manchanda and Chintagunta 2004). The application of this model to a specific drug and a large sample of physicians demonstrates that quite a large group of physicians is over-detailed. By reallocating the wasted resources from over-detailed physicians to under-detailed physicians in two different segments, prescriptions rise by 9 % and 11 %. Because the reallocated resources are evenly spread across the physicians, the authors note that the revenue gain should be even higher for a more optimized rule. Note that the total detailing budget remains constant. Thus, the increase in revenues is fully profit-relevant. The improvement in profits should be even higher because the reference base is lower than that for the revenue increase.

In another physician-level model, Manchanda et al. (2004) specify the number of prescriptions written by a physician as a negative binomial distribution (NBD) and the mean of the conditional distribution to be driven by the number of sales calls. An interesting feature of their model is the specification of the unobserved coefficient of sales call effectiveness. The assumption that detailing is set by management with partial knowledge of a physician's responsiveness implies that the independent variable is no longer stochastic. By specifying a model for the marginal distribution of detailing, which depends on conditional response parameters, the authors are able to derive unbiased estimates of detailing responsiveness. Following the optimality condition that marginal profits must equal the cost of an additional detail, the study shows that the average physician is detailed at close to an optimal level, but individual results vary considerably across physicians. At least 50 % of physicians are not detailed at optimal levels. The authors do not provide an optimal allocation plan that may be developed in future research.

Optimizing detailing expenditures across spend categories. The models above are focused on the optimization of a single communication element, detailing, which may be too restrictive in a world where managers have to balance expenditures across several communication elements interacting with each other. In addition, optimality conditions may be different depending on the extent and nature of competitive interactions. Shankar (1997) proposes a model that takes into account these types of interaction. He assumes a log–log sales response model for two competing brands, the pioneer and a follower brand. Specifically, the model is specified as follows:

$$S_{it} = \mathrm{e}^{a_{it}} A_{it}^{b_i} A_{jt}^{c_i} D_{it}^{d_i} D_{jt}^{f_i} p_{it}^{-g_i} p_{jt}^{h_i}, \quad \text{with} \quad a_{it} = \alpha_i - \frac{\phi_i}{T_{it}} \tag{19.9}$$

where S_{it} is units sales of brand i in period t, A_{it} is the advertising spending, D_{it} is the sales force spending, P_{it} is the unit price, and T_{it} is the "time in market." The terms a–h, α, and ϕ are parameters to be estimated, whereas c, f, and h represent marketing cross-effects that are associated with competitor variables indexed with j. Maximizing the profit function, Π, with respect to advertising, sales force spending and price leads to:

$$\underset{A,D,P}{\mathrm{Max}}\, \Pi_{it} = m_{it} S_{it} - A_{it} - D_{it} - F_{it} \tag{19.10}$$

where m_{it} denotes the contribution margin. Shankar uses the theorem by Dorfman and Steiner (1954) to derive the equilibrium levels of spending for advertising and sales force, respectively:

$$A^* = b_i m_i S_i^* \tag{19.11}$$

$$D^* = d_i m_i S_i^* \tag{19.12}$$

The star indicates that variables are in their optimum. This result holds under the assumption that both competitors play a Nash game in all marketing instruments or competitor *i* plays a Stackelberg follower in one or all of the instruments. The solutions (19.11) and (19.12) have to be extended by cross-effects if firm *i* acts as a Stackelberg leader in at least one of the instruments. It may be striking that the optimal solutions for the marketing budgets under competition do not depend on competitor activity levels. This is a feature specific to the double-log response model. It should, however, be noted that the optimal advertising and detailing budgets depend implicitly on the equilibrium levels of competitor budgets via the equilibrium brand sales level S^*.

The optimality conditions also allow identifying the ratio of optimal distribution of a limited marketing budget on advertising and sales force. Let R denote the fixed marketing budget that is to be allocated across advertising and sales force. Then, consistent with (19.11) and (19.12), the optimal budgets are (Dorfman and Steiner 1954)

$$A^* = \frac{b_i}{b_i + d_i} R \tag{19.13}$$

$$D^* = \frac{d_i}{b_i + d_i} R \,. \tag{19.14}$$

19.4.2 Dynamic Optimization

Optimizing expenditures across physicians and time. The evolution of a new drug is a dynamic process of growth and decline by definition, i.e., drugs follow a life cycle (e.g., Grabowski and Vernon 1990; Fischer et al. 2010). The responsiveness towards marketing activities may change over the life cycle (e.g., Osinga et al. 2010). In addition, a marketing impulse today usually has an effect on future sales for various reasons (see Sect. 19.3.3 again). Normative models that do not take into account dynamic marketing and life cycle effects are likely to yield suboptimal results.

Narayanan and Manchanda (2009) develop a structural brand choice model that allows physicians to learn about the quality of a new drug in a Bayesian manner (for a related model see Crawford and Shum 2005). Specifically, they assume that physicians are risk-averse and uncertain about the quality of a new drug. They have some prior beliefs about the quality and are assumed to be Bayesian updaters, i.e., physicians update their prior beliefs with new information they obtain through a detailing call, for example, by using Bayes rule to generate posterior beliefs. Hence, communication activities may have an informative effect because they contribute to reduce the uncertainty in physician's decision-making. A specific feature of Narayanan and Manchanda's model is that it allows for heterogeneous learning rates across physicians.

The application to a category with two drug entries and one incumbent drug reveals that learning rates are indeed heterogeneous. Additionally, the evolution of detailing responsiveness is also different across physicians. Those who are more responsive in the early periods are less responsive later and vice versa.

These findings have implications for allocating marketing resources across physicians and time. To investigate the potential gains from better allocation, authors conduct counterfactual simulations. In these simulations, they reallocate detailing calls for two drugs across physicians, time, and both dimensions according to an optimal policy that is generated from numerical optimization. Revenue gains are, on average, 5 % for better allocation across only physicians and 7 % for better allocation only over time. If allocation is optimized simultaneously along both dimensions the average gain amounts to 12 %. Since the total number of calls remains the same, the revenue gains are fully profit-relevant.

Montoya et al. (2010) choose a different approach to model the dynamics in physician's prescription behavior. They set up a nonhomogeneous hidden Markov model to assess the short-term and long-term effects of detailing and sampling activities. A hidden Markov model is a Markov process with unobserved states. The unobserved states are prescription-behavior states. The authors identify three such states in their application to 24 months of a newly launched drug. In the first state, a physician is inactive, i.e., s/he issues almost no prescriptions for the drug. In state 2, s/he prescribes the drug infrequently, whereas state 3 represents a state with high prescription frequency. Frequency is operationalized in terms of prescription probabilities.

Physicians stochastically transition among these states according to a first-order Markov process. Transitions propensities are assumed to vary across physicians. They are also assumed to be a function of marketing activities. With this model setup, it is possible to derive short-term and long-term effects of detailing and sampling that manifest in current and future drug prescriptions.

The empirical application of the model reveals that detailing is most effective in acquisition, i.e., moving physicians to higher activity states. In contrast, sampling appears to be more effective as a retention tool, i.e., physicians are retained at higher activity states.

Finally, Montoya et al. (2010) use the model and their parameter estimates to optimize the allocation of the detailing and sampling budget across physicians and time. For this purpose, they assume a partially observable Markov decision process that can handle state uncertainty. The firm is to maximize expected future cash flows that are discounted over an infinite planning horizon. The dynamic optimization problem can be solved with dynamic programming. The application to the data shows that the profit improvement potential is as high as 33 %, underlining the significant profit gains that arise from a better allocation.

Optimal budget allocation across countries, products, and spend categories. A limitation to many normative marketing spend models for pharmaceuticals is that they assume profit maximization for a single drug in a single country/category. Pharmaceutical firms, however, do not manage individual products but a portfolio of products. In addition, they are present across the globe, so limited financial resources also need to be allocated across regions.

Assuming an international firm that operates across the world and sells several products, Fischer et al. (2011b) attempt to solve the dynamic portfolio-optimization problem. To promote the drugs management can use various marketing activities that have short-term and long-term effects on sales. These effects are captured by a marketing stock variable (Nerlove and Arrow 1962). In addition, the authors assume that drug sales follow a life cycle whose shape can be influenced by (early) marketing investments. Top management sets the total marketing budget R that is fixed over the planning horizon T. But it can be adjusted during next year's planning cycle. Consistent with the budgeting practice in many firms, budget allocation decisions are made at the end of each year for the next year.

If the firm wishes to maximize the net present value of its product portfolio, Π, the following constrained dynamic profit maximization problem needs to be solved:

$$\underset{s_{ki}}{\text{Max}} \prod = \underbrace{\int_{t=0}^{T} \underbrace{e^{-rt}}_{\text{Discounting}} \left\{ \left[\sum_{k\in K} \sum_{i\in I_k} \left(\underbrace{p_{ki} - c_{ki}}_{\text{Profit contribution}} \right) \cdot \underbrace{q_{ki}\left(ET_{ki}+t, \mathbf{s}_{ki}, \mathbf{z}_{ki}\right)}_{\text{unit sales}} \right] - \underbrace{\sum_{k\in K} \sum_{i\in I_k} \sum_{n\in N_i} x_{kin}}_{\text{Marketing expenditures}} \right\} dt}_{\text{Discounted net value of product portfolic}} \tag{19.15}$$

$$\text{subject to R} = \sum_{k\in K} \sum_{i\in I_k} \sum_{n\in N_i} x_{kin}, \text{ with} \frac{dR}{dt} = 0, \ \left(\text{Budget constraint}\right) \tag{19.16}$$

$$\frac{dS_{kin}}{dt} = -\delta_{kin} S_{kin} + x_{kin}, \quad \text{with } x_{kin} \geq 0, \quad \left(\text{State variable equation}\right) \tag{19.17}$$

$$S_{kin} \geq 0, \quad S_{kin}(0) = S_{kin0}, \quad \text{and} \quad S_{kin}(T) = S_{kinT}. \quad \left(\text{Boundary conditions}\right) \tag{19.18}$$

Here, k denotes the country with the index set K and i denotes the product, whereas the set of products offered in country k may vary and is given by I_k. The index n denotes the spending category and N_i is the associated index set that may vary across products. $\mathbf{S}_{ki}$ is an N_i-dimensional row vector summarizing the activity-specific marketing stocks for product i. ET measures the elapsed time since launch of a product in $t=0$, r is a discount rate, $0<r<\infty$, p denotes price, c is marginal cost, q measures sales, $\mathbf{Z}$ is a vector of covariates, and x_n denotes activity-specific marketing expenditures. Using the calculus of variations together with the Lagrange approach, the following solution for the optimal budget can be derived:

$$x^*_{kin}(t) \cong \frac{\text{Max}\left\{w^*_{kin}(t), 0\right\}}{\sum_{l\in k} \sum_{j\in h} \sum_{m\in N_j} \text{Max}\left\{w^*_{ljm}(t), 0\right\}} R,$$

$$\forall k \in K, i \in I_k, n \in N_i, t \in [0, T], \tag{19.19}$$

with

$$w^*_{kin}(t) = \left(\underbrace{p_{ki} - c_{ki}}_{\text{Profit contribution}} \right) \underbrace{q^*_{ki}(t)}_{\text{Unit sales}} \left(\underbrace{\varepsilon_{f\left[x^*_{kin}(t)\right]}}_{\substack{\text{Sales elasticity} \\ \text{w.r.t.marketing}}} + \underbrace{\varepsilon_{g\left[x^*_{kin}(t)\right]}}_{\substack{\text{Growth elasticity} \\ \text{w.r.t. marketing}}} \right) \Big/ \underbrace{\left(r + 1 - \gamma_{kin}\right)}_{\substack{\text{Discounted marketing} \\ \text{multiplier}}} \tag{19.20}$$

where w is an allocation weight, γ measures the marketing carryover, and all other terms are defined as earlier. The star indicates that variables are in their optimum. Fischer et al. (2011b) note that this solution also holds under the assumption of Nash competition. Optimal budgets, however, are likely to be different from monopoly budgets since optimum values for sales and elasticities depend on competitor equilibrium values.

Fischer et al. apply the approach to the budget allocation process at Bayer, a global pharmaceutical and chemical firm. The authors note that solving the conditions for optimal budgets in (19.19) requires a numerical optimization algorithm. Because managers do not understand how a specific budget recommendation arises from such a black box they do not accept it. For this reason, the authors develop an easy-to-implement heuristic rule that can be used in a spreadsheet environment. The heuristic integrates three types of information in form of an attraction rule to characterize the relative attractiveness of a product in terms of its future profit generation potential:

- The long-term effectiveness of marketing investments in the product
- The profit contribution of the product
- The product's growth expectations

Model implementation at Bayer resulted into a significant profit improvement potential of more than 50 %. For the assumed 5-year planning horizon, that increase was worth of more than EUR 500 million in incremental discounted cash flows.

19.5 Conclusions and Future Research

The pharmaceutical industry is a major industry. Pharmaceutical firms are among the top marketing spenders across the world. Insofar, the industry offers the need and the field for research on marketing spending that should contribute to our knowledge. There is a solid ground of modeling approaches and empirical insights. We have gained good knowledge about the responsiveness of pharmaceutical demand towards traditional marketing activities such as detailing and professional journal advertising, but also with respect to newer activities such as DTCA. We have a good basic understanding of how to model the diffusion process of a new drug. The double-log model, the mixed logit model, and the NBD model have turned out to offer powerful modeling frameworks to describe market response in terms of brand sales, brand choice, and prescription rates. Based on the achieved

level of knowledge, I see several lines of potentially fruitful future research activities. This choice is, of course, subjective, and I do not claim to be exhaustive.

Descriptive research on budgeting behavior. The industry facts demonstrate in an impressive way how marketing-intensive the pharmaceutical business is. Expenditures are high and cover a broad range of activities. In addition, the business is truly global and competition is fierce in many markets. Research has focused so far on describing market response to marketing activities and on normative models that improve budget setting. It is, however, striking that we know almost nothing about the real behavior of pharmaceutical managers. The study by Wagner and Fischer (2011) is a first step in this direction, but we need more research to understand the drivers and conditions under which marketing budgets are set. Which role do geographic regions play in this process? How do firms use the rich supply of brand-level and physician-level data provided by leading commercial vendors for their budget decisions? What are the key objectives: profits, market share, or sales growth? How is the budgeting process organized in multinational, multiproduct firms? These questions may be addressed with different research approaches, among them survey studies, econometric models, and experimental studies.

Model building. Extant research has produced a variety of models to describe various pharmaceutical marketing phenomena. Several interesting questions have not been addressed and probably require new modeling approaches. For example, the diabetes care market offers specific features that are different from other pharmaceutical markets. Since diabetes is one of the greatest challenges to the healthcare systems of developed countries in the future, it is important to understand that market. Patients require a blood sugar meter and the corresponding test stripes for controlling blood sugar levels. Meters and stripes cannot be substituted across manufacturers. It is common practice to heavily promote and subsidize the meters in order to gain and retain patients. In promoting these devices, practice nurses and pharmacists increasingly take a gatekeeper role. We need new model approaches to describe this complex, multi-agent market and derive recommendations about spending decisions.

Another promising avenue for model building is the business for generics. Do the existing response models appropriately capture the demand and supply processes after patent expiry? By definition, the generic business model is centered on cost leadership and discount pricing. How do generic firms compete with each other and with innovating firms? Are there differences? Which role does the price really play? Given the strong focus on price, does that mean detailing and other communication activities are irrelevant? How does that resonate with the observation that the world largest generic manufacturer Teva spends 18 % of its revenues or US $ 3 billion, respectively, on marketing (see Sect. 19.1.3 again)?

Effectiveness of new marketing instruments. Empirical results show that DTCA is not very effective compared with detailing and even produces negative ROIs. An explanation for the high investments in DTCA is their relevance for brand building. We do not know much about brand building in pharmaceutical markets. What does it mean to be

a strong prescription drug brand? For whom is it relevant, the physician, the patient, or other stakeholders? Which media channels are most productive in establishing a pharmaceutical brand? Are there differences to common consumer markets?

Closely related with the challenge to better understand the branding issues is the field of digital marketing. As pointed out in Sect. 19.1.1, the increased use of the Internet and other digital media appears to be a major shift in information gathering for physicians, patients, and other stakeholders. What is the impact of these new media? To what extent should pharmaceutical firms reallocate their budgets to these channels? How should firms deal with social networks and interest groups in the Internet? What is the value of a cross-media campaign that integrates offline and online media to migrate customers to new digital information sources?

New allocation approaches. The availability of new instruments of pharmaceutical promotion also raises the questions of how to determine the optimal budget for them. It requires new modeling approaches because investments into a website, as an example, are nonrecurring, and their benefits in terms of market response are difficult to measure. Since the value of DTCA is likely to manifests in brand building and not so much in direct sales response, it would be good to adapt allocation models to this characteristic of DTCA expenditures.

Given that relationship marketing towards physicians and HMOs is gaining further importance, it would be interesting to have allocation models that allocate resources for acquiring and retaining customers. How can customer lifetime models from other industries be adapted to the specifics of the healthcare industry?

Finally, evidence-based marketing that actively uses results from clinical trials to improve the positioning of the brand appears to be a powerful tool for the future (Azoulay 2002; Venkataraman and Stremersch 2007). To use this instrument, firms need to conduct phase IV studies including drug surveillance studies. What is the optimal budget allocation that takes these investments into account?

Product and spending decisions. Decisions about the level of product quality are typically made early in the development process long before the launch of a new chemical entity. Product development has to follow a predefined process of clinical trials termed Phase I–III studies where product managers can set objectives to achieve a certain planned medical profile. However, given the stochastic nature of clinical trials, chances that a planned ideal product profile will be met are low. In addition, drug regulatory authorities such as the Food and Drug Administration (FDA) are mainly interested in the demonstration of the effectiveness and safety of a new chemical entity leaving little room for marketing to shape Phase I–III trials. Marketing usually has high impact on the design of Phase IV studies that are initiated *after* the launch of the drug. An important objective of such trials is to demonstrate the applicability of the drug to new indications that expand the market. It would be interesting to know how the design of a Phase IV study impacts the quality of its outcome that is further used in positioning and communication strategies. Is it a significant moderator of the marketing success? What is the value of comparative product promotion based on comparative Phase IV studies relative to non-comparative promotion?

Pricing and spending decisions. Pricing decisions are based on cash-flow objectives, the therapeutic benefits of a drug, competitive pressures, and government regulations. Given that pharmaceutical products need to be marketed globally to recover the immense development cost, interactions across international markets have received increased attention in recent years (Chintagunta and Desiraju 2005). Many European countries follow a reference price system where prices are set according to a reference level of one or several other countries. As an example, Italy, France, and the Netherlands use an average price of other countries whereas Greece and Spain adopt the lowest price from a list of countries. In addition, many countries require the innovating firm to document a beneficial cost-benefit ratio to warrant a certain price. Only Germany, the UK, and Switzerland—among European countries—allow markets to set prices for drugs. As a consequence, the pricing decision has become highly complex and cannot be separated from the international rollout strategy. Firms decide prices and the international launch sequence simultaneously long before the approval of the drug by the first national regulatory authority. What about the communication strategy? Which implication does the international launch sequence have on budget setting? To what extent does a fast rollout across many markets may lead to underfinanced marketing budgets because total financial resources are limited?

New pricing challenges may also arise after patent expiry when generic competitors enter the market (Gonzalez et al. 2008). Typically, price competition among generic competitors is intense leading to short-term changes in prices. The branded drug may react with short-term price decisions to these challenges. How does the competitive intensity affect the responsiveness of demand towards detailing and other communication activities? Future research could develop models that integrate decisions about marketing expenditures and price for generic drugs.

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Chapter 20
Modeling the Effects of Promotional Efforts on Aggregate Pharmaceutical Demand: What We Know and Challenges for the Future

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Abstract Pharmaceutical marketing is becoming an important area of research in its own right, as evidenced by the steady increase in relevant papers published in the major marketing journals in recent years. These papers utilize different modeling techniques and types of data. In this chapter we focus on empirical research that studies the effect of marketing on aggregate pharmaceutical demand and we start with an overview of the most important published work. We then focus on two questions that are particularly relevant for the pharmaceutical market: (1) How do marketing variables affect the diffusion pattern of newly introduced pharmaceutical innovations? (2) How do dynamics influence pharmaceutical marketing effectiveness? We conclude with a look at some issues for the future along with an associated research agenda.

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20.1 Introduction

The pharmaceutical industry is an important sector in a global societal context. For many developed countries, health expenditures exceed 10 % of GDP (OECD 2011), and expenditure on pharmaceuticals accounts for approximately 10 % of this total (CMS 2011). Consequently, government agencies, special interest groups, and the media closely follow developments in the industry. One aspect that attracts significant attention is the widely debated use of pharmaceutical marketing activities (Families USA 2002). Opponents criticize pharmaceutical marketing for being superfluous, distorting physician prescribing behavior and contributing to overuse and misuse of prescription drugs, and for being a major cause of high prices (Families USA 2001). On the other hand pharmaceutical manufacturers defend their expenditure on marketing by claiming that it is essential to optimize their return on R&D investment in order to ensure survival in the market. In addition, rapid returns from R&D, through successful marketing of existing products, not only offer incentives to invest in new therapies but also guarantee rapid market takeoff. The fast adoption of new and superior medications is beneficial for all stakeholders in the pharmaceutical market (Calfee 2002).

Stremersch (2008) and Shankar et al. (2008) observe that the scholarly attention paid to the pharmaceutical industry is increasing. This is demonstrated by the increase in the number of papers published by top journals in marketing, special sessions that are organized at mainstream marketing conferences, and the publication of this book. In this chapter we provide an overview of empirical papers which examine the effectiveness of pharmaceutical marketing on aggregate demand.

There are several reasons why both practitioners and policy makers are interested in establishing the effectiveness of pharmaceutical marketing efforts. Firstly, and particularly important to practitioners, is the extent to which promotional efforts significantly affect demand measured, for example, by the number of (new) prescriptions written, market growth, or market share. When allocating budgets it is important to know the size of promotional effects as well as whether or not they are systematic, and also whether the demand for pharmaceutical products can be considered to be price elastic or inelastic.

Secondly, it is important to clarify the function of promotion: The economic literature provides a classification where promotional efforts may have an informative function and/or a persuasive function. The informative function provides information to decision makers, thereby contributing to transparency in the market which leads to better decisions. Patients and tax payers benefit from these informational promotional efforts undertaken by pharmaceutical manufacturers. The persuasive function causes decision makers to select products out of habit rather than by evaluative choice (Leffler 1981). This may lead to misprescription and overuse (USA Today, Kaiser Family Foundation, Harvard School of Public Health 2008), for example, in cases where the promoted brand is prescribed, rather than a better or less expensive available alternative. Persuasive pharmaceutical promotional efforts receive much attention in public debate (see, e.g., Angell 2005; Chetley 1995), and in some countries such as Italy and France pharmaceutical promotional efforts are

taxed because of the allegedly adverse effects on welfare (see, e.g., The Pharma Letter 1994). The distinction between the informative and persuasive functions of promotion is especially relevant in the pharmaceutical market and highly relevant for policy makers as it touches upon the ethical question as to whether marketing efforts in this context can be justified.

Thirdly, it can be argued that demand elasticities of marketing instruments such as detailing or advertising might be very different in the pharmaceutical market compared to other markets. This can be explained by the fact that (in comparison to other markets) physicians rely more on information sources such as (medical) journal advertising due to the high-risk decisions that they sometimes have to make with regard to the optimal treatment of a patient when there is a significant level of diagnostic uncertainty (Joseph and Mantrala 2009).

Several papers have appeared in the literature specifically reviewing research on pharmaceutical marketing. The first two were Manchanda and Honka (2005) and Manchanda et al. (2005). More recently, Stremersch and van Dyck (2009) provided a broad overview of developments in the research stream on marketing for the life sciences, while another overview by Shankar et al. (2008) examined strategic questions surrounding new product development and market entry. Kremer et al. (2008) presented the first meta-analysis of pharmaceutical promotional expenditures.

The scope of this chapter is broader than Manchanda and Honka's (2005) integrative review of the literature on detailing: we focus on all marketing instruments. Compared to the other three overview papers, we take a narrower, but deeper perspective. Unlike Manchanda et al. (2005) we confine our analysis to aggregate demand. We acknowledge the fact that there are many studies on a more disaggregate demand level (notably on the physician level) that are important and answer very relevant research questions, but they are beyond the scope of the present chapter, as we explain below. Stremersch and van Dyck (2009) look at the wider healthcare market, whereas we examine only prescription drugs. Rather than Shankar et al. (2008) examination of strategic decisions regarding new product development and the earlier stages of the product life cycle, we provide an overview of pharmaceutical marketing effectiveness on different levels of aggregate demand. We therefore complement Kremer et al. (2008), by discussing the empirical studies on pharmaceutical promotion in greater detail.

We choose to focus on aggregate demand rather than individual level models for the following reasons. Aggregate models provide a comprehensive coverage of the relevant promotional variables and their relationship to demand, whereas studies which look at individual demand normally look at only one brand in a category as the individual level data on promotion is only available for that brand. This means that even where individual level prescribing data is available competitive individual level detailing data is usually absent and therefore subsequent analysis does not account for inter- and intra-individual competitive effects. Moreover, most pharmaceutical firms have access to aggregate demand data, but not necessarily to individual demand data. Finally, we observe that the body of literature on aggregate demand studies has grown large enough to provide empirical generalizations.

We organize this chapter according to the framework of Fig. 20.1. In the next section we present an overview of papers that investigate the effectiveness of

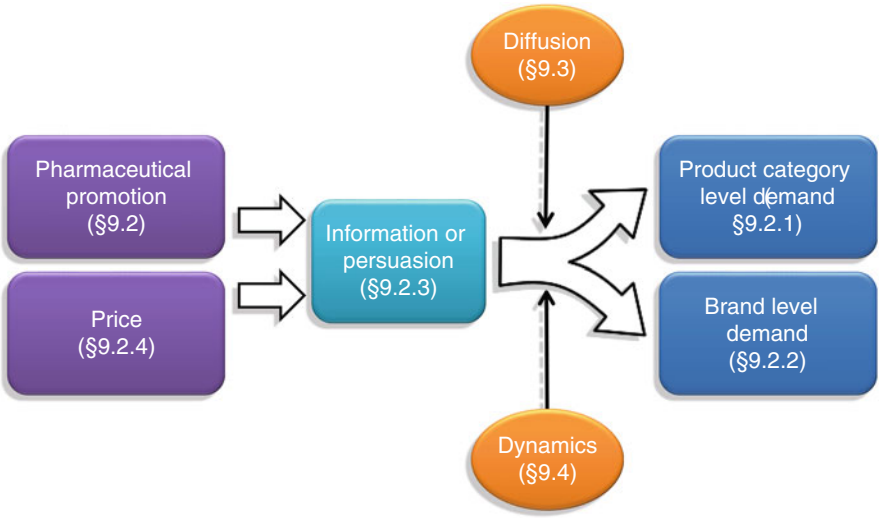

Fig. 20.1 Flow diagram of the framework of this chapter

pharmaceutical promotion. We discuss the significance and relevance of pharmaceutical promotional effects, where we distinguish between effects on product category level demand (Sect. 20.2.1) and effects on brand level demand (Sect. 20.2.2). We elaborate on the implications of the outcomes of this research and review earlier studies and what they report on informative and/or persuasive effects of pharmaceutical promotion (Sect. 20.2.3). As the type of effect of pharmaceutical promotion also affects the price sensitivity of the demand for drugs, we discuss the role of price in Sect. 20.2.4.

In subsequent sections we distinguish two specific issues regarding promotional effectiveness that are particularly important in the pharmaceutical market. Given the importance of innovation in this market and the need for rapid take off (Tellis et al. 2003), we elaborate on applications and findings of studies that investigate how marketing efforts affect the diffusion of new pharmaceutical innovations in Sect. 20.3. The turbulence in this market, caused by changes in regulation and rapid technological developments (Achilladelis and Antonakis 2001), induces complex dynamic effects of pharmaceutical promotions. We give an overview of studies that examine how these dynamics impact the effectiveness of pharmaceutical promotion in Sect. 20.4. Section 20.5 takes a look at future issues and suggests a research agenda.

20.2 Overview of Studies of Pharmaceutical Promotional Effectiveness

In Table 20.1 we summarize the key studies which examine the effectiveness of pharmaceutical promotion on aggregate demand. In the second column of Table 20.1 we report the type of model that is used to identify the promotional effect, and the

Table 20.1 Overview of key studies of pharmaceutical promotional effectiveness on aggregate demand

	Model	Endogeneity	Heterogeneity	Type of data	Key findings
(Disease) category level					
Berndt et al. (1995, 1997)	Regression	Accommodated	Not relevant	Monthly, one category (H2 antagonists), US	Marketing affects category sales moderately, all marketing instruments are significant. Elasticity estimates: 0.55 (detailing stock), 0.20 (journal advertising stock), 0.01 (DTCA stock)
Calfee et al. (2002)	Regression	Investigated	Not relevant	Monthly data of one category (statins), US	No significant effect of DTCA on new prescriptions or renewals
Chintagunta and Desiraju (2005)	Structural	Accommodated	Accommodated	Quarterly observations on one category (antidepressants) US, UK, France, Italy, and Germany	Detailing is affecting category sales significantly only for US and Italian markets. The effects are quite small (detailing elasticities are 0.09 in the US and 0.02 in Italy)
Fischer and Albers (2010)	Regression	Partly accommodated	Accommodated	Quarterly data of 86 categories	Primary demand effects are rather small. Short-term elasticities: 0.05 (detailing), 0.01 (journal advertising), 0.01 (DTCA); long-term elasticities: 0.28 (detailing), 0.09 (journal advertising), 0.07 (DTCA)
Iizuka and Jin (2005)	Regression	Investigated	Not accommodated	Monthly data of 151 categories	DTCA has a market expanding effect. This effect is about equally strong among different patient segments
Leffler (1981)	Regression	Not accommodated	Not accommodated	Cross-sectional data from 35 categories	Pharmaceutical promotion assists entry into pharmaceutical markets
Narayanan et al. (2004)	Regression	Accommodated	Not relevant	Monthly, two categories (antihistamines and antiviral), US	Category sales effects only reported for antihistamines: DTCA is significant for category sales; detailing is not

(continued)

Table 20.1 (continued)

	Model	Endogeneity	Heterogeneity	Type of data	Key findings
Rosenthal et al. (2003)	Regression	Accommodated	Not accommodated	Data from five categories, US	DTCA is more effective in increasing category sales (elasticity estimate: 0.1) than detailing (elasticity estimates range from 0.02 to 0.03, depending on method used)
Vakratsas and Kolsarici (2008)	Diffusion	Not accommodated	Not relevant	Monthly data on one new category, non-US	Journal advertising effects are stronger than those of DTCA, detailing is not significant. Pharmaceutical promotion does not affect early market adoption
Brand level					
Azoulay (2002)	Regression	Investigated	Accommodated	Monthly, four drugs in one category (H2 antagonists), US	Pharmaceutical advertising is more "informative" than "persuasive," detailing elasticities range from 0.7 to 1.2; journal advertising elasticities range from 0.17 to 0.63
Bhattacharjya and Vogt (2003)	Regression	Accommodated	Not accommodated	Quarterly data on 11 molecules in one category (beta blockers), US	Prices increase whereas promotional activities decrease over a drug's life cycle. Price sensitivity is lower later in the cycle. Advertising is not significant
Berndt et al. (1995, 1997)	Regression	Accommodated	Not accommodated	Monthly, four drugs in one category (H2 antagonists), US	Detailing has larger sales response than journal advertising
Berndt et al. (2003b)	Regression	Investigated	Accommodated	Monthly, four drugs in one category (H2 antagonists), US	Detailing elasticities of about 1, minor differences across products
Ching and Ishihara (2010)	Structural	Accommodated	Accommodated	Monthly, two drugs in one category (ACE inhibitors), Canada	Depending on initial priors of drug quality, learning affects detailing effectiveness

Chintagunta and Desiraju (2005)	Structural	Accommodated	Accommodated	Quarterly observations on four brands in one category (antidepressants), data from five countries: US, UK, France, Italy, and Germany	Detailing elasticities are comparable across the US, Germany, and Italy (around 0.2). Detailing elasticities are larger for the UK (.55) and France (2.43)
Currie and Park (2002)	Structural	Accommodated	Not accommodated	Yearly, 35 drugs in one category (anti depressants), US	Advertising is primarily informative and therefore beneficial to society; the "persuasive" effects of detailing and journal advertising are insignificant
De Laat et al. (2002)	Regression	Not accommodated	Not accommodated	Monthly data on 140 brands in 11 categories, The Netherlands	Pharmaceutical marketing elasticity equals 0.3. Pharmaceutical marketing lowers price sensitivity
Dekimpe and Hanssens (1999)	VAR	Accommodated	Not relevant	Monthly, two drugs in one category, US	Journal advertising has relatively small but persistent (and significant) effects on prescriptions. Sales response to detailing is stronger in the short run, insignificant in the long run
Gatignon et al. (1990)	Regression	Not accommodated	Accommodated	Cross-sectional data from 68 drugs in 11 categories, US	Detailing is significant and has positive effect on market share of new introductions. Market growth is the strongest moderator (positive effect)
Hurwitz and Caves (1988)	Regression	Accommodated	Not accommodated	Yearly data of 29 drugs in different categories, US	Advertising is largely persuasive
Fischer and Albers (2010)	Regression	Investigated	Accommodated	Quarterly, 2,831 brands in 86 categories, US	Estimated short-term own marketing mix effects are relatively small, with considerable variation across brands and across instruments. Long-term effects are larger than short-term effects. Order of magnitude: detailing—journal advertising—DTCA

(continued)

Table 20.1 (continued)

	Model	Endogeneity	Heterogeneity	Type of data	Key findings
Hahn et al. (1994)	Diffusion	Not accommodated	Accommodated	Monthly, 21 brands in seven categories, US	Promotion is positively related to trial rate for most brands. The size of the effect is positively related to market growth and product quality attributes
Kolsarici and Vakratsas (2010)	Augmented Kalman filter	Not accommodated	Not relevant	Monthly, one drug in a new category, non-US	Brand advertising messages are more effective than category advertising messages. Average elasticities are: 0.12 (detailing), 0.04 (physician journal advertising), 0.05 (brand advertising), 0.04 (category advertising)
Leeflang et al. (1992)	Regression	Not accommodated	Not relevant	Monthly, one drug in the hypnotics and sedatives category, UK	Detailing more effective than journal advertising and direct mail
Leeflang and Wieringa (2010)	Regression	Not accommodated	Accommodated	Monthly, 49 brands in five categories, The Netherlands	Large degree of heterogeneity in promotional effects. Detailing effects only significant and positive for 10 % of the brands, this percentage is 6 % for journal advertising and 4 % for direct mail. Marketing expenditures do not affect the price elasticity
Leffler (1981)	Regression	Not accommodated	Not accommodated	Cross-sectional data from 51 new products in 35 categories	Detailing has a significant positive effect on the entry success of therapeutically important new drugs
Lilien et al. (1981)	Diffusion	Not accommodated	Accommodated	Quarterly, two drugs in different categories, US	Heterogeneity in detailing effectiveness among products; optimal level depends on stage in life cycle

Montgomery and Silk (1972)	Regression	Not accommodated	Not relevant	Monthly, one drug, country of origin not specified	Heterogeneity in effectiveness of promotional instruments: journal advertising is most effective, followed by samples and literature and direct mail
Murphy et al. (1992)	Regression	Not accommodated	Not accommodated	Yearly data on 87 drugs	Promotional effectiveness is moderated by therapeutic novelty
Narayanan et al. (2004)	Mixed logit	Accommodated	Partly accommodated	Monthly, six drugs in two categories (antihistamines and antiviral), US	Detailing and DTCA affect demand synergistically, detailing raises price sensitivity, and detailing has a higher return-on-investment (ROI) than does DTCA
Narayanan et al. (2005)	Structural	Not accommodated	Partly accommodated	Monthly, three drugs in one category (antihistamines), US	Marketing efforts primarily have indirect effects 6–14 months after introduction, the direct effect dominates subsequently. Detailing is more effective than DTCA and other marketing efforts
(Neslin 2001)	Regression	No	No	Monthly data on 391 branded drugs, US	Medical journal advertising has highest ROI, followed by physician meetings and events, detailing, and DTCA. Detailing ROI is higher for large and more recently launched brands
Osinga et al. (2010)	Kalman filtering	Accommodated	Accommodated	Monthly, 89 drugs in 39 categories, US	Persistent effects of marketing efforts aimed at the physician are more likely than assumed so far, the likelihood is much higher early in the product life cycle

(continued)

Table 20.1 (continued)

	Model	Endogeneity	Heterogeneity	Type of data	Key findings
Parsons and Vanden Abeele (1981)	Regression	Not accommodated	Not relevant	Monthly, one drug in the prophylactic drugs category, Belgium	Detailing effectiveness is moderated by samples and handouts. Its overall elasticity is positive, but smaller than one
Rao and Yamada (1988)	Diffusion	No	Yes	Monthly, 19 brands prescribed by three types of physicians, US	Detailing effectiveness increases as the drug is rated to be more innovative and when it is appropriate for a larger range of ailments
Rizzo (1999)	Regression	Not accommodated	Not accommodated	Yearly data of 46 brands in five categories, US	Detailing systematically lowers price sensitivity. Detailing elasticities around 0.2
Rosenthal et al. (2003)	Regression	Accommodated	Not accommodated	Monthly data of all brands in five categories, US	No evidence of significant effects of detailing and DTCA on brand level demand
Shankar (1997)	Structural	Accommodated	Accommodated	Monthly, a pioneer and a late entrant in a chronic disease category, US	Optimal allocation of the pioneer's marketing actions depends on the structure of competition, the impact of the late entrant on its elasticities, and the elasticities of pioneer and late entrant
Shankar (2009)	Structural	Accommodated	Partly accommodated	Monthly data of 40 brands from eight categories, US	It may be advantageous to spend aggressively on the high-elasticity marketing variable early to build market share and escalate it over the life cycle to maintain market dominance
Shankar et al. (1998)	Diffusion	Not accommodated	Not accommodated	Monthly, 13 drugs in two categories, US	Innovative late entrants can reduce marketing effectiveness of the pioneer

Shankar et al. (1999)	Regression	Not accommodated	Not accommodated	Monthly, 29 drugs in six categories, US	Marketing effectiveness is larger for pioneers than for growth-stage entrants, which have in turn larger effectiveness than mature-stage entrants
Windmeijer et al. (2006)	Regression	Investigated	Not accommodated	Monthly data on 140 brands in 11 categories, The Netherlands	Pharmaceutical marketing elasticity equals 0.3. Pharmaceutical marketing lowers price sensitivity
Wittink (2002)	Regression	Not accommodated	Not accommodated	Monthly data on 392 branded drugs, US	Meeting expenditures, detailing, and journal advertising have highest ROI for large brands ($500MM+) launched after 1997. DTCA provides its best returns for large brands launched from 1998 to 2000. Additional resources allocated to journal advertising for small brands ($25–100MM), in addition to large brands, could provide very positive returns

third column indicates whether or not the model accounts for endogeneity of the promotional variables. When a study accommodates endogeneity in other variables than promotional variables (e.g., price) we classify this study as partly accommodating endogeneity. Studies that investigate endogeneity, and find that this is not a concern, are labeled as "Investigated." Column four shows whether heterogeneity of the promotional effects across brands/categories is accounted for. Some studies do not estimate brand-specific parameters, but report brand-specific marginal responses to marketing variables (induced by, e.g., interaction effects). Such studies are labeled as partly accommodating heterogeneity. The fifth column describes the type of data used and the geographical location of the study. The last column summarizes the key findings for each study. We categorize these studies according to two levels of demand (Leeflang et al. 2000): category- and brand level. It is important to distinguish between these two levels of demand as pharmaceutical promotions are likely to affect them to a different extent. Brand level sales are primarily driven by "own" marketing efforts and to a lesser extent by competitive expenditures. The resulting sales effect can be seen as a sum of "market stealing" (brand switching) effects and "market making" (category expansion) effects (see, e.g., De Laat et al. 2002), whereas sales at the product category level are the result of market making effects only. In Sect. 20.2.1 we review studies that examine product category level effects. In Sect. 20.2.2 we focus on the effects of marketing activities on brand level demand.

20.2.1 Product Category Level Demand Effects of Pharmaceutical Promotion

One feature of the product category studies in Table 20.1 is that promotional expenditures have only small effects on (category) demand (Berndt et al. 1995, 1997; Chintagunta and Desiraju 2005; Rosenthal et al. 2003). Fischer and Albers (2010) report primary demand elasticities that are averaged across a large number of categories. The average short-term elasticities are smaller than 0.05 for all instruments. Long-term elasticities are larger, but still well below one, indicating inelastic response. The conclusion is that pharmaceutical marketing activities typically have only moderate effects on the prescription behavior of physicians, consistent with Manchanda et al. (2005) and Kremer et al. (2008). On the one hand, this does not provide much support for the argument that pharmaceutical marketing is generating unwanted demand effects by stimulating overprescription and misuse (see, e.g., Avorn and Solomon 2000). On the other hand, this finding may support the claim that marketing expenditures contribute to increased costs of pharmaceutical treatment (Spurling et al. 2010) because large amounts of marketing effort are needed to generate sizeable sales effects. We discuss the relationship between marketing and drug prices in greater detail in Sects. 20.2.3 and 20.2.4.

The question of which marketing instrument is most effective in stimulating product category demand is highly relevant to policy makers, because this would identify the main driver for category expansion. This could, in turn, guide the selection of

appropriate communication tools to generate awareness for under-treated ailments, and also discourage the use of certain instruments for categories where pharmaceutical treatment is less effective or where additional treatment is deemed unnecessary, i.e., to prevent overprescription. Unfortunately, there is no consensus about which marketing instrument is the main driver for category demand in the pharmaceutical market. Most studies appear to find that detailing is most effective, followed by journal advertising and direct-to-consumer advertising (DTCA) (Berndt et al. 1995, 1997; Fischer and Albers 2010), but there are notable exceptions. Narayanan et al. (2004) find that detailing is not significant and that DTCA is the main category expansion driver. This finding is confirmed by Rosenthal et al. (2003), but is contradicted by Calfee et al. (2002), who discover no effect of either DTCA or other pharmaceutical marketing instruments on new prescriptions or renewals in a disease category. Vakratsas and Kolsarici (2008) find that journal advertising is the most effective instrument, followed by DTCA and that detailing is not significant. There is a need for reconciling these different findings, for example, by determining which variables moderate the effectiveness of the different instruments on category demand.

The type of analysis that is used to determine the effects of promotional efforts on category demand may moderate promotional effectiveness in several ways. As we discuss in Sect. 20.4.4, Fischer and Albers (2010) derive category sales effects from brand-sales models. They argue that this method is more accurate than the more common approach of inferring category sales effects from category sales models and this might explain some of the differences observed across studies. Similarly, analyses that account for endogeneity tend to produce different results than those which do not (Kremer et al. 2008). In a number of studies category demand data are pooled over categories. Leeflang and Wieringa (2010) demonstrate that pooling across categories should be avoided as such studies (e.g., Iizuka and Jin 2005) are more likely to generate biased results than those studies which do not.

Another possible set of moderators may be found in market characteristics. For example, Fischer and Albers (2010) find considerable differences between short-term and long-term elasticities. This might indicate that the age of the product category moderates promotional effectiveness, which possibly affects some instruments more than others. Further research here is needed as, despite the growth in the number of studies on category level demand, the body of knowledge is still not sufficiently large to identify empirically the relevance of possible moderators.

20.2.2 Brand Level Demand Effects of Pharmaceutical Promotion

The number of studies that examine pharmaceutical promotional effectiveness at the brand level is considerably larger than at the category level. Compared to category level outcomes most brand level studies report somewhat stronger promotional effects, but the effects are still reported to be moderate (Azoulay 2002; Berndt et al. 2003b; De Laat et al. 2002; Kolsarici and Vakratsas 2010; Windmeijer et al. 2006), or small

or insignificant (e.g., Currie and Park 2002; Leeflang and Wieringa 2010; Montgomery and Silk 1972; Parsons and Vanden Abeele 1981; Rosenthal et al. 2003). Vakratsas and Kolsarici (2008) argue that the low level of marketing effectiveness may be due to saturation effects.

A second important observation from Table 20.1 is that the effectiveness of promotional expenditures exhibits a large degree of heterogeneity (Leeflang and Wieringa 2010; Manchanda et al. 2005; Narayanan et al. 2004). The larger number of studies at the brand level also allows the discussion of possible moderators in greater detail. We distinguish four different categories of moderators: (1) the type of promotional instrument, (2) product category characteristics, (3) market characteristics, and (4) model/data characteristics (Kremer et al. 2008).

Ad (1) Moderating effects of type of promotional instrument. Montgomery and Silk (1972) find that brand level sales effectiveness differs by instrument and they recommend the inclusion of disaggregated promotional tools. Almost all later studies that accommodate instrument-specific differences confirm this heterogeneity in effectiveness. The general finding is that detailing is the most effective promotional tool, whereas DTCA is least effective at the brand level (Fischer and Albers 2010). The effectiveness of other instruments such as journal advertising, meeting expenditures, and direct mail is generally found to be lower than that of detailing, but higher than DTCA. More generally, the group of direct to physician (DTP) instruments has a stronger influence on demand than DTCA (Narayanan et al. 2004). These outcomes correspond with Kremer et al. (2008) who estimate the following instrument-specific elasticities: 0.32 for detailing, 0.123 journal advertising, and 0.073 for DTCA. The detailing elasticity estimate is remarkably close to that measured in a meta-analysis of personal selling by Albers et al. (2010) who report an average detailing elasticity of 0.31.

There are several authors who find that effect duration differs by promotional instrument (e.g., Dekimpe and Hanssens 1999; Leeflang et al. 1992; Montgomery and Silk 1972). Consequently, it is important not only to accommodate lagged effects for the different promotional instruments but also to allow for heterogeneity in their dynamic response.

Some authors have investigated interactions between pharmaceutical promotion instruments. Parsons and Vanden Abeele (1981) find a negative interaction between samples and printed information that sales representatives leave at a physician's office after a sales call. Such a negative interaction effect is sometimes referred to as "jamming" (Azoulay 2002). Narayanan et al. (2004) find significant positive interactions between detailing and DTCA, where, interestingly, DTCA effectiveness benefits more from detailing efforts than vice versa. They find that other marketing activities (journal advertising, meetings, and events) impact negatively on DTCA and detailing effectiveness.

Ad (2) Moderating effects of product characteristics. The studies in Table 20.1 suggest that product characteristics might influence promotional effectiveness. Shankar et al. (1999) find significant order of entry effects: marketing effectiveness reduces when a brand enters the market later. Rao and Yamada (1988) find that

detailing effectiveness is larger for more innovative drugs and drugs that treat a broader range of ailments. Murphy et al. (1992) find that promotional effectiveness is moderated by therapeutic novelty. Hahn et al. (1994) find that pharmaceutical promotion has a stronger effect on trial rate when the new drug is of higher quality and when the corresponding therapeutic market is growing. However, Kremer et al. (2008) find no significant moderating effects of product characteristics.

Ad (*3*) *Moderating effects of market characteristics.* The fifth column in Table 20.1 indicates that studies look at a wide range of therapeutic categories, and promotional effectiveness might differ by therapeutic category. There is evidence that therapeutic category affects diagnosis uncertainty (Joseph and Mantrala 2009), and this might cause physicians to utilize wider information sources such as detailing and journal advertising for some prescription decisions. The level of pharmaceutical expenditure also differs across categories, and this could lead to different degrees of saturation across categories (Vakratsas and Kolsarici 2008). Gatignon et al. (1990) find that market growth is a strong and positive moderator of detailing effectiveness. These findings are confirmed by Kremer et al. (2008) who find significant differences in responsiveness among therapeutic categories, and conclude that there are interactions between the types of marketing instrument.

Another market characteristic that might influence sales responsiveness is the country under study. Differences in (self) regulation on, for example, the use of promotional instruments, cultural differences, and different saturation levels might cause heterogeneity in promotional effectiveness across countries (Chintagunta and Desiraju 2005). However, Kremer et al. (2008) do not find systematic evidence of such effects in their meta-analysis.

Ad (*4*) *Moderating effects of model and data characteristics.* The third column of Table 20.1 indicates that slightly more than half of the studies accommodate endogeneity. Studies that do not assume that promotional expenditures are exogenous would potentially result in a correlation between promotional expenditures and the error term and create a bias in the promotional effect estimates. If promotional expenditures are set as a percentage of sales, this will generate endogeneity, which, when ignored, will lead to a positive bias (Shugan 2004), which means that the promotional effects are overestimated. Indeed, Kremer et al. (2008) find that studies that accommodate endogeneity report promotional elasticities that are significantly lower than studies that do not.

The fourth column of Table 20.1 indicates whether heterogeneity in promotional effectiveness across brands or categories is accounted for. We have already discussed that promotional effectiveness is highly heterogeneous, across instruments (see Ad (1) above) and across therapeutic categories (see the previous subsection). Leeflang and Wieringa (2010) establish that promotional effectiveness also differs between brands within a category. Hence studies that pool brands, categories, or instruments deserve special attention, because the results of the study might be affected by the pooling decision. As an example of this phenomenon De Laat et al. (2002) investigated the effects of promotional investments on prescribing behavior by pooling across 140 brands in 11 categories. Leeflang and Wieringa (2010), using the same

data, demonstrate that pooling across brands within categories and across brands in different categories obfuscates the underlying heterogeneity. What is more important, they find that by conducting brand level analyses, the conclusions regarding the effectiveness of pharmaceutical instruments are diametrically opposed to the findings of De Laat et al. (2002).

We conclude that brand level demand effects of pharmaceutical marketing are generally positive and significant, but moderate in size. Effectiveness is moderated by the type of marketing instrument: detailing appears to be the most effective, followed by journal advertising, meeting expenditures, and direct mail. DTCA appears to be the least effective instrument at the brand level. We also observe that the effectiveness of pharmaceutical promotion differs across therapeutic categories and that this interacts with the type of marketing instrument used. Another general conclusion is that pharmaceutical marketing efforts usually have substantial lagged effects. These findings have important consequences for budget allocation decisions across products and markets, and time. The implications for researchers in this market are that they should account for differences in effectiveness and in lag structures of promotional instruments, and accommodate interaction effects.

20.2.3 The Function of Pharmaceutical Promotion

We now turn to the function of promotion in pharmaceutical markets. Several studies that investigate this issue distinguish between the informative and the persuasive functions of promotional efforts. The persuasive function leads to a direct sales effect as it creates market power via investing in promotions for ethical drugs and developing goodwill towards the product. This makes physicians prescribe out of habit rather than by evaluative choice (Leffler 1981). The information function represents an indirect effect, with promotional instruments serving as information sources for prescribers, with the assumption that they learn (and subsequently prescribe) by being exposed to the promotional instrument (Hurwitz and Caves 1988; Leffler 1981). The information function also serves to reduce uncertainty for the risk-averse doctors (Coscelli and Shum 2004).

These functions are investigated in two distinct research streams. In the first, promotion has either a persuasive or an informative function, but not both. This stream assumes that the function is persuasive when promotional efforts reduce price elasticity (e.g., Hurwitz and Caves 1988; Leffler 1981), and this leads to negative welfare effects as it causes physicians to become more loyal to the promoted brand, irrespective of its price (De Laat et al. 2002). On the other hand, promotion has an informative effect when it increases price sensitivity with the resulting positive welfare benefit of physicians responding more strongly to price changes and more efficient allocation of prescribing resources. Some studies find a dominant information effect of promotional instruments (e.g., Leffler 1981; Narayanan et al. 2004), whereas others find a more pervasive persuasion effect (De Laat et al. 2002; Hurwitz and Caves 1988; Rizzo 1999; Windmeijer et al. 2006). Leeflang and Wieringa (2010) find no evidence of persuasive pharmaceutical promotion effects.

The second research stream considers both the persuasive and informative functions of promotion. It uses a structural approach where the informative function is viewed as a means for decision makers to update their prior beliefs and reduce uncertainty about the true quality of the new product (Narayanan et al. 2005). Because this function of promotion affects demand by facilitating learning, it is also called the indirect effect. The direct or persuasive effect then consists of all demand effects that are not indirect (e.g., goodwill). One advantage is that this approach allows for simultaneous occurrence of both effects. Currie and Park (2002) find that advertising is primarily informative and therefore beneficial to society. Their results show that firms advertise heavily when launching a new brand in order to provide information about the benefits. This generates demand, which provides learning opportunities which in turn means that firms can reduce their advertising, eventually to zero, since continued learning is accrued from the increasing cumulative experience with the product. This is partially consistent with the findings of Narayanan et al. (2005) who report that marketing efforts have mainly indirect effects 6–14 months after the drug is launched, but that marketing expenditures thereafter are not reduced to zero with the subsequent primacy of the persuasive function.

A related study by Azoulay (2002) takes a somewhat different approach. He does not distinguish between the two functions of marketing but develops a separate measure for scientific information and finds that its influence on pharmaceutical demand is weaker than the effect of marketing efforts, but still significant and positive. Moreover, he finds that scientific information is an important driver of marketing efforts, and concludes that marketing may perform an important informative function.

We conclude that both functions of promotion appear to play a role in the pharmaceutical market. However, the empirical evidence on their relative importance still generates mixed results. This is in agreement with the medical literature, where a wide range of views is reported among health professionals about pharmaceutical promotion: many perceive it as a useful and convenient source of information, others find that promotion may be misleading (Spurling et al. 2010).

20.2.4 The Role of Price

There are three reasons why the role of price is fundamentally different in the pharmaceutical industry (compared to other markets). Firstly the industry is subject to strict price regulation (Danzon and Chao 2000; Stremersch and Lemmens 2009), Secondly price is affected by the special cost conditions which result from high sunk R&D costs but virtually no marginal costs (Berndt et al. 1995). Finally the role of price is strongly affected by the complexity that results from the multi-agent structure of the pharmaceutical market (Gönül et al. 2001).

Intermediary agents such as insurance firms, health maintenance organizations, or government agencies cover most of the cost of prescription drugs (Manchanda et al. 2005), so that the effect of price also depends on the patients' insurance

coverage and the value of co-payments. In the United States, insurance coverage determines whether the influence of price is direct or indirect. People without health insurance experience a direct price effect, because they must pay for their prescribed products themselves. Consumers with health insurance experience an indirect influence of the price of the product through the co-payments they have to make. Co-payments generally vary across the different brands in a product category, as well as between the different brands and generic equivalents. The preferred status of certain products, as determined by an insured consumer's health plan, determines the co-payment levels, and generic products usually require lower co-payments than brands (Manchanda et al. 2005). We thus assume that consumers who are insured are indirectly influenced by price, because the level of co-payments tends to relate to the retail price level. Haaijer-Ruskamp and Denig (2001) also find that situational features moderate the effect of the price level: in the case of serious or acute illnesses, price has only a minor influence.

The decision making agent is the physician and Gönül et al. (2001) find that considerations about drug efficacy and patients' conditions represent the primary drivers in the decision process, clearly overriding price concerns. Hence physicians, working in the interest of their patients, do not have a financial stimulus to be price-sensitive, and they tend to be unaware of the retail price of specific drugs (Hurwitz and Caves 1988).

There is little consensus about the price elasticity of demand. Some authors find absolute price elasticities larger than one, so that the demand for pharmaceutical products can be classified as price elastic (e.g., Chintagunta and Desiraju 2005; Rizzo 1999), others find (much) smaller price effects (De Laat et al. 2002; Narayanan et al. 2005; Windmeijer et al. 2006), and some find no significant effects of price (Leeflang and Wieringa 2010; Shankar 1997, 2009; Vakratsas and Kolsarici 2008). Rosenthal et al. (2003) even find positive and significant price coefficients, but claim that this is due to the fact that the price variable is measured with error and that it has no close relationship with co-payments.

The studies in Table 20.1 suggest several possible moderators for the apparent heterogeneity in price sensitivity. Some studies find product-specific differences in price sensitivity (Chintagunta and Desiraju 2005; Rizzo 1999) and this might be related to formulary coverage (Gonül et al. 2001). Prices reportedly rise over the product life cycle, with lower price sensitivity later in the cycle (Bhattacharya and Vogt 2003).

Chintagunta and Desiraju (2005) also conclude that market characteristics moderate price sensitivity. They find significant differences in price levels and price sensitivity for the same product across different geographic markets due to variation with respect to price regulation and insurance coverage. Another market characteristic that affects price sensitivity is the presence of generics. The effects of generic entry on pricing depend on the degree of regulation in the country and the price (in-) elasticity of demand before generic entry. The possible level effects range from decreasing to increasing prices (Danzon and Chao 2000). Generics might lower the average price level of products with the same active ingredients, because they increase competition (Manchanda et al. 2005). Some authors find price increases

after generic entry and explain that this may reflect firms taking payoffs from their prior investments in advertising. However, price elasticity of demand increases after generic entry (Bhattacharjya and Vogt 2003).

We conclude that the literature provides mixed results regarding the price elasticity of pharmaceutical demand. Future research that sheds more light on this issue is highly relevant, given that many governments are focusing on reducing national health care budgets, which generates pressure on the pharmaceutical industry to reduce their prices (see also Sect. 20.5).

20.3 Pharmaceutical Promotion and Macro-Level Diffusion Models

Pharmaceutical companies depend on continuous innovation and the successful commercialization of new drugs not only represents a key performance metric but is also the main means of recovering the huge investment in R&D. Diffusion models are useful tools for analyzing and predicting the market penetration of new drugs and provide insights into the effects of pharmaceutical marketing resource allocation which help managers to optimize their decisions. In this section we review macro-level diffusion models in pharmaceutical marketing. These models describe the market-level sales of a new product and focus on understanding the development of the focal new product's position in the market and its response to managerial and environmental variables (Roberts and Lattin 2000). Given our focus on macro-models, we consider neither individual level diffusion models (see, e.g., Chatterjee and Eliashberg 1990) nor models within the proportional-hazard framework (see, e.g., Helsen and Schmittlein 1993; Jain 1992; Jain and Vilcassim 1991; Van den Bulte and Iyengar 2011).

We address two questions: which pharmaceutical marketing instruments are found to affect the diffusion of pharmaceutical innovations and how should they be included in diffusion models?

20.3.1 The Bass Framework

Diffusion models are developed for capturing the typical sales pattern that is associated with the diffusion process of new products. The development of diffusion models is based on the framework developed by Bass (1969). In its basic form, the Bass model has two parameters, the coefficient of innovation and the coefficient of imitation. The coefficient of innovation, also known as the coefficient of *external influence*, indicates what portion of the non-adopters will try the product due to their propensity to innovate. The coefficient of imitation, also known as the coefficient of *internal influence*, is related to the influence that current adopters exert on future trialists of the innovation. The Bass model was initially developed for durables

where only the adoption process is of interest. Later extensions of the Bass model also accommodate repeat purchases; these models are known as trial-repeat diffusion models.

20.3.2 Bass Framework Extensions: Pharmaceutical Marketing Variables

Diffusion models are commonly criticized for their implicit consideration of the effects of marketing variables (such as price and advertising) on the diffusion process. Explicit inclusion of marketing variables in diffusion models not only provides a better description of reality but also provides suggestions for altering the diffusion process by manipulating the marketing variables. The importance of including marketing mix variables in diffusion models has been highlighted by several researchers (see, e.g., Bass et al. 2000; Bass et al. 1994; Mahajan and Muller 1979; Mahajan and Wind 1986). In this subsection we review several empirical applications of macro-level diffusion models in the pharmaceutical industry and examine which marketing variables they include and in which part of the diffusion model the variables are included.

We distinguish several approaches to the inclusion of marketing variables in diffusion models. Firstly one can incorporate the effects of marketing variables into the size of the *potential market* (see, e.g., Berndt et al. 2003b) which is comparable to a market expansion effect (see Sect. 20.2.1). Another approach accounts for the effect of marketing variables on the *probability of adoption*. The literature points to three possible ways for marketing variables to affect the adoption rate:

(a) As an external influence (see, e.g., Hahn et al. 1994; Lilien et al. 1981; Rao and Yamada 1988; Ruiz-Conde et al. 2011) where marketing variables affect the adoption decision of a potential adopter without being influenced by information from an early adopter.
(b) As an internal influence (see, e.g., Ruiz-Conde et al. 2011) where marketing variables stimulate interpersonal communication. For example, the internal influence of price should be perceived as a process where the decision of non-adopters is affected by social interaction with adopters concerning (fluctuating) prices of the new product.
(c) As a mixed influence in which case marketing variables affect the trial rate jointly through external and internal influence (see, e.g., Ruiz-Conde et al. 2011; Shankar et al. 1998; Vakratsas and Kolsarici 2008).

A final way of incorporating marketing variables is to account for their effect on the repeat rate (see, e.g., Lilien et al. 1981; Rao and Yamada 1988).

Most of the published studies reveal the importance of explicitly considering the parameters of external and internal influences on the rate of adoption of new products (Chandrasekaran and Tellis 2007). Extensions of the mixed influence diffusion models are recommended but are also more complex to estimate

(see, e.g., Van den Bulte (2000) for studies on internal influence diffusion models and Van den Bulte and Lilien (2001) and Desiraju et al. (2004) for studies on internal influence diffusion models in pharmaceutical markets). We now discuss the studies that explicitly incorporate pharmaceutical marketing variables into macro-level diffusion models of mixed influence and emphasize those parts that are related to marketing variables. When models are trial-repeat models, we distinguish between trial or adoption rate and repeat rate. The studies are listed in Table 20.2.

Lilien et al. (1981) propose a trial-repeat diffusion model where own and competitive detailing efforts are taken into account. In their model, detailing affects the trial rate through external influence, whereas competitive promotion affects repeat sales. The authors find significant, although small, own and competitor effects of detailing.

Rao and Yamada (1988) provide support for Lilien et al. (1981) by analyzing 21 prescription drugs (results for two drugs are not shown) and showing that "own" and competitive promotional activities affect the diffusion process.

Hahn et al. (1994) include the effects of two aggregate promotional variables ("own" and competitive expenditures on detailing and medical journal advertising) on external influence. In the most extensive version of their model both "own" and competitor's promotional efforts affect the trial rate through external influence. Their model is validated using data for 21 prescription drugs from different unspecified categories. They conclude that promotional efforts affect external influence.

Shankar et al. (1998) propose a version of the Hahn et al. (1994) model to study the effects of late entry in prescription pharmaceutical markets. Their results suggest that innovative (non-innovative) late mover diffusion has a negative (nonnegative) effect on the effectiveness of the pioneer's marketing spending. They also find that the effectiveness of pioneer marketing spending is significantly affected by innovative late mover diffusion but not by non-innovative late mover diffusion.

Berndt et al. (2003b) examine the role of consumption externalities in the demand for four prescription drugs within the US antiulcer drug market. They propose a dynamic system where diffusion equations are used to describe the dynamic adjustment process. In their model price and detailing affect the potential market, and they conclude that detailing increases the industry saturation level. They find that the estimated price elasticities are somewhat low and explain this in terms of the political pressure on pharmaceutical pricing (Sect. 20.2.4). They also suggest that the large detailing elasticities they find may reflect a rising marginal cost of detailing.

Vakratsas and Kolsarici (2008) propose a switching regime dual-market diffusion model for prescription drugs. They accommodate an "early" market corresponding to prescriptions for patients with severe problems and a "late" market corresponding to prescriptions for patients with mild problems. Although they use the Bass model to capture the diffusion process for the first market, only the innovation parameter is considered (i.e., they only accommodate external influences). For the late market, they use the Generalized Bass Model (Bass et al. 1994) to incorporate the effect of marketing efforts. They use monthly category level data comprising the number of new prescriptions within a new therapeutic category of a lifestyle-related disease (the category name is not revealed). Their findings suggest that the early market is defined by an exponential distribution attributed to

Table 20.2 Overview of diffusion studies that include pharmaceutical marketing variables into the mixed influence diffusion models

Author(s)	Type of diffusion model	Marketing instruments included	The way marketing variables are included	Type of data	Key findings
Lilien et al. (1981)	Trial-repeat model	Own and competitive detailing	Own promotional efforts affect the trial rate through external influence and competitive promotional efforts affect the repeat rate	Two prescription drugs (US market)	Significant but small own and competitor detailing effects are found
Rao and Yamada (1988)	Trial-repeat model	Own and competitive detailing	See Lilien et al. (1981)	Twenty prescription drugs (US market)	Significant but small own and competitor detailing effects are found
Hahn et al. (1994)	Trial-repeat model	Own and competitive aggregate detailing and medical journal advertising	Two options: (1) own and competitor's promotional efforts affect the trial rate through external influence; (2) only own promotional efforts affect the trial rate through external influence	Twenty-one prescription drugs (US market)	Promotional efforts affect the trial rate through external influence
Shankar et al. (1998)	Trial-repeat model	Own and competitive aggregate detailing and medical journal advertising	Own and competitors' promotional efforts affect the trial rate through both external and internal influences	Thirteen prescription drugs (US market)	Marketing spending of non-innovative late entrants is significantly less effective than those of pioneers and innovative late movers. An asymmetry in competition associated with innovative late entry is also revealed
Berndt et al. (2003b)	Trial model	Own detailing (also the average industry quality adjusted price is considered)	Own promotional efforts affect the trial rate through the potential market	Four prescription drugs (US market)	Significant estimates are obtained for detailing
Vakratsas and Kolsarici (2008)	Trial model	Own detailing, medical journal advertising and direct-to-consumer advertising (DTCA)	Own promotional efforts affect the trial rate through both external and internal influences	A number of new prescriptions (confidential data from a non-US market)	Medical Journal advertising and DTCA affect the trial rate, detailing does not
Ruiz-Conde et al. (2011)	Trial-repeat model	Own and competitive detailing, medical journal advertising, physician meetings, and DTCA	Own and competitors' promotional variables affect the trial rate through: (1) external influence, (2) internal influence, or (3) both external and internal influences	Thirty-four prescription drugs (US market)	Promotional efforts affect the trial rate. The external influence formulation is the most appropriate for the majority of the drugs

accumulated prelaunch demand that is not influenced by marketing efforts, with the diffusion process of new drugs in the late market influenced by marketing efforts. They find that medical journal advertising and DTCA are statistically significant but that detailing is not. They point out several possible explanations for the relative ineffectiveness of detailing, such as higher saturation in detailing than medical journal advertising or the absence of serious side effects for the drugs in the analyzed category.

Ruiz-Conde et al. (2011) extend the model of Hahn et al. (1994) by incorporating the effect of company and competitor promotional efforts separately. In contrast to existing studies on pharmaceuticals, their model accommodates heterogeneity in the effects of different marketing instruments (detailing, medical journal advertising, physician meetings, and DTCA). The authors test several versions of their model on 34 prescription drugs from three different categories. They find that longitudinal relationships exist both for "own" and competitor marketing efforts with "own" (competing) marketing expenditures increasing (decreasing) the trial rate. However, the most disaggregated version of their model (which accounts for the separate effects of the four marketing instruments) suffers from severe multicollinearity.

There are three important papers on diffusion of new drugs that are not included in Table 20.2 because they incorporate neither marketing variables nor repeat sales within the complete Bass theoretical framework (i.e., innovation/external influence and imitation/internal influence).

Berndt et al. (2002) consider physician detailing and medical journal advertising (similar to the variables studied by Hahn et al. (1994)), but in addition they include price (the industry average price per patient day of therapy). They propose a share model as a semi-log specification (by using the logistic diffusion expression) to examine the impact of price, marketing efforts, and other variables (e.g., product quality) on the demand of new antidepressant drugs in the United States. They find that marketing efforts have a positive and highly significant impact on the rate of diffusion. Regarding the role of price, they find that the long-run industry demand price elasticity is negative and significant, but that within the therapeutic class, market shares of individual products are not price sensitive.

Van den Bulte and Joshi (2007) study 33 data series with one of them consisting of monthly sales of a prescription drug. They consider a two-segment structure with asymmetric influence: the influential segment, consisting of physicians who are more in touch with new developments, and the segment of imitators whose own adoptions do not affect the members of the influential segment. Their model allows diffusion researchers to operationalize the theories of asymmetric influence in the absence of micro-level diffusion data and to estimate parameters from real data.

Guseo and Guidolin (2009) propose a model with a dynamic potential market size that considers the Bass model as a nested special case. They assume that the communication network is not observable. They test the performance of their model with weekly data on the diffusion of a new drug in two geographical areas of Italy. Their model yields higher values of R^2 and the F-test than the Bass model. Their results show that the imitative adoption pattern is significantly different

between the two analyzed geographical areas, while the innovation adoption pattern is essentially equal. They show that the higher value for the imitative influence parameter in one area is the result of a more effective communication strategy.

20.3.3 Conclusions

Today the new interdependencies among consumers, such as word-of-mouth communication, network externalities (especially, online social networks) and social signals, new types of product category, and different kinds of consumer behavior (such as multiple purchases of a new product by a single purchaser), increase the complexity of the diffusion process of new products. This complexity obliges researchers to develop and use new modeling approaches (e.g., Fok and Franses 2007; Sood et al. 2009) and to continually adapt their methods of describing and modeling these diffusion processes. This continuous development causes diffusion modeling in marketing to remain an active research field, as reflected in the more recent review papers on innovation diffusion (Frenzel and Grupp 2009; Meade and Islam 2006; Peres et al. 2010). More research into, and reports of, the actual use of diffusion models in marketing is an ongoing request in the literature. Although the main application areas, in terms of practical impact, are consumer durables and telecommunications (Meade and Islam 2006), the pharmaceutical sector is one of the key industries of interest in today's new diffusion modeling efforts (Mahajan et al. 1990, 2000; Peres et al. 2010).

We now return to the initial questions posed: which are the pharmaceutical marketing variables that are mainly investigated? And where and how should they be included in the diffusion models? The most important and most researched marketing variable is detailing and its effect on the diffusion process of prescription drugs is always significant and has the expected sign (i.e., positive for own detailing, negative for competitive detailing), except in one study (where the authors present several explanations to justify the lack of significance). The influence of other marketing variables such as medical journal advertising and physician meetings is also investigated and their impact on the trial rate is revealed with the expected sign. However, as pharmaceutical marketing activities are highly correlated (also reported by Gatignon et al. 1990; Rizzo 1999) most studies combine them into an aggregated variable. The effect of DTCA is also investigated in Ruiz-Conde et al. (2011) who demonstrate its relevance on the diffusion process.

The studies reviewed here provide insights into where and how to include pharmaceutical marketing variables into diffusion models. Only one study (Berndt et al. 2003b) considers the effect of marketing variables on the size of the potential market. Three studies (Hahn et al. 1994; Lilien et al. 1981; Rao and Yamada 1988) assume that promotional efforts affect the diffusion process via external influence and find significant corresponding coefficients. Two studies (Shankar et al. 1998; Vakratsas and Kolsarici 2008) assume that promotional efforts affect the diffusion process via both external and internal influences, and also find significant

corresponding coefficients. The meta-analysis of Sultan et al. (1990) suggests that the coefficient of internal influence is sensitive to marketing variables for the 213 applications they examined. Only one study (Ruiz-Conde et al. 2011) does not make a priori assumptions about how promotional instruments affect the diffusion process of pharmaceuticals, and a family of diffusion models is analyzed to find the appropriate specification for the inclusion of marketing instruments in the adoption rate (through the internal and/or external influence). The results indicate that the adoption rate is affected by promotional variables via external influence for the majority of the analyzed drugs.

Lilien et al. (1981) and Rao and Yamada (1988) investigate the influence of marketing efforts on the repeat rate and find a significant effect. This result suggests more research on the repeat rate is needed to better understand the complete diffusion process of prescription drugs.

The lessons from the studies discussed here are that own (competitive) marketing variables positively (negatively) affect the diffusion process of new drugs and hence their incorporation into the macro-level diffusion models is recommended. However, in a pharmaceutical setting, as in other contexts (Meade and Islam 2006), there is no consensus regarding the most appropriate way of including marketing variables into diffusion models.

20.4 Dynamics in Pharmaceutical Marketing Effectiveness

20.4.1 Introduction

In the previous section we provided an overview of studies on macro-level diffusion models and concluded that pharmaceutical marketing efforts affect the diffusion process of new drugs. This, however, leaves unanswered the question of how effective marketing efforts are for pioneering brands, as compared to early or late followers, i.e., does marketing work equally well in speeding up the diffusion process for brands that enter at different stages of the *category* life cycle?

Other important questions relate to the timing of marketing efforts: given that a brand is to enter a category, should the majority of the available marketing budget be allocated to the months immediately following the launch, or should one save the bulk of the budget for later periods when competition is possibly more intense? How should the marketing budget be allocated around the moment of patent expiration? And finally, do the recommendations differ for different marketing instruments? For example, do we need to allocate physician-oriented marketing efforts in the same way over time as advertising targeted at patients? To answer these questions it is essential to understand how marketing effectiveness varies over the *brand's* life cycle.

Once a category matures, brands compete heavily for sales and/or market share with the aim of optimizing profits. Of great interest to managers and policy makers is the extent to which pharmaceutical marketing expenditures, aimed at increasing

brand-related metrics, affect total category sales. Does the complex dynamic system of manufacturer support for their own brands (and possible reaction to competitor activities) translate into higher category sales or do the competitive effects cancel each other out?

In this section we answer the above questions by providing an overview of studies into the *dynamics* of pharmaceutical marketing effectiveness. We first describe how marketing effectiveness is related to the category life cycle. Next, we focus on the effectiveness of different marketing instruments over the brand's life cycle. We then discuss how dynamics in brand level marketing affect category sales. We conclude this section by indicating how these dynamics can be modeled.

20.4.2 Pharmaceutical Marketing Effectiveness Over the Category Life Cycle

Conceptually, pioneering brands may enjoy advantages over later followers but in some situations they may also face serious disadvantages (Lieberman and Montgomery 1988). Based on an empirical analysis Urban et al. (1986) show an inverse relationship between order of entry and market share and Kalyanaram et al. (1995, p. G215) conclude that "for consumer packaged goods and prescription antiulcer drugs, the entrant's forecasted market share divided by the first entrant's market share roughly equals one divided by the square root of order of market entry." Fischer et al. (2010), who analyze the categories of calcium channel blockers and ACE inhibitors in four countries, find that early entrants achieve peak sales later, indicating that these brands enjoy a longer period of growth, and eventually obtain higher peak sales and also higher cumulative brand sales.

Bowman and Gatignon (1996) show that early entrants command higher marketing effectiveness then later entrants, furthermore they find the main effects of order of entry to be minimal in size indicating that later entrants do not necessarily end up with lower market shares but that with later entry it becomes increasingly expensive to obtain market share.

Shankar et al. (1999) analyze 29 brands from six categories and investigate the effect of the stage of the category life cycle at which a brand is launched on its marketing effectiveness. Here it must be noted that the concept of entry point according to the stage of the category life cycle is different from the concept of order of entry: the second brand may enter when the category is still growing or it may be launched when the category has already reached maturity. Even after controlling for order of entry effects, Shankar et al. (1999) find that pioneers enjoy higher marketing effectiveness than growth-stage and mature-stage entrants. Any advantage for growth-stage entrants derives from the higher response to perceived product quality and faster growth as compared to pioneers and mature-stage entrants. These findings can be explained by the pioneering brand(s) paving the way for the fast followers. The limited advantage for pioneering brands is confirmed by Berndt et al. (2003b) who find that in the antiulcer drug category, Zantac achieved high market share

despite delayed entry. These authors attribute the success of this brand to a high product quality combined with a high level of detailing.

We conclude from the literature that pioneering brands and brands that enter during the growth stage of a category have significant advantages over later entrants. In terms of marketing effectiveness pioneering brands gain most benefit, whereas growth-stage entrants enjoy highest response to perceived product quality. The first result should be interpreted with some care as in some new categories a large unfulfilled demand exists at the time the first drug "creates" the category (Vakratsas and Kolsarici 2008). One should be careful not to attribute the high initial demand for this pioneering brand to the marketing efforts around the launch period. When dealing with such market situations Vakratsas and Kolsarici recommend the specification of a dual-market diffusion model to distinguish between the sales contribution of the early market, which exists before the product is launched and that is not affected by marketing efforts, and the late market that develops after entry, possibly due to marketing actions (see Sect. 20.3.2).

20.4.3 Pharmaceutical Marketing Effectiveness Over the Brand's Life Cycle

Having discussed the influence of stage of the category life cycle at which a brand enters on their marketing effectiveness, we now turn to the allocation of the available marketing budget over time. Should a manufacturer spend most of the budget just after the launch, when the brand is more mature, or distribute it evenly over time? To answer this question we focus on the marketing effectiveness over the *brand's* life cycle.

There are several reasons as to why the effectiveness of pharmaceutical marketing expenditures should change over time, most importantly the changing role of marketing over the brand's life cycle. When a drug is launched physicians have no experience with the drug and are uncertain about the drug's efficacy. Some physicians may be only partly aware of the drug's attributes. In this stage of the brand's life cycle marketing efforts are used by manufacturers to inform physicians about the drug and its true attributes, herewith only indirectly affecting sales (Narayanan et al. 2005). Gradually physicians will become fully informed about the new drug's true quality and will increase their number of prescriptions if satisfied with the quality. Now the role of marketing changes to a more persuasive one (see Sect. 20.2.3). Marketing efforts are used to remind physicians about the drug, and possibly to counter the more intense competition which prevails, thus leading to a direct sales effect (Narayanan et al. 2005). It must be noted that in this phase marketing efforts do not have a solely persuasive function as the informative role still applies when marketing instruments are used to communicate the results of new clinical developments.

Narayanan et al. (2005) confirm the changing role of marketing over the brand's life cycle. Analyzing three brands from the antihistamine market, they show that the informative (indirect) effect of detailing dominates during the brand's introductory

period whereas the persuasive (direct) effect of detailing dominates subsequently. Total marketing effectiveness declines with the brand's age.

Osinga et al. (2010) analyze marketing effectiveness for 89 US prescription drugs from 39 categories and confirm the findings of Narayanan et al. (2005). Osinga et al. (2010) distinguish between *persistent* marketing effects, for those efforts that permanently affect the sales level, and *transient* marketing effects, for those efforts that only temporarily affect the sales level, and show that both permanent and transient marketing effects decline in size as the brand matures. In fact, their results indicate that persistent effects may only be obtained within the first 2 years following the introduction of the brand.

Both Narayanan et al. (2005) and Osinga et al. (2010) focus on temporal differences in physician-oriented marketing expenditures. Kolsarici and Vakratsas (2010) complement these findings by paying attention to the dynamics in the effectiveness of pharmaceutical DTCA, where they make the interesting distinction between *category* advertisements, those advertisements that communicate information about the disease without promoting any brand, and *brand* advertisements which may not contain any therapeutic information. Kolsarici and Vakratsas analyze the effects for a single non-disclosed brand which is first advertised from the 25th month after its introduction. The results indicate that category advertising effectiveness declines over time due to the market becoming educated about the disease, whereas brand advertising effectiveness increases, possibly because it requires an already educated market.

A very interesting situation arises when a brand faces generic competition after patent expiration, i.e., competition from drugs that have the same active ingredient but that are sold without a brand name at lower prices. In many countries including the United States, pharmacists are allowed or required by law to substitute a generic equivalent unless the physician indicates that the patient can only receive the brand name drug (Hellerstein 1998). In these countries the brand name drug will lose ground once generics enter the category. Using US data, Osinga et al. (2011) find that sales of generic products derive from the equivalent branded drug, implying that physicians do not switch from other branded drugs in the category to the generic. Gonzalez et al. (2008) analyze UK data and arrive at a similar conclusion: only a small segment of price-sensitive physicians adopts the generic at the expense of nonequivalent brand name drugs in the same category. These results imply that the marketing effectiveness for the brand name drug significantly declines after patent expiration because positive effects on sales will be largely captured by generics. However, physicians and patients can show strong habit persistence (Coscelli 2000), and so a positive significant marketing effect before patent expiration will partly transfer to the period after patent expiration, i.e., even some time before patent expiration the brand name drug partly "supports" generic equivalents with its marketing expenditures. This implies that marketing effectiveness declines as the moment of patent expiration approaches (Osinga et al. 2011; also see Berndt et al. 2003a). It must be noted that in less regulated markets marketing effectiveness may actually increase after patent expiration as shown by Keller and Pauwels (2009) using data from Switzerland.

The literature indicates that physician-oriented marketing effectiveness declines over the brand's life cycle. As for DTCA, category advertisements may be more effective when patients are not yet fully educated about the disease treated by a drug, however, once they are educated, brand advertisements have higher effectiveness. In countries where pharmacists are required to dispense generic drugs instead of more expensive brand name equivalents, the brand's pharmaceutical marketing effectiveness declines when approaching patent expiration.

20.4.4 Brand Level Marketing Efforts and Category Sales

We have seen that pharmaceutical marketing efforts speed up a brand's diffusion process. In case of a first entrant, when brand sales are equal to category sales, this means that the marketing efforts help shape category sales. However, what is the effect on category sales once competition in a category increases? Do the brands' marketing efforts still lead to an increase in category sales or do they cancel each other out? Fischer and Albers (2010) answer this question by determining the "own" and competitive effects of detailing, professional journal advertising, and DTCA for 2,831 drugs covering 86 US prescription categories. The analyzed drugs have a median order of entry of 17 and over three quarters of them can be classified as generic or me-too drugs, highlighting the competitive environment in which they operate. Interestingly, Fischer and Albers (2010) use brand level analyses to obtain category level effects and show that all marketing instruments have a positive and significant effect on category sales where detailing shows the largest effect size. However, when including competitive effects the total effect sizes decline substantially with the detailing effect no longer significantly different from zero. Potentially, detailing thus has the largest effect on category sales, however, due to intense competition the individual brands' effects completely cancel each other out.

20.4.5 Conclusion and Modeling Implications

We have described the complex dynamics in the effectiveness of pharmaceutical marketing instruments. First, we indicated how effectiveness is influenced by the stage of the life cycle at which a brand is launched. In particular, we concluded that pioneering brands and brands that enter during the growth stage of a category have significant advantages over later entrants. Second, given a specific entry point, marketing effectiveness varies over the brand's life cycle. With regard to physician-oriented marketing instruments we find that the effectiveness is highest immediately after introduction. Subsequently effectiveness diminishes to arrive at lower levels in the brand's mature stage. Some time before patent expiry long-term marketing effectiveness declines even further in countries where pharmacists are required to substitute the generic equivalent for the prescribed brand. Category DTCA is most

effective when patients are not yet fully educated about the disease treated by the drug whereas brand advertisements are more effective once patients are educated. Finally, detailing is potentially most effective in increasing category sales, however, competitive effects reduce the effectiveness to levels not statistically different from zero. These results are of great value to managers responsible for the allocation of marketing budgets over brands and over time as well as for policy makers needing to understand the complex dynamics when developing health care policy.

Given their importance to managers and policy makers, as well as their contribution to model fit, temporal differences in pharmaceutical marketing effectiveness are not to be ignored. First, modelers need to ensure that model parameters of brands that are introduced at different stages of the category life cycle are not pooled. Second (and particularly when focusing on new brands, or brands that are close to patent expiration), it is important to specify models with time-varying parameters. Several methods for incorporating time-varying parameters are available to researchers. Particularly well-suited are the state space and related dynamic linear models used by Kolsarici and Vakratsas (2010), Osinga et al. (2010), and Keller and Pauwels (2009). These approaches are increasingly popular in marketing, due to their flexibility and suitability for analyzing long-term phenomena (Leeflang et al. 2009). Other suitable approaches for estimating time-varying parameters include the penalized splines method (e.g., Stremersch and Lemmens 2009) or moving- or rolling-window analysis (e.g., Pauwels and Hanssens 2007). Third, modelers need to be careful when interpreting the influence of pharmaceutical marketing on category sales. Fischer and Albers (2010) show that it pays to perform analyses at the brand level, even when being interested in category level effects.

20.5 Conclusions and a Research Agenda

This chapter reviewed studies on the effectiveness of pharmaceutical marketing on aggregate demand. We first presented an overview of earlier research in this field and subsequently considered two challenges that are particularly relevant for the pharmaceutical market: how marketing variables affect the diffusion pattern of newly introduced pharmaceutical innovations and how dynamics influence pharmaceutical marketing effectiveness.

From the overview in Sect. 20.2 we conclude that marketing efforts generally have positive, but moderate effects on pharmaceutical demand. We also find that the response to pharmaceutical marketing is heterogeneous, both at the product category level and at the brand level. The wide range of marketing instruments, products, categories, and markets that these studies cover suggest moderators that might explain the heterogeneity in the observed effects. The meta-analysis of Kremer et al. (2008) confirms that the marketing instruments differ in their effectiveness. For the brand level studies detailing is found to be the most effective instrument, followed by journal advertising, meeting expenditures and direct mail. DTCA appears to be the least effective at the brand level. The efficiency ranking of instruments is less clear at the

product category demand level: some studies report that DTCA is the main category expansion driver, but most studies report that detailing is also the most important instrument at the category demand level. More research into this issue is needed.

We also conclude that the effectiveness of pharmaceutical promotion differs across therapeutic categories. This might be due to different saturation levels (Vakratsas and Kolsarici 2008) or perhaps by different degrees of diagnosis uncertainty across therapeutic categories. Fischer and Albers (2010) provide yet another explanation: they find that effectiveness of detailing and journal advertising is higher in chronic care categories than in acute care categories.

The studies in this chapter suggest several other moderating variables such as country effects, order of entry effects, and model characteristics. However, Kremer et al. (2008) do not find significant effects for most of these variables, with the notable exception that models which account for endogeneity in promotional expenditures find significantly lower estimates of promotional effectiveness.

In Sect. 20.3 we focused on some important studies that investigate how marketing variables affect the diffusion process. The general conclusion is that "own" detailing and other "own" marketing variables such as medical journal advertising and physician meetings speed up the diffusion process, but there is little consensus on how this occurs. We provide an overview of the different approaches for including marketing variables in the published diffusion models and conclude that it is not clear which provides the best representation of reality. More research into this issue is needed.

In Sect. 20.4 we considered three questions. First, we described how marketing effectiveness is related to the category life cycle, and concluded that pioneering brands have the highest marketing effectiveness, whereas brands that enter during the growth stage of a category have highest response to perceived product quality. Secondly, we focused on the effectiveness of different instruments over the brand's life cycle and found that the effectiveness of instruments that are aimed at the physician declines over the brand's life cycle. For DTCA we conclude that category advertisements may be more effective when patients are not yet fully educated about the disease that is treated by a drug. Once the patients are educated brand advertisements have higher effectiveness. Thirdly, we investigated how marketing affects category sales when competition in a category increases. The finding is that detailing may have the largest effect on category sales, but that due to intense competition individual brand efforts completely cancel each other out.

We conclude that the review of the research presented in this chapter leaves several questions unanswered about the effectiveness of pharmaceutical marketing and that these provide interesting topics for further research. Besides the unanswered questions of today it is of great interest to identify the questions of tomorrow. We conclude this chapter with a discussion of three themes that we expect to provide the most fruitful future areas of research.

1. Research on pharmaceutical demand in developing countries.
2. Research on regulatory changes.
3. Research on the role of the internet channel in the pharmaceutical market.

Ad (*1*) *Research on pharmaceutical demand in developing countries.* The demand for pharmaceutical products in developing countries is expected to grow much faster than in developing countries (IMS 2010). These countries are characterized by very different clinical and economic characteristics. This suggests great potential for research projects that identify appropriate marketing strategies that are tailored to the specific needs of the pharmaceutical markets in the developing world. In comparison to developed countries, increasing category demand is still very relevant for developing countries, hence, the type of research that we reviewed in Sect. 20.2.1 is very relevant for managers and policy makers that are working in these countries. Future studies may want to focus on which policy measures enhance category demand. Another potential research area results from the low incomes in developing countries where price is likely to have a stronger influence on pharmaceutical demand than in developed countries (see Sect. 20.2.4), and consequently (generic) competition is likely to be fierce. In some countries (notably India) we already observe many competing branded versions of the same drug—for example, there are over 200 branded atorvastatins on the market varying fivefold in price and with a number of companies marketing more than one brand. It will be an interesting challenge to study how best to market drugs under such conditions. Related topics include the analysis of diffusion patterns and dynamics in emerging markets.

Ad (*2*) *Research on regulatory changes.* The increasing healthcare costs in many countries because of ageing societies and worldwide growth in prevalence of chronic diseases puts greater pressure on healthcare budgets that are already stretched (Kaiser Family Foundation 2010). To contain costs, health care policy makers and payers (insurers, but also patients) increasingly influence physicians' prescribing behavior. This restricts the choice sets of physicians, which will lead to a further reduction in effectiveness of pharmaceutical promotion. This is confirmed by studies that find that physicians do not consider communication by the industry to be most influential. Instead, regulatory boundaries, peer opinions, and scientific information are deemed to be much more important to their prescription decisions (Babor et al. 1996). However, physicians' opinions on this point are known to be biased (Wazana 2000).

With the more dominant role of insurers and other intermediary agents it is likely that new reimbursement plans emerge which encourage prescription of cheaper alternatives (including generics). Also, other countries may follow the examples set by Italy and France to tax pharmaceutical promotional expenditures. As a consequence, drug manufacturers will increasingly have to compete on price, and this will provide researchers with excellent opportunities for investigating (changes in) price sensitivity. Some studies have begun to appear in this area such as Stremersch and Lemmens (2009) who study the effects of regulatory changes on sales growth. Many questions remain unanswered and present topics for future research: How do regulations change category demand? How do they influence generic uptake? How long does it take for the market to fully absorb a regulatory change?

Another highly relevant future research avenue would be to assess the consequences of regulatory changes for the optimal allocation of pharmaceutical

marketing instruments. Here it is important to realize that the increasing influence of parties other than the physician on the prescription decision will lead to an increase in the use of marketing instruments aimed at these parties. Future studies should focus on multiple players in the chain and answer questions of how they affect pharmaceutical demand and how they should be approached by marketing efforts. One particularly notable, and currently under-researched, party is the pharmacist. The pharmacist is the last professional in the pharmaceutical channel and increasingly responsible for drug choice. For example, the decision to dispense a generic instead of a branded drug is made mostly at the pharmacist level. Future research should pay attention to the pharmacist's new role due to regulatory changes and assess the effects of this shift in responsibilities on category- and brand level demand and new product diffusion.

Ad (*3*) *Research on the role of the internet channel in the pharmaceutical market.* Facilitated by the internet, the role of the patient is changing. Patients now have better access to prescription guidelines, co-payments, and alternative therapies. They also communicate with each other and with pharmaceutical manufacturers via blogs, forums, and other social media and this opens up extended possibilities for the industry to communicate with patients via online DTCA. At the same time we see an expanding self-medication sector due to prescription drugs that are switched to over-the-counter (OTC) products (Mahecha 2006), leading to a further empowerment of the patient. Camacho et al. (2010) explore the changing role of the patient in medical decision making. They observe a trend towards more participatory decision making and develop a patient-centered marketing approach, where both patients and physicians are targeted by marketing efforts where the focus is on the patient rather than on the patient's disease or the physician. This requires a change in marketing, which until now has mainly aimed at influencing the physician's decision. This also implies that DTCA will become more important and may explain the current high level of expenditures. We believe that it is important to study how these developments affect category- and brand level demand, promotional effectiveness, price elasticities, and whether internet empowered patients change diffusion patterns of newly developed drugs.

In this chapter we have indicated the many opportunities which remain to model the (aggregate) demand for pharmaceuticals. We also show that there are still many issues to be investigated and that the outcomes are likely to depend on the modeling approach and the situation studied and we specify some future research avenues in this highly interesting and challenging area.

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Chapter 21
Direct-to-Consumer Advertising of Pharmaceuticals: An Integrative Review

Qiang Liu and Sachin Gupta

Abstract This chapter provides an integrative review of direct-to-consumer advertising (DTCA) of prescription pharmaceuticals. We introduce the history and current trends of DTCA in the USA and in other countries. Then, we discuss research methods and databases appropriate for DTCA studies. We review past literature on DTCA related to different stakeholders: (1) DTCA and patients; (2) DTCA and physicians; (3) welfare effects of DTCA and government regulation; (4) DTCA and pharmaceutical firms. Our review of the literature indicates that this topic has received attention in multiple fields, including marketing, health economics, medicine, public policy, and law and economics. However, it remains a "hot" topic with near daily coverage in the media, providing rich fodder for new and interesting research questions that are important to firms, patients, and policy makers. Finally, we have identified a few unresolved research questions that we believe are significant and worthy of future research.

21.1 Introduction

Anyone who watches television or reads newspapers or magazines in the USA cannot help but notice the dramatic upsurge in the repetition of phrases such as "ask your doctor" and "tell your physician" (see Fig. 21.1 for an example). This is a direct outcome of the explosive growth in direct-to-consumer advertising (DTCA). We begin this chapter with a short history of DTCA that brings us to current expenditures on DTCA in

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Fig. 21.1 An example of a direct-to-consumer advertisement in print. *Source*: http://www.pfizerpro.com/hcp/lipitor/patient-education-center, accessed on November 8, 2011

comparison with other marketing activities of pharmaceutical firms. Our subsequent discussion reviews the literature on the effects of DTCA and is organized around patients and physicians, followed by a more public policy perspective based on the welfare effects of DTCA including its cost effectiveness. We then discuss the implications reported in the literature for firms' decisions as well as competition between firms.

21.1.1 Recent History of DTCA in the USA

Detailed and excellent accounts of the history of regulation of DTCA in the USA are available (for instance, Palumbo and Mullins 2002; Pines 1999), hence we limit our discussion here to a few salient events in the regulated growth of DTCA. Although the advertising of prescription drugs directly to consumers had always been legal, US pharmaceutical companies advertised only to physicians till the early 1980s. The first instance of a print advertisement directed to consumers is believed to be in 1981 by Boots Pharmaceuticals for the ibuprofen product, Rufen. This was followed by other drug companies who voluntarily submitted direct-to-consumer (DTC) ads to the FDA. This shift in the marketing strategy and expenditures of pharmaceutical companies from physicians to patients is a significant development and may be attributed to two kinds of forces. First, increasing limits on the effectiveness of marketing to physicians, such as growth of managed care and their attempts to contain drug costs, and growing restrictions on sales representatives' access to physicians. Second, the social climate had changed in favor of patients having a bigger say in their own health care and a greater desire for information, thereby making advertising directed to patients potentially more effective. Camacho et al. (2010) note that there is a trend towards more participatory decision making, in which doctors and patients together bear responsibility for medical decisions.

The FDA called for a voluntary moratorium on DTCA in 1983 while it studied this somewhat unusual and unanticipated form of promotion. The moratorium was ended in 1985. Thereafter, spending on DTCA continued to grow but at a slow pace. An important aspect of the FDA regulations governing prescription drug advertising is a requirement of a "brief summary" describing the effectiveness of the drug and its risks. The brief summary must provide the drug's side effects, contraindications, warning and precautions, as well as indications for use. While this requirement was easy to satisfy in print advertising, it was too impractical for a 30-s TV advertisement. In a major change to its regulation of DTCA in 1997, the FDA allowed a broadcast advertisement to fulfill the brief summary requirements by reference to a telephone number, a web site, a print ad, etc., thereby making it feasible to create a 30-s commercial. As a consequence, spending on DTCA especially on TV has grown rapidly since 1997.

In 2005 the US pharmaceutical industry trade association, PhRMA (Pharmaceutical Research and Manufacturers of America), announced voluntary guidelines for DTCA practices. The guidelines are intended to address concerns about both the timing and the content of DTC advertisements. These were revised in 2008 (http://www.phrma.org/sites/default/files/pdf/phrmaguidingprinciplesdec08final.pdf) and 26 companies have become signatories to these guidelines.

21.1.2 DTCA Today in the USA: Expenditure on DTCA

DTCA expenditure on prescription drugs in the USA grew explosively, from $0.15 billion in 1993 to $4.07 billion in 2010 (see Fig. 21.2). In the last few years, expenditures on DTCA have fallen from a high of $4.91 billion in 2007, consistent with a

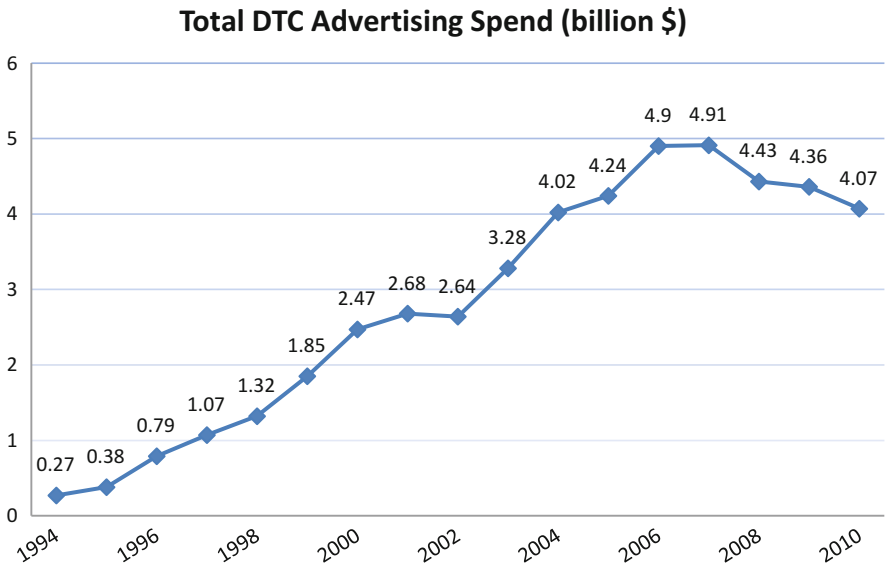

Fig. 21.2 Total direct-to-consumer (DTC) advertising spend in the USA. *Sources*: (1) 2005–2010 data are from IMS Health: http://www.imshealth.com/portal/site/imshealth/menuitem.a953aef4d73d1ecd88f611019418c22a/?vgnextoid=bb967900b55a5110VgnVCM10000071812ca2RCRD. (2) 1994–2004 data are from Frank et al. (2002) and Donohue et al. (2007), both of which cite IMS Health

decline in overall promotional spending of pharmaceutical products. The share of DTCA in overall promotional spending of pharmaceutical products has been rising over the years and has reached as much as 40 % in 2010. Detailing by the sales force to physicians remains the dominant form of marketing spending, but is losing ground to DTCA (see Fig. 21.3). Figures 21.4 and 21.5 show that TV and print media account for over 95 % of the total spending on DTCA. Another characteristic of DTCA spending is its highly concentrated nature, in terms of a few companies accounting for a large share of overall spending (see Table 21.1). This is in part because DTCA is largely used to promote brands in a few therapeutic categories only (see Table 21.2). Iizuka (2004) examines this phenomenon and finds that drugs that are new, of high quality, and for under-treated diseases are advertised more frequently. He also finds that firms advertise more when the number of potential patients, rather than the number of current patients, is large. Donohue et al. (2007) similarly note that drugs that are advertised tend to be new and those used to treat chronic diseases.

In recent years there has been tremendous growth in online DTCA expenditures by US firms, especially utilizing Web 2.0 technology. This form of marketing occurs via Facebook pages, Twitter feeds, blogs or RSS feeds, dedicated You Tube channels, and so forth. The size of the expenditure on online DTCA is not readily available. One estimate (http://adage.com/article/news/pharma-online-spending-hit-1-billion-year/146223/) puts the total spending on online advertising by the US pharmaceutical and the healthcare industry in 2010 at $1 billion.

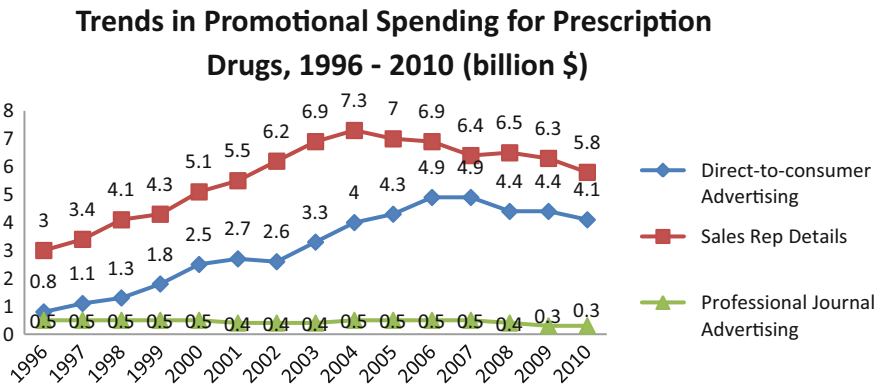

Fig. 21.3 Trends in promotional spending for prescription drugs in the USA. *Sources*: (1) 2005–2010 data are from IMS Health: http://www.imshealth.com/portal/site/imshealth/menuitem.a953aef4d73d1ecd88f611019418c22a/?vgnextoid=bb967900b55a5110VgnVCM10000071812ca2RCRD. (2) 1994–2004 data are from Frank et al. (2002) and Donohue et al. (2007), both of which cite IMS Health. Chesnes and Jin (2011), used with permission

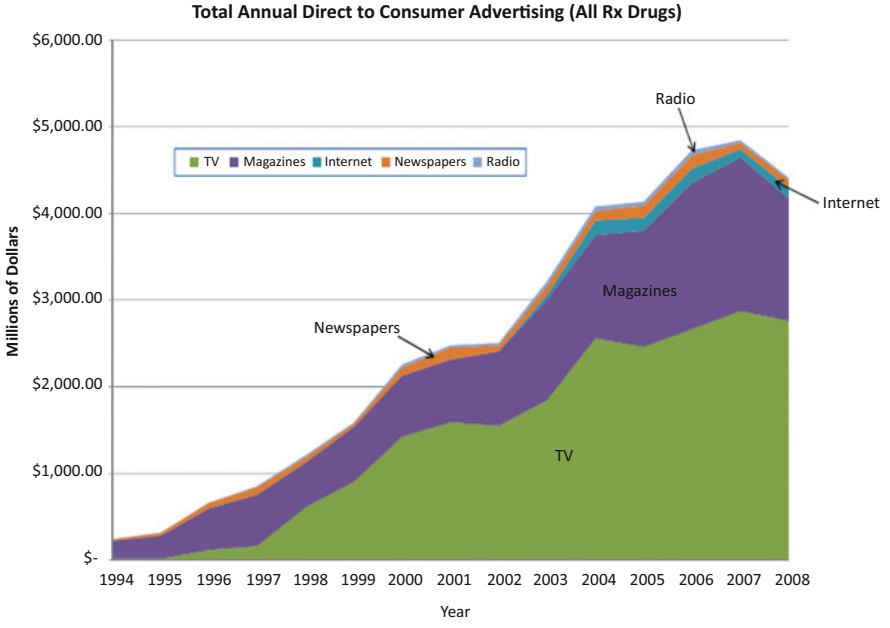

Fig. 21.4 Total annual direct-to-consumer advertising (DTCA) by medium and year. *Source*: Chesnes and Jin (2011), used with permission

The growth of online DTCA raises some critical concerns. One is that the US FDA has not issued guidelines for this form of DTCA leading to concerns about patient safety. Liang and Mackey (2011a) note that "online DTCA has emerged as an unregulated marketing tool for illegitimate and illicit sources alike, and consumers

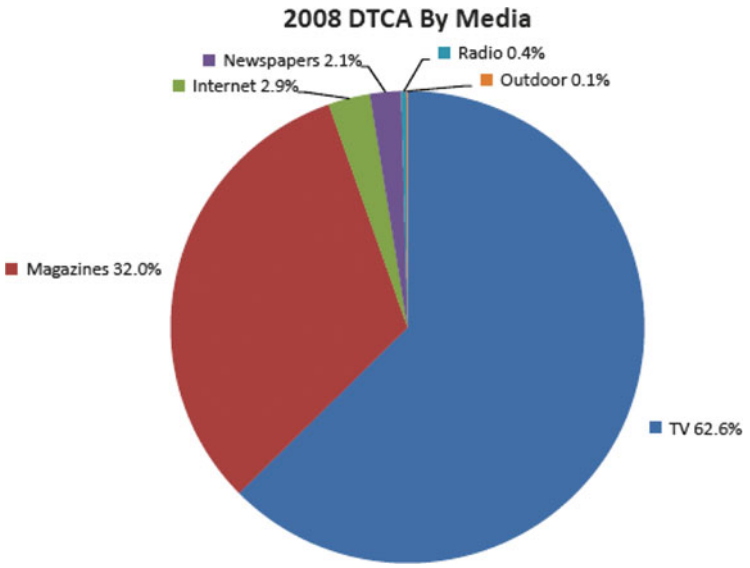

Fig. 21.5 DTCA by media in 2008. *Source*: Liu and Gupta (2011)

Table 21.1 Top companies—DTC advertising (millions) in the USA in 2010

Rank	Company	DTC dollars	% of total spending
1	Pfizer	$967.5	22.3
2	Eli Lilly & Co.	$470.8	10.8
3	AstraZeneca	$422.7	9.7
4	GlaxoSmithKline	$338.6	7.8
5	Bristol-Myers Squibb	$330	7.6

Source: Kantar Media. US measured media ad spending in 17 media

Table 21.2 Top products—DTC advertising (millions) in the USA in 2010

Rank	Brand	DTC dollars	% of total spending
1	Pfizer's Lipitor	$272.0	6.3
2	Lilly's Cialis	$220.6	5.1
3	Lilly's Cymbalta	$206.0	4.7
4	GSK's Advair Diskus	$200.5	4.6
5	BMS's Abilify	$155.7	3.6

Source: Kantar Media. US measured media ad spending in 17 media

lack information on whether such information is valid." In a study of the online DTCA marketing practices of the top ten global pharmaceutical firms and the largest ten drugs of 2009, Liang and Mackey (2011b) found that all ten firms had a presence in Facebook, Twitter/Friendster, and sponsored blogs and RSS feeds. More worryingly, however, nine out of the ten drugs had a noncorporate marketing presence by

illegal online drug sellers, which are pharmacies that promote sales of prescription drugs without a prescription.

21.1.3 DTCA in Other Countries

New Zealand is the only country other than the USA in the Organization for Economic Cooperation and Development (OECD) countries that allows DTCA of prescription drugs. New Zealand experienced similar growth in DTCA as the USA from its beginning circa 1995, with unsuccessful attempts to change the liberal legislation on DTCA. In the European Union, a 5-year pilot project of allowing DTCA for AIDS, asthma, and diabetes was proposed by the European Commission, but rejected by the European Parliament in 2003. Despite this, pharmaceutical companies, media industries, and the European Commission have continued to push for watering down this strict ban on DTCA in the European Union.

Canada presents an interesting case study. Although DTCA is prohibited in Canada, regulations permit two forms of advertising—disease-oriented or help-seeking advertising that does not mention a specific brand but discusses a condition and suggests that consumers ask their doctor about treatments, and reminder advertisements that mention the brand name but no health claims or statements about the use of the product (Mintzes 2006).[1] However, as many as 30 % of English-speaking Canadians are routinely exposed to DTCA via cable and satellite television of US stations which are governed by US regulations.

A critical concern with the growth of online advertising is that such media reach patients in countries where DTCA is not legal. Liang and Mackey (2011a, b) provide a stark example: although GlaxoSmithKline's blog site and AstraZeneca's community Facebook page indicate that they are intended for US residents and customers only, non-US users have no access restrictions. This practice then amounts to an "illegal export" that may need to be regulated.

21.2 Research Methods Appropriate for Measuring DTCA Effects

An important area of DTCA research has been the measurement of DTCA effects. Many different research methods have historically been used to measure advertising effects, and we see a similar spectrum in the literature on DTCA. One important difference, however, is that the motivation for DTCA research is typically not to test theories of consumer information processing but instead to measure the size of

[1] In a recent study Kolsarici and Vakratsas (2010) creatively use the Canadian regulatory requirement that ads of the two kinds be clearly distinct to specify and estimate an econometric model of effectiveness of generic vs. brand advertising.

DTCA effects and their managerial or societal significance. As a consequence of this emphasis, we rarely if ever find the use of controlled experiments either in the lab or in the field in DTCA studies. The two most common research approaches we find in the DTCA literature are surveys and uncontrolled observational designs.

The use of surveys is widespread (Herzenstein et al. 2004; Iizuka and Jin 2005; Murray et al. 2003; Robinson et al. 2004; Wilson and Till 2007). There is a significant challenge in using surveys to reliably measure the effects of DTCA because there is typically no control group that has not been exposed to DTCA. Some survey-based studies have tried to creatively overcome this inherent limitation. An example is Mintzes et al. (2003) that compares patient and physician survey responses between two sites—Sacramento, CA, where DTCA is legal, and Vancouver, Canada, where DTCA is illegal, to assess DTCA effects. Despite this limitation, surveys are an important source of information about patient and physician attitudes, as well as of DTCA effects on variables such as patient requests, which need to be measured as self-reports.

In addition to customized surveys, there is an opportunity for researchers to use syndicated survey data. An example is the National Ambulatory Medical Care Survey (NAMCS). In the survey, nonfederal office-based physicians complete a one-page questionnaire for each patient visit sampled during a 1-week reporting period. The survey data include physician characteristics, patient demographics (age, sex, race, ethnicity), and visit characteristics (patients' symptoms, complaints or other reasons for the visit, physician's diagnoses, diagnostic and therapeutic services ordered or provided at the visit including medications, expected sources of payment, visit disposition, time spent with physician, etc.).

The second common approach to study DTCA effects is uncontrolled observational designs. These studies rely on comparisons of data between cross-sectional units, or across time within units, or panel studies that use both cross-sectional and time-series variation (Calfee et al. 2002; Liu and Gupta 2011; Narayanan et al. 2004; Stremersch et al. 2011; Wosinska 2002). In order to draw valid inferences about DTCA effects one needs good observational data and appropriate statistical analyses that adequately control for potentially confounding covariates. An example of a panel-based study is Liu and Gupta (2011) who explain variation in number of patient visits and number of patient requests across geographic units in the USA and across months using DTCA expenditures in these same units as explanatory variables. A hierarchical Bayesian negative binomial model is used to measure the effects of DTCA expenditures while accounting for alternative explanations.

In recent years the availability of good observational data has grown, both for the "causal" variables (advertising) and for the "effect" variables (e.g., prescription sales). Kantar Media (http://www.kantarmedia.com, previously known as TNS Media) traces advertising expenditures on all branded drugs since 1995. The data are available weekly, monthly, and yearly. Further, the data are available at the Designated Media Area (DMA) level or the US national level. Expenditures in 11 different media, including network TV, national newspaper, magazine, internet, and radio, are reported. On the effects side, IMS Health (http://www.imshealth.com) is the major provider of prescription sales data by brand and market. ImpactRx (http://www.impactrx.com) maintains a large physician panel that records prescriptions written by physicians, as well as details of detailing visits, patient visits, diagnoses, patient requests, and so forth.

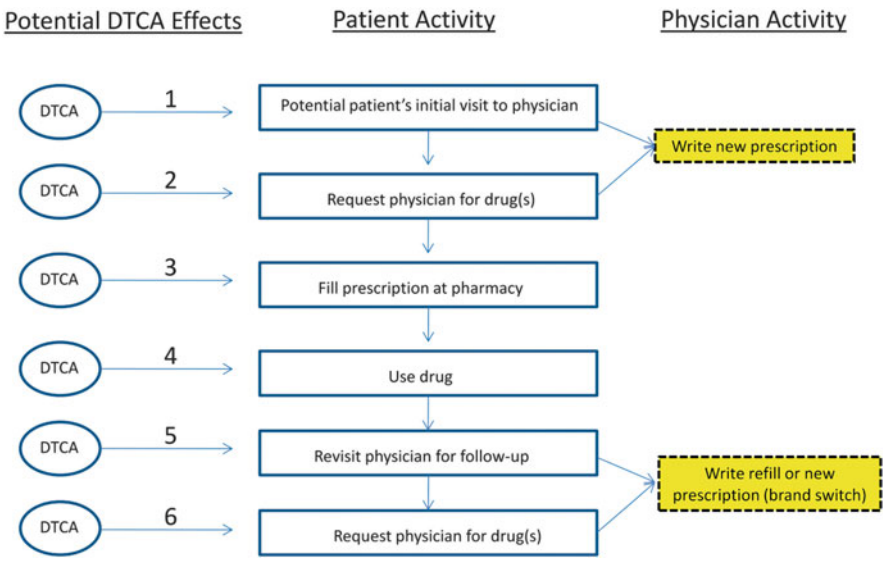

Fig. 21.6 Conceptual map of how DTCA influences the process of patients seeking and receiving treatment from physicians

21.3 Review of Past Research

21.3.1 Patients

It is useful to think about how DTCA influences patients in the process of seeking and receiving treatment from physicians. Patients' response to DTCA involves several decisions and behaviors (Fig. 21.6 provides a schematic view of various effects of DTCA on how patients seek and receive treatment from physicians). First, a patient needs to decide whether to make an appointment with a physician for diagnosis of a condition, to initialize a treatment, or, in the case of a chronic condition, to continue an existing treatment. During the physician interaction the patient needs to decide whether to discuss the advertised drug with the physician or request the physician to prescribe the drug. Subsequent to the physician visit, the patient needs to decide whether to fill the prescription and comply with the drug regimen as prescribed. We discuss each of these stages in turn.

21.3.1.1 Visits to Physicians

Using national aggregate data for the drug class statins for 1996–2000, Calfee et al. (2002) report the surprising result that DTCA does not have an effect on the number of patient visits to physicians. For the same drug class, Liu and Gupta (2011) analyze DMA level DTCA expenditure data, and patient visits data at the same

level, from 2002 to 2004 using a hierarchical Bayesian negative binomial model. They find that DTCA expenditures have a positive and persistent effect on the number of visits to physicians by newly diagnosed hyperlipidemia patients. In particular, they report that in this category an additional expenditure of $221 on DTCA generates one additional newly diagnosed patient visit. Liu and Gupta (2011) consider alternative explanations for the contradictory findings. These include the conjecture that having gained experience with DTCA, firms may be using advertising more effectively in the later period considered by Liu and Gupta (2011), or differences in model specifications and data (regional vs. national) between the two studies may be driving the different results.

Using data pooled across 151 drug classes, Iizuka and Jin (2005) report a positive, statistically significant effect of DTCA on patient visits. In particular, they find that every $28 increase in DTCA leads to an additional drug visit within 1 year. The lower amount relative to Liu and Gupta (2011) is possibly due to averaging across a large number of drug classes that differ in effectiveness of DTCA. Cantor (2010) collected individual measures of advertising exposure to print advertising and specifies a model in which the variation in ad exposure used to estimate the key parameters is orthogonal to individual unobservable variables that may drive both ad exposure and healthcare seeking behaviors. The study confirms that DTC advertising does have some influence on the likelihood of an individual to visit a healthcare practitioner.

Using data from the Medical Care Expenditure Panel Survey of individuals who have no previously diagnosed medical condition, Hosken and Wendling (2010) find that drug advertising is an important determinant of an individual's decision to go for a "check-up" visit, which by definition is designed to diagnose conditions that patients may be unaware they have. The authors interpret their finding as affirming the "informative" role of advertising, i.e., advertising provides information to consumers and thereby increases demand for the category. They also find large differences in the effects of advertising across demographic groups. For instance, women are more responsive than men, blacks and whites are more responsive than Hispanics, and the highly educated are more responsive than the less educated.

Bradford et al. (2006) found that DTC advertising of COX-2 inhibitors Vioxx and Celebrex increased the flow of osteoarthritis patients to physician offices each month. More recently, Bradford et al. (2010) examined using a duration model how DTC advertising affects the delay between diagnosis and pharmacological treatment for patients suffering from a common chronic disease. They find that on average television advertising had the effect of lengthening the time patients wait to begin therapy after being diagnosed. However, this average is composed of reduction in waiting time among patients who are good clinical candidates for the therapy and an increase in time for poor candidates. This finding supports the idea that advertising matches patients with treatments, and therefore is informative.

Overall, recent evidence for DTCA's effect on increasing the number of patients seeking diagnoses and treatment, as reflected in number of patient visits to physician offices, is quite strong and robust across therapeutic categories and studies.

21.3.1.2 Patient Requests for Advertised Drugs

Mintzes et al. (2002, 2003) collected data in Sacramento, CA, where DTCA is legal, and Vancouver, British Columbia, where DTCA is illegal, using a matched set of patient–physician questionnaires, each of which covered a single consultation. With this creative design, they examined how DTCA affects patient requests and physician prescribing decisions in two different policy environments. They found that advertising leads to more requests for advertised medicines, and that requests drive more prescriptions. They also found that physicians were often ambivalent in these cases about the choice of treatment (i.e., the particular drug they prescribed), suggesting that appropriateness of treatment may suffer due to patient requests.

Herzenstein et al. (2004) analyze data from 1,081 adults surveyed by the FDA in 1999 to understand the effects of consumers' attitude towards DTCA. They find that consumers with more favorable attitudes towards DTCA are more likely to search for information about the advertised drug and also more likely to ask their physician about the drug. Importantly, they also find that physicians are more likely to prescribe the advertised drug to these patients. Wilson and Till (2007) analyzed survey data from about 2,300 household respondents to develop a structural equation model of DTC advertising effectiveness. Confirming the results of Herzenstein et al. (2004) and others, they find that consumers who are greatly involved in their healthcare and possess positive attitudes towards DTC advertising are more likely to contact a doctor about the prescription drug after viewing a DTC advertisement.

Using data gathered by a market research company from a physician panel in which physicians report patient requests they received, Liu and Gupta (2011) find that own-brand DTCA expenditures increase the number of patient requests for two leading brands in the cholesterol-lowering category but do not benefit a smaller share brand. They also find that competing drugs' DTCA expenditures have a positive spillover effect on the number of patient requests for the leading brand in the category.

Not unexpectedly, multiple studies confirm that DTCA encourages patients to talk with their physicians about their ailments and to request specific drugs. Such patient behavior also influences physicians' prescription behavior (more on this in the next section).

21.3.2 Physicians

Although DTCA is not intended to influence physicians directly, they are obviously affected by it. Literature on how physicians perceive DTC advertising is relatively scarce, is based entirely on surveys, and leads to ambiguous findings. Gönül et al. (2000) find that more experienced physicians, physicians who see more patients, or those who have more exposure to pharmaceutical advertisements (brought by patients) are more accepting of DTC advertising. Murray et al. (2003) conducted a cross-sectional survey of a nationally representative sample of US physicians to determine their perceptions of the effects of patients discussing information from

DTCA on time efficiency, requests for specific interventions, health outcomes, and the doctor–patient relationship. They found that DTCA has complex effects on quality of care and health service utilization. DTCA results in patients making almost as many inappropriate requests as appropriate ones. In a finding echoing Mintzes et al. (2003), physicians reported that they often acquiesced to patient requests even if they were clinically inappropriate, as long as the patient was not harmed.

An interesting, positive indirect effect of DTCA on physician behavior is found by Young et al. (2008) who report that physicians engage in more shared decision making behavior when faced with patients who request either general or brand-specific medications.

Robinson et al. (2004) found in a mail survey of 523 Colorado physicians and 261 national physicians, and a telephone survey of 500 Colorado households, that most physicians have negative views of DTC pharmaceutical advertising. They believe that advertisements do not provide enough information on cost, alternative treatment options, or adverse effects. Interestingly, less than a quarter of the physicians believed that these ads changed their prescribing practices.

21.3.3 Welfare Effects of DTCA and Government Regulation

21.3.3.1 Is DTCA Market Share Stealing or Category Expanding?

A key question about DTCA is the nature of its impact on drug sales: does DTCA expand the category, or does it primarily lead to stealing market share from competing drugs in the category? This question is not only relevant to assess the nature of competition between firms that invest in DTCA but also central to the debate about the societal effects of DTCA and hence to public policy and regulation.

Consistent with the argument of proponents that DTCA plays an important informational role, DTCA should mainly have a category expanding effect on drug sales. Further, it should be cost effective in reducing underdiagnosis or under-treatment. However, consistent with opponents' arguments, DTCA should mainly affect a drug's market share within a therapeutic class and/or it should not be cost effective even if it has a category expanding impact. We review next the literature pertinent to this debate.

Using data from insurance claims of high cholesterol patients, Wosinska (2002) concludes that DTCA increases the likelihood of a drug being prescribed by physicians but only for drugs on the formulary. She also finds that the marginal impact of DTCA on prescription choices is significantly lower than that of detailing. Narayanan et al. (2004) examine aggregate sales and marketing promotions of second-generation antihistamines from April 1993 through March 2002. They report that whereas DTCA has a significant effect on category sales, detailing does not. In contrast, both detailing and DTCA affect drug market shares, but detailing has a much larger effect than DTCA in generating market share. Fischer and Albers (2010) suggest a new method for measuring primary demand effects with aggregate data at the

brand level and apply their model to 86 pharmaceutical categories in the US market for the period 2001–2005. They find that primary demand effects of marketing promotions are rather small and DTCA is less effective than detailing in driving primary demand.

Rosenthal et al. (2003) investigate the effect of DTCA and detailing on drug sales in five therapeutic classes using monthly aggregate data from August 1996 through December 1999. They find that DTCA has been effective primarily in expanding the sales of the entire class instead of any individual drug. Using antihistamines as an example, Iizuka and Jin (2007) show that DTCA has little effect on the choice of brand despite the massive DTCA expenditure incurred in this class.

Donohue et al. (2004) analyze claims and benefits data for individuals diagnosed with depression and find a small positive effect that DTCA spending increases the likelihood of receiving medication treatment, i.e., category expansion effects. They conjecture this may occur because an individual who is undergoing psychotherapy for a previous episode of depression may, upon being exposed to DTCA, request medication treatment in combination with or in lieu of behavioral treatment. By contrast, they found that providing free samples did not increase the likelihood of a depressed individual receiving medication treatment.

It has been argued that advertising tends to attract patients to the physicians' office who have less severe afflictions and may in fact not be good candidates for medication. Coupled with the survey-based finding described previously that physicians sometimes acquiesce to patients' requests for medications even if they are not clinically appropriate, as long as they don't harm patients, this raises a concern that DTCA leads to suboptimal use of physician time and drug resources from a societal point of view.

Thus, it appears from the literature that the category expanding effects of DTCA are fairly well established, with two caveats. One, the magnitude of the effect is generally small, and two, the "quality" of patients brought in remains an area for further exploration. The unique ability of DTCA to drive potential patients to visit physicians for diagnosis and treatment gives it an edge relative to physician-directed promotions such as detailing. The brand-switching effects of DTCA are less clear.

21.3.3.2 Health Disparity and DTCA

Another question with significant public policy implications is whether the effects of DTCA vary across patient subgroups. A robust and well established finding in the social sciences literature is the relationship between socio-economic status (SES) and health. In general, there are significant disparities in medical testing, treatment and health outcomes associated with SES. For example, the 1990 National Health Interview Survey (Piani and Schoenbom 1993) found that patients of higher SES (college educated and white race) reported a higher likelihood of cholesterol testing.

Since DTCA can be an important form of consumer information about diseases and pharmaceutical products, it is useful to explore whether the response to DTCA varies across patients.

Differences in response to DTCA across patients arise due to different levels of exposure to media and advertising, varying levels of need, current diagnosis, and treatment, and differences in access to and type of health care (for instance, health insurance). Using data from two nationwide surveys, Gönül et al. (2000) find that patients who have an ongoing need for health care, that is, those with children or with a chronic condition requiring medication, value prescription drug advertising more highly.

Iizuka and Jin (2005) do not find differences in effectiveness of DTCA in generating physician visits across patients with different insurance. On the contrary, Hosken and Wendling (2010) report that highly educated patients and women, in particular women with Medicaid insurance, are the most responsive to drug advertising while Hispanics are the least responsive to advertising. Avery et al. (2008) analyze exposure to advertisements for pharmaceutical products that treat ten categories of health conditions. They find that some groups, most notably Blacks, unemployed consumers, those who do not work full-time, as well as consumers with less schooling and lower incomes are exposed to more DTC advertisements.

Liu and Gupta (2011) find that the effectiveness of DTCA in generating new patient visits varies substantially across patients grouped by insurance status. Specifically, they report that while older patients (those on Medicare) and patients on indemnity are not responsive to DTCA in terms of visits to physicians, poorer patients (those on Medicaid) and patients on managed care plans are very responsive to DTCA.

21.3.3.3 DTCA Cost Effectiveness

Much of the empirical work on DTCA attempts to address the question of social usefulness of DTCA by distinguishing between its impacts on expanding the therapeutic category vs. changing brand shares. However, even if DTCA expands category demand, thereby reducing underdiagnosis and under-treatment, the question remains whether it is a cost-effective instrument for this purpose. Atherly and Rubin (2009) use published information (i.e., they base their analysis and conclusions on previous literature) to analyze the economic value of DTCA. They find that DTCA is likely to be cost effective if the advertised drugs lead to increased demand for treatments that are themselves cost effective, and if patients driven to the treatment by DTCA are similar to other patients (those not driven by DTCA). Liu and Gupta (2011) estimate the cost effectiveness of DTCA of statins by combining their estimates of the effectiveness of DTCA in driving patients to visit physicians with published information (drawn from the literature) of the effectiveness of statins in extending patients' life expectancy and the cost of such treatment. They conclude that DTCA of statins is cost effective despite several conservative assumptions about the benefits of DTCA.

21.3.3.4 Regulation

Worldwide, promotion and distribution of prescription pharmaceuticals is strictly regulated by government agencies. As noted previously, this is especially true for DTCA which has been banned in all but 2 of the 34 member countries of the OECD.

In the USA, pharmaceutical companies must adhere to FDA regulatory guidelines which call for all DTC advertising to be accurate, to provide substantial evidence for any claims that are made, to provide a balance between the risks and benefits of the advertised drug, and to maintain consistency with labeling approved by the FDA. Questions such as the efficiency of regulation and its impact on drug sales and on social welfare have drawn researchers' attention in the past decade.

Based on a time-varying coefficient model, Stremersch and Lemmens (2009) find that differences in regulation of the pharmaceutical industry substantially contribute to cross-country variation in sales. Specifically, they report that prohibition of DTCA tends to hurt sales.

Campbell (2011) discusses the potential effects of a ban on DTCA of new prescription drugs. She argues that a ban or moratorium on DTCA may lead to reduced awareness of the drug's availability among individuals who would benefit from it. She further points out that a moratorium on DTCA might affect other marketing strategies used by drug manufacturers (like detailing to physicians) and the quantities and prices of drugs sold. Chen (2011) estimates physicians' choice and learning process and uses a policy simulation to study the effect of a ban on DTCA. The finding is that if drug advertising is prohibited, diffusion of new drugs will be slowed down to different degrees. The effect is stronger for the relatively better new drugs in the therapeutic class.

21.3.3.5 Compliance

Noncompliance with prescribed drug regimens is a very significant and widespread problem. Noncompliance has adverse consequences for the patient, the drug manufacturer, as well as society (Wosinska 2005). Given the proven success of advertising in influencing consumer attitudes and behaviors in a variety of contexts, encouraging compliance with prescribed therapy would seem to be a natural and desirable role for DTCA.

The relationship between advertising exposure and compliance is complex. Bowman et al. (2004) argue that, on the one hand, a positive relationship is expected because advertising serves a reminder role and reinforces positive compliance behavior. On the other hand, patients who feel empowered by advertising may make changes to their dosage schedule without consulting their physician, thereby leading to a negative relationship. They also conjecture a role for patient heterogeneity: if DTCA attracts marginal consumers to the treatment—those who have minimal symptoms—the average level of compliance in the category may be reduced by increased advertising. In their data for four categories and three segments of consumers, results are mixed.

Wosinska (2005) uses prescription claims data to examine compliance in the category of cholesterol-lowering drugs. Contrary to many industry surveys, she finds that the impact is small in economic terms. However, since the goal of the advertising was primarily acquisition of new patients and not improving compliance, she considers this a spillover effect. She also finds that brand advertising spills over to improved compliance of users of other brands in the category. A negative effect on compliance

occurs for patients who receive new information from advertising about risks associated with the therapy.

Using medical and pharmacy claims of beneficiaries from a group of largely self-insured companies in the USA, Donohue et al. (2004) study the effects of DTCA and other promotional activities on the likelihood that a depressed individual received antidepressant medication for the appropriate duration. They find small positive effects of category-level DTCA, but no effect of DTCA of the particular treatment taken by the individual.

21.3.4 Pharmaceutical Firms and DTCA

As more in-depth understanding of the impact of DTCA on demand for prescription drugs emerged in the literature, researchers began to explore pharmaceutical firms' DTCA decisions, especially in a competitive framework. Using brand-level advertising for 1996–1999, Iizuka (2004) studies the determinants of magnitude of DTCA across multiple prescription drugs. As noted previously in this chapter, he finds that drugs that are new, of high quality, and for under-treated diseases are more frequently advertised. Furthermore, firms advertise less as the number of therapeutic and generic competitors gets larger. Osinga et al. (2010) offer a unique investor perspective on why firms spend vast amounts of money on DTCA even though such advertising only has moderate effects on brand sales and market share relative to detailing. Investors value DTCA positively because it leads to higher stock returns and lower systematic risk, but higher idiosyncratic risk which does not impact investors who hold well-diversified portfolios. In a theoretical framework with two pharmaceutical firms providing horizontally differentiated (branded) drugs, Brekke and Kuhn (2006) find that DTCA and detailing are complementary strategies. If DTCA increases the number of patient visits, it makes it more profitable for firms to spend more on detailing to get physicians to prescribe their drugs. They also show that firms benefit from DTCA if detailing competition is not too fierce, which is true if detailing investments are sufficiently costly. Interestingly, if detailing is not sufficiently costly, firms actually prefer a ban on DTCA.

Amaldoss and He (2009) propose and test a competitive model of DTC advertising. Recognizing that DTCA could be brand-specific to varying degrees, they find that the brand specificity of DTC advertising can have an inverted U-shaped relationship with detailing, DTC advertising, and profits. Furthermore, an increase in the cross-price sensitivity between competing prescription drugs is not always detrimental to firm profits. A laboratory test was conducted to lend qualitative support to some of their model predictions.

21.4 Conclusions and Future Research

To conclude, we first summarize in Table 21.3 the findings of a number of studies that estimate the short- and/or long-term DTCA elasticities. To put these effects in context, the average short-term brand elasticity of advertising in general is

Table 21.3 DTCA elasticities reported in the literature

Authors	Year	Short-term DTCA elasticity	Long-term DTCA elasticity
Berndt et al.	1995	0.008	0.053
Calfee et al.	2002	–	–
Wittink	2002	0.004	–
Wosinska	2002	0.032	–
Rosenthal et al.	2003	0.091–0.114	–
Narayanan et al.	2004	0.023	
Iizuka and Jin	2005	0.014–0.024	0.031–0.053
Fischer and Albers	2010	0.01	0.074
Liu and Gupta	2011	0.012	0.03

estimated in a recent meta-analysis of consumer product markets to be 0.12 and the average long-term elasticity to be 0.24 (Sethuraman et al. 2011). Sethuraman et al. (2011) point out that their estimates of advertising elasticities are significantly smaller than those reported in earlier meta-analyses. In Table 21.3, the short-term DTCA elasticity averages about 0.02 with a range of 0.01–0.11. The long-term DTCA elasticity averages about 0.05 with a range of 0.03–0.07. We recognize that there are many conceptual and methodological challenges in comparing elasticities across studies. Notwithstanding these, it is striking that the reported DTCA elasticities are squarely in the lower half of the distribution of advertising elasticities. This is unsurprising given the very different role of consumer advertising, as well as lower importance relative to marketing to physicians, in driving prescription drug sales. This is an important consideration in the determination of the marketing mix for prescription drugs, a question we return to subsequently.

Our review of the literature indicates that several interesting and important questions related to DTCA remain unexplored or underexplored. We divide our discussion of these questions into two broad domains: demand side and supply side.

Demand side

(a) We believe there is considerable room to understand better the heterogeneity in patient responsiveness to DTCA using market data. Liu and Gupta (2011) study differences in responsiveness of insurance groups. Another important variable of interest is severity of condition. A commonly heard critique of DTCA is that it attracts patients with less severe afflictions to the physician's office, and further, these patients receive drug treatment as a result of requests they make of their physicians, when in fact they are not ideal candidates for medication. This important question has not, to our knowledge, been empirically examined. In addition to patient types, future researchers might also want to examine how DTCA in different media impacts potential patients differently. Liu and Gupta (2011) find, for instance, that DTCA in print vs. TV influences patients from different insurance groups differently.

Another relevant question related to patient heterogeneity deals with the impact of DTCA on patient requests. Stremersch and van Dyck (2009) note that prior research shows differences based on patient gender. Women have been found to be

more concerned with their health as well as to interact more assertively in health care settings. Further, physicians are more empathic to female than to male patients. All of these suggest that females may be more responsive to DTCA than males.

(b) While a large body of research has studied DTCA effects empirically, the typical study examines only one or a few therapeutic categories or products. An exception is Iizuka and Jin (2005) who have data for multiple therapeutic categories but estimate a pooled effect of DTCA. As a result, it has not been possible to develop an empirical understanding of the determinants or correlates of effectiveness of DTCA. We believe with the increased availability of data for multiple therapeutic categories, it is time to develop a broader understanding of the drivers of DTCA elasticities. An attempt in this direction is made by Kremer et al. (2008) in a meta-analysis, and by Fischer and Albers (2010) using their own estimated DTCA elasticities of primary demand. Some of the factors that may be useful to study are the nature of the condition being treated (for instance, chronic vs. acute), the maturity of the category or product (e.g., established vs. new product), the size of the market (i.e., large vs. niche patient population), number of competing products in the category, and so forth.

Supply side

The following are some questions that we believe are insufficiently researched on the supply side and would be potentially valuable to firms:

(a) The determination of optimal marketing mix strategies, including direct-to-physician and DTC promotional activities. Are there synergies in effects across activities, and how can these be used to manage the marketing mix better? Narayanan et al. (2004), for example, find the positive interaction between DTCA and detailing.
(b) How should a firm manage its DTCA expenditures over the patent life of a brand drug? In most molecule markets all forms of marketing expenditures, including DTCA, are essentially eliminated once the patent on the brand expires. The reason is that after patent expiration most prescription volume shifts to generic drugs that are priced much lower than the brand. However, the brand drug continues to enjoy a small market share at a high price (typically) because of some patients who are loyal to the brand (Frank and Salkever 1997). Thus, the brand's goodwill that has been created over its patent life continues to yield returns to the firm after expiration of the patent. Related questions are the level of persistence of DTCA effects on patient requests and on prescription writing.
(c) As discussed previously, there has been demand for a possible moratorium on DTCA of new drugs for a period of 2 years after approval of the drug by the FDA. The primary concern driving this demand is that potential risks of a new drug are not fully discovered during the approval process, and it is therefore risky to promote these drugs. Merck's Vioxx is often held up as an example of this risk. Such a ban is likely to have wide reaching consequences both for the affected pharmaceutical firms and for patients and society. For instance, one possible

response of new drug manufacturers is to expand their marketing efforts to physicians, in an effort to substitute for advertising (Campbell 2011). Obviously competing firms (manufacturers of incumbent brands in the category) would need to rethink their optimal marketing strategies and expenditures in the event of a ban. Further, sales and market shares of all drugs in the category, especially the new drug, will be affected. Another concern is that some individuals who would benefit from the new drug might remain unaware because of the advertising ban, thereby lowering overall welfare.

One approach to address this question is to develop a structural model of the competitive market that incorporates both the demand for the prescription drug and equilibrium marketing decisions of competing firms. Such a model would enable the researcher to then consider the advertising moratorium as a counterfactual and simulate the consequences of this event.

In conclusion, our review of the literature on DTCA indicates that this topic has received attention in multiple fields, including marketing, health economics, medicine, public policy, and law and economics. However, this remains a "hot" topic with near daily coverage in the media, providing rich fodder for new and interesting research questions that are important to firms, patients, and policy makers. In fact, we found that the literature was so vast and diverse that it was challenging to identify and summarize a representative subset in this chapter. In this chapter we have identified a few unresolved research questions that we believe are significant and worthy of future research.

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Chapter 22
How DTCA Influences Prescription Pharmaceutical Markets

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Abstract This chapter focuses on the potential influence of direct-to-consumer advertising (DTCA) on firm strategy, patients, physicians, and policy change. Particularly, we identify the chain of DTCA influence through which public policy actions, such as DTCA (de)regulation, prompt firm decisions as to whether or not to engage in DTCA, which drugs to pick for direct-to-consumer communication, and how much to allocate to DTCA versus the marketing-mix direct-to-physician (DTP). We highlight the importance of disentangling DTCA effects on the two main stakeholders, patient and the physician, to unravel the intricacies of prescription decisions. With this aim, we analyze a data set for three top-selling classes in the USA, namely, proton-pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), and HMG-CoA reductase inhibitors (Statins). The results confirm extant research and suggest that DTCA exhibits oversaturation effects later in the life cycle of a therapeutic class and is unlikely to be the major driver of pharmaceutical sales. On the other hand, DTP spending appears to be more influential and resistant to life cycle effects.

22.1 Introduction

The drug prescription decision is highly complex and involves multiple stakeholders. As a result, policy changes regarding prescription pharmaceuticals tend to attract a lot of attention and invite heated debates. One such hotly debated policy

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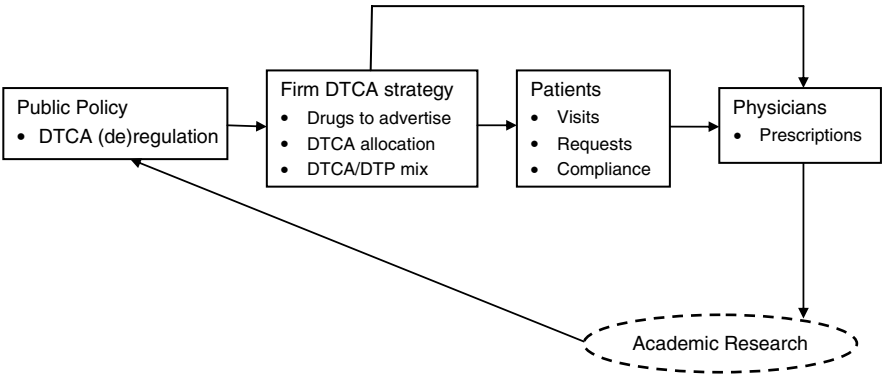

Fig. 22.1 Chain of DTCA influences

change is the deregulation of direct-to-consumer advertising (DTCA) in the USA, prompted by the "reinterpretation" of the Food and Drug Administration (FDA) rules in 1997 (e.g., Pines 1999).[1] The arguments of DTCA proponents and critics are well-documented (e.g., Gellad and Lyles 2007 for an overview). Briefly, proponents suggest that DTCA increases awareness for new treatments and underdiagnosed conditions, empowers consumers by providing more information, and strengthens the patient–physician relationship by providing a basis for a more meaningful interaction during visits. Critics counter by supporting that DTCA does not educate the consumer since it does not provide clear information about indications and risks and may over-state the benefits of a treatment, adds to the workload of physicians who may have to accommodate additional visits triggered by DTCA and address patient questions regarding information received by DTCA, and can lead to higher prices. Naturally, proponents predominantly identify with the pharmaceutical business community (e.g., Holmer 2002), while the medical and health community (Hollon 2005) contains a fair amount of critics (see also recap in Gellad and Lyles 2007). In economic terms, proponents of DTCA support a "constructive" or informative effect, according to which information availability and potentially welfare are increased through DTCA, whereas critics advocate a "destructive" or combative effect, according to which DTCA increases sales and prices of marginally innovative drugs. It is worth noting that the extent of the debate is rather disproportionate to DTCA's budget allocation by drug manufacturers, who still focus predominantly on direct-to-physician (DTP) activities.

The potential influence of DTCA on firm strategy, patients, physicians, and further possible policy changes, depicted in Fig. 22.1, will be the topic of this chapter. Figure 22.1 captures the chain of potential influences due to the introduction of DTCA and encapsulates main issues to be discussed in this chapter. Public policy

[1] Interestingly, Lyles (2002), in his historical perspective on DTCA, notes that prior to 1930 direct-to-consumer communication was rather the norm in the USA.

actions, such as DTCA (de)regulation, prompts firm decisions as to whether or not engage in DTCA, which drugs to pick for direct-to-consumer communication, and how much to allocate on DTCA vs. the rest of marketing-mix DTP. The marketplace influence of DTCA then extends over two distinct stakeholder groups, mainly patients and physicians. The former, besides being the "consumers," also assume the role of potential influencers by submitting specific requests to the latter triggered by DTCA. The latter are decision makers who may also be influenced by DTCA messages. Thus, when DTCA effects are measured in terms of prescriptions, as frequently is the case, it is difficult to disentangle the effects on the two possible agents, patient and physician. Due to the complexity of the decision and the multiple layers of DTCA influence, academic research can play a vital role as a catalyst for policy assessment and changes since it can provide a rigorous evaluation of these effects. It then follows that an examination of research on the various DTCA effects is of paramount importance.

One could identify two eras of research on the nature of the DTCA effect. The first covers the 5-year period after the reinterpretation (1997–2002), during which much of the literature, mainly appearing in health science journals, focused on the DTCA debate with very little evidence from formal econometric analyses. Advocates of each side typically relied on selected figures from surveys, predominantly the ones conducted by FDA and *Prevention* magazine, to provide arguments for or against DTCA (e.g., Calfee et al. 2002; Lexchin and Mintzes 2002). While there is little disagreement that DTCA raises the awareness of patients for available medications, the extent to which such ads are educational is fiercely debated (e.g., Holmer 2002; Wolfe 2002). In particular, balance, clarity, and quality of risk and benefit information are concerns frequently raised by the critics. However, due to lack of econometric analyses up to that point most researchers agreed that definitive answers regarding the effects of DTCA, good or bad, could not be provided.

After 2002, econometric analyses started featuring more prominently in the literature, particularly in marketing and economics, which allowed for a more formal quantification of the arguments made in the pre-2002 era. It is worth noting that for a topic producing heated and highly polarized arguments, surprisingly little econometric research has been done.[2] Nevertheless, this research has managed to provide some econometric answers to the questions raised by both proponents and critics of DTCA. The econometric analyses are mostly based on industry data, such as sales, market share, DTCA, and other (DTP) marketing expenditures, and cover a few or multiple drug classes. Only a few studies use individual-level claims data.

The rest of the chapter is organized as follows. Before we proceed with the review of related academic literature, we provide a framework and discussion for DTCA regulation around the world. Following the academic literature review, we

[2]The meta-analysis by Kremer et al. (2008) examines 156 DTCA elasticities from 17 studies. Of those, two analyze data before the 1997 clarification and three were working papers at the time of the publication. Since then relatively few econometric studies have been published, most notably Fischer and Albers (2010) and Kolsarici and Vakratsas (2010).

discuss the relative effects of DTCA and DTP activities. We illustrate the differences between DTCA and DTP with an original analysis of some of the most DTC advertised therapeutic classes immediately after the 1997 deregulation in the USA. We conclude with an appraisal of the current state of affairs and directions for future consideration and research.

22.2 DTCA Around the World: A Closer Look at the Regulatory Environment

DTCA is strictly regulated worldwide and is banned by law in all but 2 of the 30 country members of the Organization for Economic Cooperation and Development (OECD), USA and New Zealand. Although legislation is undeniably the major determinant of DTCA status and form, the interpretation of the related clauses, the efficiency of the regulatory bodies, their task performance, and the viewpoints of other stakeholders influence considerably the practice of DTCA, rendering it a highly complex issue (Peppin 2006).

New Zealand and the USA are the two most liberal countries regarding consumer-directed pharmaceutical advertising. New Zealand has a self-regulatory system, the Therapeutic Advertising Pre-vetting System (TAPS), managed through the Association of New Zealand advertisers, which is responsible for the preclearance of advertising messages. Unlike New Zealand, DTCA in the USA is centrally regulated. The FDA reviews the ads based on the *Food, Drug and Cosmetics Act* (FDCA). FDCA prohibits false and misleading claims which fail to present risk–benefit information in a balanced manner and poses a series of requirements for DTCA messages. First, drug companies are required to provide a "brief summary" of all risk-related information such as contraindications, warnings, major precautions, and non-serious adverse affects in a product's package labeling as well as in any promotional material. Second, firms are required to send the ads they launch to FDA, which then examines whether they comply with federal legislation. In 1997, the FDA released a draft guidance allowing the drug companies to replace the "brief summary" in TV broadcasts with major risks of the product in the audio or audio-visual parts of the commercial, with the condition that they refer the viewers to adequate sources of information such as a physician, a Web site, or a toll-free number where they can get more information. With this clarification guideline, DTCA came to be seen as an attractive way of reaching patients, with total spending amounting to a stable 40 % of the annual pharmaceutical promotional expenses between 2005 and 2010 (IMS Health 2011).

FDA recognizes three types of DTCA based on the content of the promotional message. *Help-seeking advertisements* contain information about the therapeutic category, symptoms, conditions but do not mention any specific drug name or treatment alternative. Thus, help-seeking messages can be considered as informative or "constructive" as they mainly raise awareness about a disease or condition. *Reminder advertisements* contain the drug name only, and must by law refrain from presenting

any information regarding the disease. Thus, reminder messages are by requirement more combative or "destructive," generating market power rather than informing, since they exclusively promote the brand. These two types of ads are not subject to any regulations. However, *product claim advertisements*, which combine both brand and disease information, are regulated by FDA to comply with the *fair balance requirement*, which necessitates a fair representation of risks and benefits of the drug.

Australia, the European Union, and Canada prohibit DTCA. However, in Canada, pharmaceutical firms can use certain types of consumer-directed advertisements, on account of reinterpretation of the provisions (Peppin 2006). Rules regarding advertisement of pharmaceutical drugs are outlined in *the Food and Drugs Act and Regulations* (FDR) and governed by Health Canada. According to Section C.01.044 (1) of Canada's Food and Drugs Act, advertising of prescription medicines (e.g., drugs listed in *Schedule F of the Regulations*) should be limited to the drug's name, price, and quantity, essentially allowing for *reminder* type messages. Two policy statements released by Health Canada in 1996 and 2000 essentially provided a reinterpretation of the Act and its regulations. The first statement aiming to clarify the boundaries between information and advertising, stated that the agency "recognizes the importance to the pharmaceutical industry and to the general public of being able to disseminate and access non-promotional information regarding drugs for human use" (Health Canada, January, 1996). This declaration implicitly served as an approval for *help-seeking advertisements*. The second statement relaxed the FDR even further and explained that firms can advertise prescription drugs as long as they do not combine "…promotional information on a specific prescription only drug and a particular disease or condition in a single advertisement." The same rule prohibits the airing of such announcements sufficiently close in time, the use of same actors, and common executional elements such as music and mood, to inhibit typical viewers easily link the two messages (Health Canada, November, 2000). In sum, pharmaceutical firms can use reminder (brand-only), or help-seeking (disease-only) messages, but product claim ads that combine brand and disease information are prohibited by the federal legislation.

Although the responsibility of governing and enforcing regulations lies with Health Canada, other bodies such as the Pharmaceutical Advertising Advisory Board (PAAB) and Advertising Standards Canada (ASC) became influential and are partially accountable for the intricate nature of DTCA practice in Canada. PAAB is made up of various stakeholders, such as industry representatives, health practitioner organizations, journal editors, and consumer organizations, and is mainly responsible for the preclearance of physician-directed prescription drug advertising. ASC's primary focus is the advertising of over-the-counter drugs to the public. Although there is no preclearance option for consumer-directed advertising, PAAB and ASC provide regulatory advice on the compliance of promotional messages with the federal regulations in response to the voluntary requests from the pharmaceutical firms. The complaints, however, are only handled by Health Canada.

Table 22.1, adapted from Kolsarici and Vakratsas (2010), provides a global taxonomy of DTC advertising with respect to regulations. We use two classification criteria to capture regulatory effects: content, which refers to the information each

Table 22.1 DTCA regulations worldwide

		Product claim messages	Help-seeking messages	Reminder messages
Regulatory content	Therapeutic category information	√	√	X
	Symptoms	√	√	X
	Health claims	√	√	X
	Risk information	√R	NR	NR
	Price information	√	X	√
	Brand name	√	X	√
	Dosage information	√R	X	√
	Direct to a physician	√R	√	NR
Regulatory context	USA and New Zealand	√	√	√
	Canada	X	√	√
	Australia and EU	X	X	X

NR: not required, √: allowed, √R: required, X: forbidden

message type may contain, and context, which refers to the country in which each type of ad is allowed in practice. Regarding the latter, one can clearly distinguish between three types of regulatory regimes: "liberal" (USA, New Zealand), "moderate" (Canada), and "strict" (all others).

22.3 Academic Research on DTCA Influence

Table 22.2 summarizes the main conclusions from research on DTCA effects. The shaded cells indicate conclusions for which more studies are needed to further solidify them. In sum, the evidence so far does not support a "destructive" effect of DTCA:

(a) Brand sales elasticities are low and comparable to the elasticities for consumer packaged goods. For example, in their meta-analysis, Kremer et al. (2008) found that the average DTCA elasticity is 0.07.
(b) DTCA has mainly a (small) market expansion effect, either through increased category sales or doctor visits (e.g., Iizuka and Jin 2007; Iizuka and Jin 2005; Liu and Gupta 2011). The meta-analytic study of Fischer and Albers (2010) found the long-term DTCA elasticity of category sales to be 0.08.
(c) There is no evidence to support that DTCA is associated with higher prices (e.g., Narayanan et al. 2004; Capella et al. 2009). Further, Iizuka and Jin (2007) found no interaction between price and DTCA.

Thus, it seems that DTCA does not contribute to increased health costs besides the increased drug utilization effect which is desirable from a public health perspective (GAO 2002). In fact, Liu and Gupta (2011) found that DTCA for cholesterol-lowering drugs is cost-effective by reducing the under-diagnosis and under-treatment, in other words the category expansion effect of DTCA counterweighs its market-share stealing effect.

Table 22.2 Evidence for constructive effects of DTCA

Conclusion	Support
DTCA has a small but significant market expansion effect.	Rosenthal et al. (2003) Iizuka and Jin (2005) Vakratsas and Kolsarici (2008) Fischer and Albers (2010) Wosinska (2002) Liu and Gupta (2011)
The impact of DTCA on brand sales is small	Stremersch, Landsman and Venkataraman (2012) Kolsarici and Vakratsas (2010) Kremer et al (2008) Iizuka and Jin (2007) Narayanan, Manchanda and Chintagunta (2005) Narayanan, Desiraju and Chintagunta (2004) Donohue and Berndt (2004) Rosenthal et al (2003)
DTCA is concentrated on new, high quality drugs for largely untreated conditions	Iizuka (2005)
DTCA does not lower price elasticities and hence should not increase prices	Narayanan, Desiraju and Chintagunta (2004) Capella et al (2009)
DTCA can increase the likelihood/accelerate treatment after diagnosis	Donohue and Berndt (2004) Bradford et al (2010)
DTCA has a significant but economically small effect on compliance. Brand DTCA has positive spillover effects on compliance for other brands.	Wosinska (2005) Donohue and Berndt (2004)

☐ Sufficient empirical evidence

☐ More evidence is needed

Although these conclusions do not provide indisputable evidence for the constructive effect of DTCA, they nevertheless reject the "destructive" view. The bulk of the evidence has focused on the brand and category sales (prescriptions) effects of DTCA and their comparison to DTP activities. However, some studies have focused on other dimensions of DTCA consequences. Narayanan et al. (2004) as well as Capella et al. (2009) examined DTCA interactions with pricing and detailing and found (as per (c) above) that DTCA is not significantly associated with higher price sensitivity and prices. Stremersch et al. (2012) investigated DTCA effects on drug requests, Wosinska (2005) focused on compliance, Bradford et al. (2010) on therapy initiation, and Donohue and Berndt (2004) on both. They found

that DTCA has a positive effect on compliance (Donohue and Berndt 2004; Wosinska 2005) and therapy initiation (Bradford et al. 2010; Donohue and Berndt 2004). Wosinska (2005) and Donohue and Berndt (2004) used claims data and Stremersch et al. (2012) and Bradford et al. (2010) panel data allowing for individual-level analyses. In fact, Stremersch et al. (2012) integrate three different databases including physician-level panel data, promotional spending, and US Census information in order to investigate the role of physician specialty and spatial characteristics (e.g., race, income, education, age, urbanization) on drug requests. Their study suggests that both spatial characteristics and physician specialty have influence on the number of patient requests. Specifically, specialists receive more drug requests but these are not necessarily translated into prescriptions particularly when compared to the requests to the primary care physicians. Moreover, requests occur more frequently in designated market areas (DMA) with minorities; however, similar to the case with specialists requests from minorities translate less into prescriptions. Cox et al. (2010) investigate patients' interpretation of the risk disclosure in product claim ads and the moderating role of media-context and media-induced mood on their response to information such as the frequency and severity of the product risk. Their findings indicate patients in positive media-induced moods (e.g., via use of pleasant images, up-beat music) more carefully evaluate the risk-related information when forming product use intentions when compared to patients not in positive affective stage who tend to overestimate the likelihood of adverse effects.

There has been very little research on the effect of the different types of DTCA messages (help-seeking, reminder and product claim), although they provide a very good opportunity for testing whether DTCA effects are constructive or combative. This may be due to the fact that, at least in the USA, most ads are of the product claim variety (e.g., Lee-Wingate and Xie 2010). The study by Kolsarici and Vakratsas (2010) is the only one that addresses this issue from an econometric perspective. Analyzing drug sales and pharmaceutical expenditures for the pioneering drug in a newly established category, they compare the effectiveness of help-seeking and reminder advertising, likening the former to a category message and the latter to a brand-specific message. They find that help-seeking ads are more effective in the beginning of the product life cycle as they inform a potentially large untapped market. However, as competition enters and the market matures, reminder ads become more effective. Overall, reminder advertising has a slightly higher elasticity than help-seeking advertising but both are low (0.038 vs. 0.053), consistent with most other econometric studies (Kolsarici and Vakratsas 2010). Lee-Wingate and Xie (2010) compare product claim and help-seeking ads in an experimental setting and find that the latter is more effective in terms of generating stronger behavioral intention to seek treatments for the ailments advertised.

The informational content of DTCA, and in particular the amount of brand-related information contained in DTCA messages, has also been the subject of two game-theoretic studies. Amaldoss and He (2009) use a "brand specificity" parameter to capture the degree of brand-related information in DTCA messages and find that it has an inverted-U shaped relationship with profits. A moderate degree of brand specificity helps a firm to differentiate and avoid free-riding, but a very high

degree of brand specificity makes DTCA less synergistic as it has a limited market expansion effect. Bala and Bhardwaj (2010) also consider the "constructiveness" vs. the "combativeness" of DTCA and find that when the market is largely untapped firms should utilize constructive DTCA, whereas when the market is mature firms should employ combative DTCA. These findings are in agreement with the previously discussed empirical results of Kolsarici and Vakratsas (2010).

22.3.1 Strategic Implications for Firms

From a strategic perspective the evidence suggests that pharmaceutical firms are quite selective, and hence deliberate, in their decision to advertise: DTCA advertising is highly concentrated on new, high quality drugs with upside potential (Iizuka 2004). According to marketing theory these types of markets offer the best opportunity for high advertising elasticities as there is a bigger potential to educate consumers (e.g., Vakratsas and Ambler 1999).

However, given the small economic effect of DTCA, particularly on brand sales, the question is why firms continue to advertise directly to consumers. Current evidence cannot adequately provide an answer to this question. One possibility is that firms attempt to gain the long-term loyalty of patients (and potentially physicians). Although the critical issue of prescription switching has not been researched, Wosinska's (2005) results on positive brand advertising spillover effects on competing drug compliance (Table 22.2) suggest that such an effect may be unlikely. Another possibility is the stock-market explanation recently offered by Osinga et al. (2011). The lack of a definitive answer on why firms utilize DTCA despite low returns may be traced to the scarcity of individual-level analyses. Given that advertising is one of the most versatile marketing tools with many potential effects, these need to be investigated more thoroughly. For example, if DTCA initiates some form of hierarchy of effects according to which DTCA prompts more information search (possibly online) that results in a patient visit where a meaningful interaction between the patient and the physician takes place before a prescription decision is made, there are many steps to be traced. To our knowledge this issue has not been comprehensively investigated via a formal econometric analysis and the main reason is that it imposes daunting data requirements. In our conclusion section we will discuss in more detail such data requirements that can potentially move the issue of DTCA influence forward.

22.3.2 Remaining Concerns

The lack of empirical evidence on potentially "destructive" effects does not "absolve" DTCA as there remain a number of legitimate concerns regarding the content and form of delivery to consumers. Even proponents of deregulation admit

that ads lack clarity especially regarding risk information (e.g., Calfee et al. 2002). Also most critics emphasize that although ads increase awareness of consumers, thus being to a certain extent informational, they are not educational enough and tend to favor benefits at the expense of prevalence and risk information (e.g., Frosch et al. 2007). Patients also agree that ads mostly make drugs seem better than they are (e.g., Berndt 2005). In fairness to pharmaceutical advertisers, in particular in the case of the TV medium, it would be very difficult to produce a fully educational message that would satisfy all stakeholders. However, given the mostly market expansion effects of DTCA, more information about the disease, conditions, and symptoms with a good balance of risk information may lead to long-term benefits for both patients and firms thus producing to social welfare.

There have also been calls for more evidenced-based information in ads (e.g., Hollon 2005), which could benefit both pharmaceutical advertisers and patients as it would lead to better choices for the latter, thus rewarding the most innovative of the former. However, provision of such type of information in DTCA messages requires closer monitoring and reviewing, which has been an Achilles heel for FDA. Donohue et al. (2007) provide an interesting discussion of data showing a decline in the number of regulatory letters sent by FDA to pharmaceutical advertisers. The authors attribute this mostly to staffing issues, resulting in inadequate monitoring, rather than increased compliance with regulations by the pharmaceutical firms. Given the risk generated from potential advertising misinformation in this case, a closer monitoring of the situation could again benefit all stakeholders.

22.4 DTCA vs. DTP

A comparison of the effectiveness of DTCA and DTP activities could provide further insights into the overall influence of DTCA and, consequently, of consumers on drug prescriptions. With free-sampling and detailing still enjoying the lion's share of pharmaceutical expenditures (e.g., Donohue et al. 2007), the "niche" effect of DTCA mainly on market expansion may be well-justified and expected. Two studies have undertaken the task of investigating the effectiveness of both DTCA and DTP efforts on a large scale. The first is the meta-analysis by Kremer et al. (2008) and the second is the study by Fischer and Albers (2010) on category effects of pharmaceutical marketing activities. The latter is not meta-analytic but uses a large number of therapeutic categories (86 accounting for 85 % of the US pharmaceutical market) and controls for methodology, as the same is applied to all data.

The evidence in Kremer et al. (2008) clearly suggests that DTCA elasticities are much smaller than detailing elasticities. The average predicted elasticity for DTCA is 0.073, whereas for detailing is 0.326. DTP advertising (physician journal) elasticity is also greater than that of DTCA at 0.123. Fischer and Albers (2010) propose a "corrected" form of the category-level market response model and corresponding elasticities, from which competitive interaction effects are removed and find that even in terms of market expansion detailing is more effective than DTCA, challenging previous

studies on the issue. Specifically, they find that the long-term competition-neutral elasticity is 0.082 for DTCA, whereas for detailing is 0.278 and 0.109 for DTP advertising. Thus, although the measures and methodologies used are quite different, there is remarkable agreement between the two studies. Thus, the consolidated evidence suggests that DTP activities have a much larger effect on prescriptions than DTCA, rendering the physician as the primary decision-making agent in the prescription process. This, from a public policy perspective, puts the onus back on the physicians who not only have to evaluate the most appropriate regimen for their patients but also have to achieve this after filtering out information directed to them as well as to their patients. Our empirical analysis, presented in the next section, will revisit the issue of the relative effectiveness of DTCA and DTP expenditures.

The magnitude of the DTCA effect should be put into perspective. Although DTCA elasticities are "small" and comparable to those for consumer packaged goods (Kolsarici and Vakratsas 2010; Kremer et al. 2008; Iizuka and Jin 2007; Narayanan et al. 2005; Donohue and Berndt 2004), two points are worth noting: First, DTCA is addressed to patients who are primarily *influencers* and are removed at least one step from the final (prescription) stage of the decision-making process (Fig. 22.1). Second, as Wosinska (2005) also noted, DTCA is unique in that it contains negative information (risks) about the advertised brand. Considering these two hurdles, achieving effectiveness levels close to those of consumer packaged goods is noteworthy. But the final answer on the effectiveness of DTCA cannot be given unless more research is done on how exactly DTCA works its influence all the way to the physician's office as well as during the physician–patient exchange. Analysis of individual patient–physician level data with models that quantify the hierarchy of effects (e.g., Chandukala et al. 2011) is a promising avenue to achieving these goals.

22.5 Empirical Illustration: DTCA and DTP Effects Over the Life Cycle

In this section we conduct our own empirical analysis to illustrate the effects of DTCA previously discussed and their relative effectiveness compared to DTP marketing. We further examine whether DTCA effects exhibit dynamics over the life cycle of different therapeutic classes.

22.5.1 Data

The data set, obtained from SDI Health, includes annual agent-level sales and promotional spending information for three top-selling classes in the USA, namely, proton-pump inhibitors (PPIs), selective serotonin reuptake inhibitor (SSRIs), and HMG-CoA reductase inhibitors (Statins). The data cover a 12-year period between 1996 and 2007 for a total of 22 agents (i.e., 7 Statins, 10 SSRIs, and 5 PPIs). We selected these classes

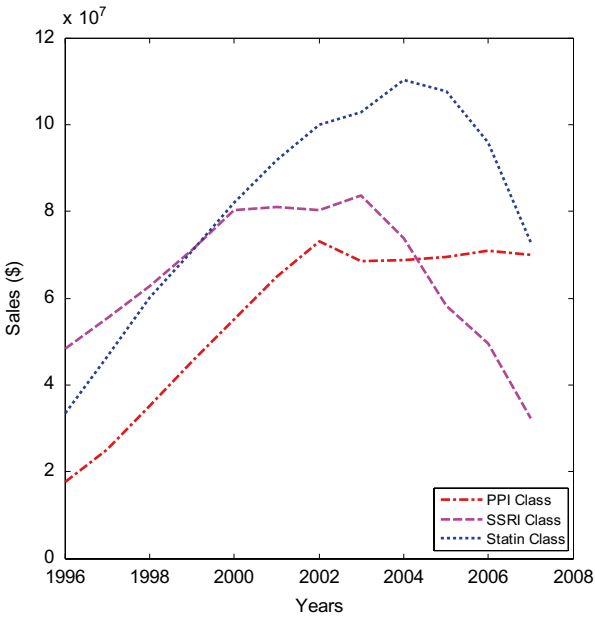

Fig. 22.2 Sales evolution by class

as they contain many "blockbuster" drugs such as Lipitor, Prilosec, and Prozac. They also experience a decline in sales during the observation window, thus allowing us to test life cycle DTCA and DTP effects. The decline should be primarily attributed to patent expirations associated with agents in these product classes. Specifically, the SSRI class experienced its first patent expiration in 2001 (Prozac) with more following later, in PPIs Prilosec lost its patent in 2002 and introduced an OTC version in 2003, and finally Zocor in Statins lost its patent in 2006.

Promotional variables include DTCA, detailing (DET), and physician journal advertising (PJA), Internet and promotional meeting and events audits (PMEA), all in US dollars. Figure 22.2 depicts the sales evolution for the three classes. Figure 22.3 illustrates the allocation of the budget to the aforementioned promotional activities. Not surprisingly, detailing and DTCA account for more than 85 % of promotional expenses, both significantly larger than any other alternative. Figure 22.4 captures the evolution of DTCA and detailing for all three classes. DTCA exhibits the highest rate of increase in spending, starting at a mean annual spending of $6.3 million per agent in 1996, and rapidly moving up to $40.2 million in 2004 where it reaches its peak (Fig. 22.4). Mean DTCA spending per agent in the top three drug classes under investigation increased by 560 % in the 8 years following the FDA clarification. In addition, Fig. 22.5 suggests that DTCA expenditures constitute a fairly constant proportion of detailing over time, further suggesting that DTCA may be anchored to detailing for budgeting purposes. We further examine this by looking at detailing to DTCA expenditure ratios for each class over time in Fig. 22.6. Drugs in PPI and statin classes indeed appear to allocate a fairly constant proportion of detailing to DTCA but the picture for SSRI is somewhat different, characterized

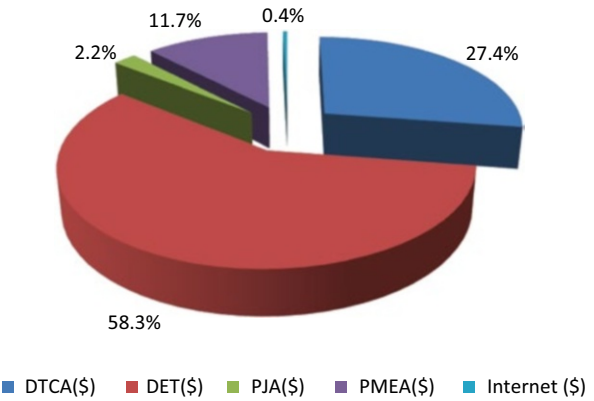

Fig. 22.3 Allocation of the promotional budget

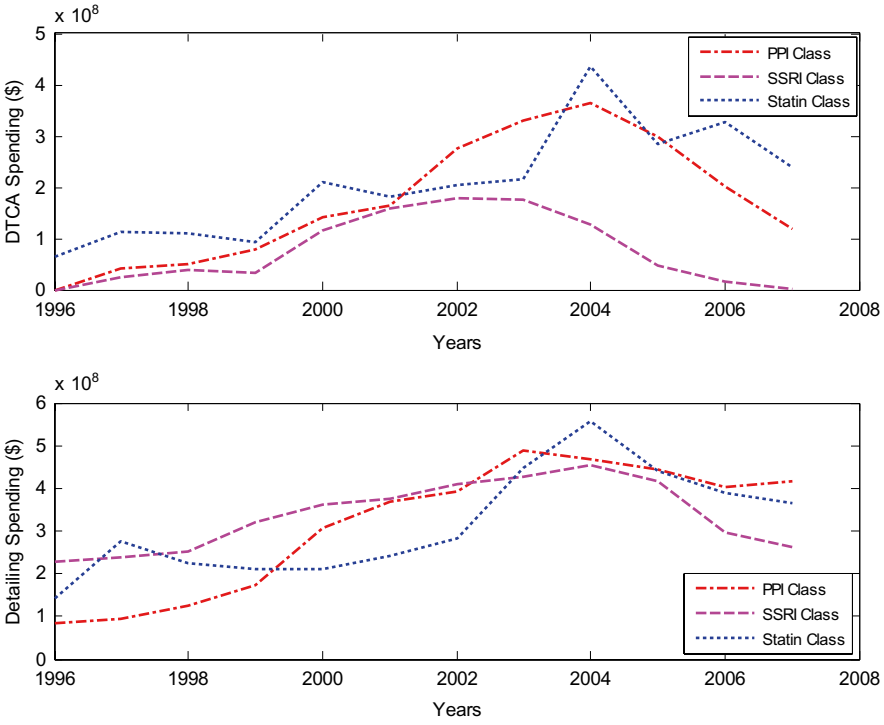

Fig. 22.4 DTCA and detailing evolution by class

first by a detailing-heavy allocation followed by a resurgence of DTCA (after Prozac's patent expiration) and a return of the detailing-heavy allocation. When analyzing our findings from the empirical analysis we will also discuss whether a constant proportion allocation to DTCA should be recommended.

Figures 22.2, 22.4, and 22.5 suggest that both sales and promotional expenditures experience a decline around the year 2004, most likely due to patent expirations

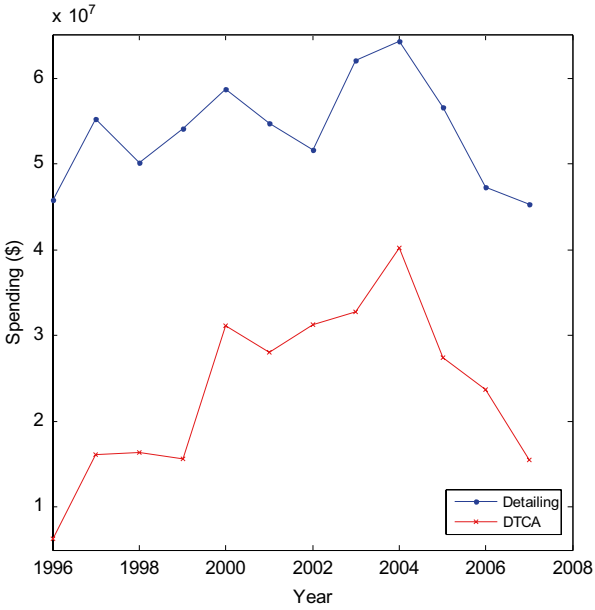

Fig. 22.5 Mean spending for DTCA and detailing

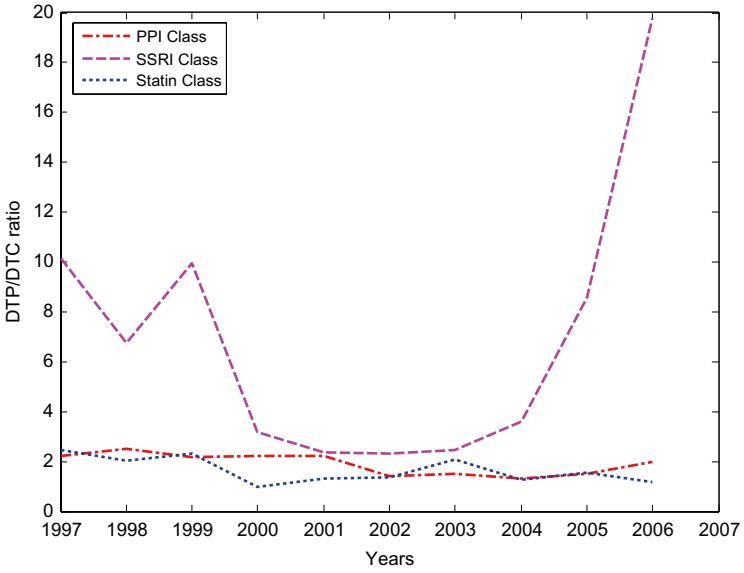

Fig. 22.6 Physician vs. patient directed marketing spending ratios

discussed earlier. Thus, that year could serve as a benchmark for changes in the response to different promotional activities. Indeed, our analysis suggested that 2004 is the optimal breakpoint for analyzing changes in market response to promotional expenditures. We therefore divided the observation period into two windows:

Table 22.3 Descriptive statistics

	DTCA ($)	Detailing ($)	PJA ($)	Sales ($)
Pre-peak window (1996–2004)				
Mean	27,774,640	57,927,635	2,482,573	12,687,292
Standard deviation	47,159,463	46,374,352	3,671,366	12,178,225
Minimum	0	60,146	0	831
Maximum	240,354,997	223,023,132	20,106,593	62,540,586
Count	141	141	141	141
Post-peak window (2005–2007)				
Mean	23,213,881	51,989,808	1,183,187	9,498,299
Standard deviation	53,834,173	70,012,387	2,560,772	14,384,164
Minimum	0	0	0	215
Maximum	225,843,864	243,330,312	9,943,405	63,218,640
Count	66	66	66	66
All years (1996–2007)				
Mean	26,320,485	56,034,415	2,068,276	11,670,512
Standard deviation	49,299,702	54,917,372	3,405,590	12,972,946
Minimum	0	0	0	215
Maximum	240,354,997	243,330,312	20,106,593	63,218,640
Count	207	207	207	207

the first window covers the "pre-peak" DTCA spending period between 1996 and 2004, while the second window covers the 3 years following the DTCA peak between 2005 and 2007 (see Table 22.3 for descriptive statistics). We then performed cross-sectional sales response analyses for the "pre-peak" and "post-peak" windows, respectively, as well as for the whole observation window. A couple of points are worth mentioning here. First, the data exhibit enough variance in promotional spending across agents in each window as coefficients of variation for each year range between 1.28 and 2.78. Second, our main point of interest lies in the change of average response pattern rather than agent heterogeneity, which would have imposed more data requirements. For this reason, we pool the data across agents and over time for each window, assuming no agent-specific effects.

22.5.2 Model Specification

Advertising response often exhibits threshold and saturation effects (Simon and Arndt 1980; Vakratsas et al. 2004), requiring a specification that accommodates both increasing and decreasing returns to scale. In order to capture the nonlinear nature of advertising response and allow for a possible S-shaped pattern, we employ the logistic specification in (22.1) (Leeflang et al. 2000, p. 81, Equation 5–53). We account for category-specific idiosyncrasies through the use of dummy variables in the numerator:

$$S_{it}^{j} = \frac{\exp(\alpha_0 + \alpha_1 D_{1it}^{j} + \alpha_2 D_{2it}^{j})}{1 + \exp(-(\beta_0 + \beta_1 \mathrm{DTCA}_{it}^{j} + \beta_2 \mathrm{DET}_{it}^{j} + \beta_3 \mathrm{PJA}_{it}^{j}))} \tag{22.1}$$

Table 22.4 Estimation results

	Pre-peak window	Post-peak window	All years
Intercept for class effects (α_0)	5.8704	6.5475	5.8740
	(59.40)	(45.42)	(86.72)
PPI class dummy	−0.4478	0.0499	−0.4082
	(−3.49)	(0.36)	(−4.07)
SSRI class dummy	−0.2790	−0.8565	−0.2835
	(−2.46)	(−5.99)	(−3.03)
Intercept for promotion effects (β_0)	−2.4436	−3.2831	−2.5781
	(−6.19)	(−10.08)	(−7.80)
DTCA	0.0020	−0.0007	0.0019
	(3.00)	(−3.51)	(3.26)
DET	0.0028	0.0018	0.0030
	(3.87)	(5.26)	(5.15)
PJA	0.0052	0.0295	0.0047
	(0.99)	(3.74)	(0.98)
R^2	0.5294	0.8867	0.5987

t-Values in parenthesis

where *S*, DTCA, DET, and PJA stand, respectively, for sales, DTCA, detailing, and PJA (all measured in dollars) for drug *i* in year *t* of window *j* and D_1 and D_2 represent the dummy variables for PPI and SSRI classes, respectively. Preliminary analysis suggested that the other promotional variables do not have a significant effect and were subsequently dropped from the model to ease exposition. Note that there are two intercept terms, one (α_0) for the class effects and one (β_0) for the promotional effects.

Table 22.4 contains the results of the analysis for each of the three windows (pre-peak, post-peak, and all years). In general, detailing and PJA are more effective than DTCA ("All years" column), confirming previous empirical findings, but in the pre-peak window the gap in effectiveness, particularly between DTCA and detailing, is smaller. This is not surprising since the window covers the deregulation period where DTCA was considered as a novelty and hence a larger effect is expected. However, in the post-peak period the situation dramatically reverses for DTCA which has a small but significant negative effect (Figs. 22.7, 22.8, and 22.9). This clearly suggests that DTCA influence fatigue which is consistent with informational effects, since these tend to occur earlier in the life cycle (e.g., Kolsarici and Vakratsas 2010), as previously discussed studies also indicated. It further suggests that DTCA is not a major driver of drug sales as it cannot reverse the sales decline after 2004, but it rather seems to contribute to it with its negative effect. It should be noted that this post-peak oversaturation of DTCA effects cannot be attributed to excess exposure to DTCA since average expenditures decreased post-peak (Table 22.3). On the other hand, detailing and PJA continue to have a significantly positive effect on sales post-2004, which, along with the greater magnitude of the corresponding

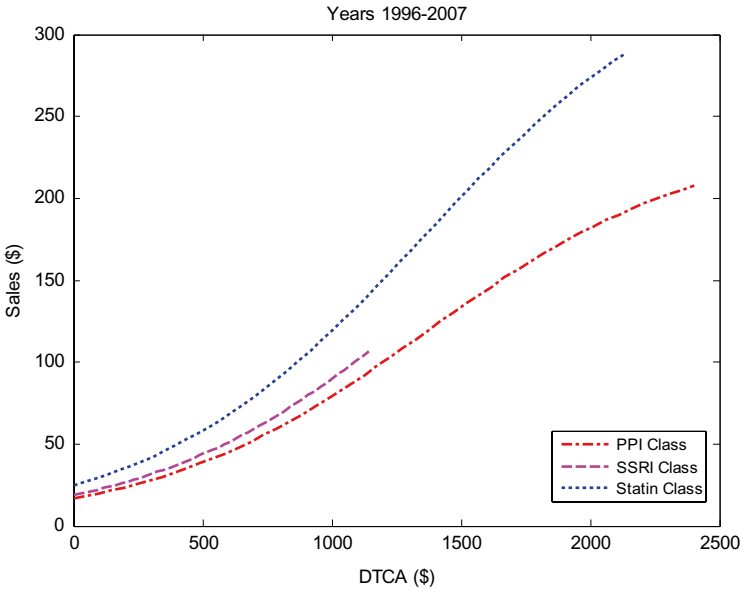

Fig. 22.7 DTCA response functions

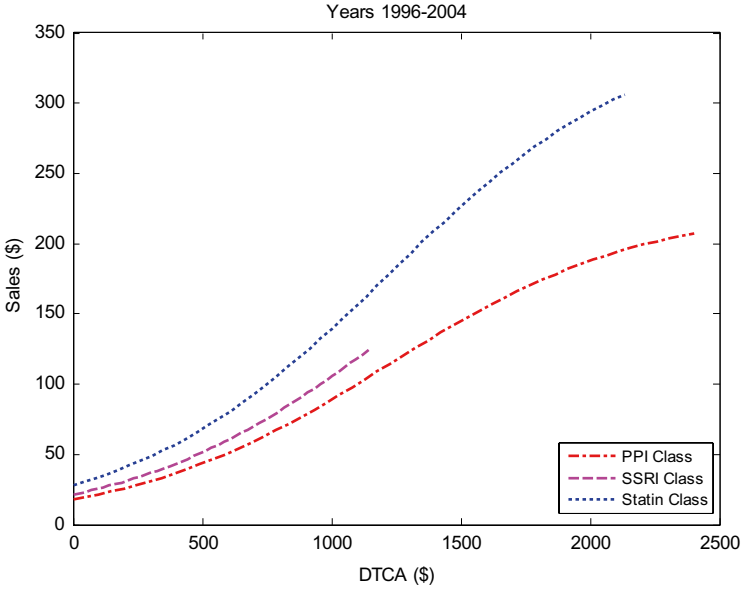

Fig. 22.8 Pre-peak DTCA response functions

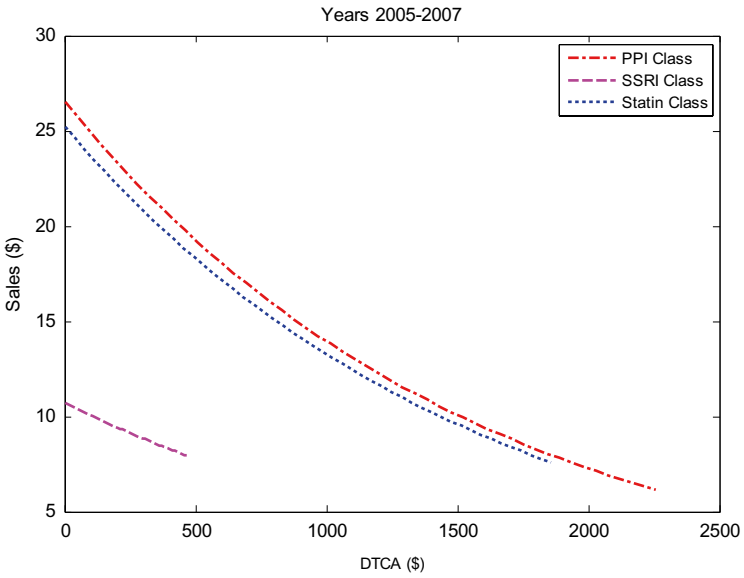

Fig. 22.9 Post-peak DTCA response functions

coefficients, suggests that DTP activities are the major drivers of pharmaceutical sales for the three classes examined. It is worth noting that PJA is more significant post-peak. This provides indirect support to the idea that physicians remain the primary decision makers as DTP activities are more effective and that it pays off to keep a mature drug in a physician's top-of-mind. Of course, in the case of maturity the role of generics and mandatory switching to them required by some insurance organizations will certainly be a contributing factor, but given the physician's decision-making function there are gains to be made from DTP in maturity. Thus, given DTP's higher resistance to fatigue, firms should allocate a higher proportion of resources to DTP activities post-peak rather than using a constant DTP to DTCA ratio throughout the life cycle.

In sum, our empirical analysis suggests that DTCA effects exhibit considerable dynamics over the product life cycle as evidenced by their oversaturation in the post-peak period of our data. We also confirmed previously discussed findings that DTP expenditures are more effective than DTCA. In addition, DTP effects do not dissipate as dramatically as DTCA but are rather resistant to therapeutic class life cycle transitions. Thus, our results collectively provide further support for the argument that DTP remains the most dominant form of communication. In addition, from a more casual observation perspective, the concurrence of sales and promotional peaks may not be coincidental but rather a result of a deliberate decision by firms to pull their resources from declining markets. In other words, as classes mature firms turn their attention and shift their expenditures to other, growing classes to maximize their return on investment (e.g., Iizuka and Jin 2005). This is certainly an area worthy of further investigation.

22.6 Conclusion: Current Situation and Moving Forward

The current state of DTCA affairs seems to be consistent with the evidence on the small and potentially constructive effect of DTCA: the debate now is much less intense, DTCA (and drug) expenses have flattened after a period of high growth (IMS Health 2011), and DTCA is an accepted fact by most stakeholders as the prevailing perception is that it is "here to stay." The growth of Internet communications and social media could have also contributed to the dampening of DTCA criticism as much more, frequently unregulated, information regarding drug therapies is widely available to consumers today. Hence concerns regarding the informational content of consumer communications can no longer be solely focused on DTCA. All these points lead to the realization that DTCA has probably reached a steady state.

However, there is still much to be learned about the effects of DTCA. In particular, there is very little evidence on its welfare effects. Whether patients receive more appropriate treatments as a result of DTCA and whether DTCA improves compliance and leads to more timely diagnoses are all important issues that have been severely under-researched. In order to facilitate such research, we need appropriate databases that focus on the individual patient–physician interaction. This of course requires that privacy issues will be addressed but questions regarding welfare effects cannot be answered unless such data are analyzed at the individual level. Aggregate-level research should also be useful in investigating this issue as some earlier studies on physician–patient interaction through the examination of detailing-DTCA synergies have shown. Narayanan et al. (2004) found a positive DTCA-detailing interaction, suggesting that there is some balancing of information acquired by both agents (patients and physicians) from different sources. A combination of individual and aggregate-level studies would help researchers and public policy makers in obtaining more insights and evaluate how patient-level DTCA effects produce aggregate-level outcomes in terms of total prescriptions.

In addition, despite the proliferation of online communication and regulation stipulation that TV DTCA should refer viewers to a Web site as part of the "adequate provision" requirement, no research has yet attempted to link offline advertising and online communication. Even if conducted at the aggregate level, research linking offline and online communications should provide a good sense of the magnitude of consumer search initiation due to DTCA. If the role of DTCA is to increase consumer awareness and trigger further information search, a substantial amount of online activity should be expected after exposure to DTCA. As previously discussed, information search potentially triggered by DTCA could ignite a hierarchy of effects leading up to a doctor visit and the interaction between patient and physician. Thus a "deconstruction" of the DTCA effect and its mapping to the complex prescription decision process is necessary in order to fully understand the extent of DTCA influence.

As our empirical analysis has shown, along with the findings of Iizuka and Jin (2005), it appears that firms are rather deliberate regarding their DTCA strategy. There are still many questions to be answered related to this issue: (a) how did the

introduction of DTCA change firm strategies regarding the allocation of the marketing mix? This will require detailed databases that cover a sufficiently long period before a policy shift (i.e., 1997 in the USA). (b) Do firms coordinate DTCA and DTP activities? Our data showed that frequently DTCA is allocated as a given proportion of DTP allocation but our findings suggested that perhaps this is not the most suitable option. In addition, after discussing with pharmaceutical executives, the authors were surprised to find that firms do not always make DTCA and DTP decisions simultaneously, (c) how do prices, DTCA, and DTP are related and what is the role of regulation and out-of-pocket pay? Although there is limited evidence supporting DTCA and pricing interactions, there are many factors that enter the pricing decision in the pharmaceutical industry such as co-payment, insurance coverage limits, and generic substitution. Only after carefully examining these, a definitive answer can be provided.

Finally, more econometric studies are necessary to further investigate the effect of informational content on prescriptions. Regulations offer opportunities for experiment-like conditions by allowing three different types of ads with varying content: help-seeking, reminder, and product claim. So far only Kolsarici and Vakratsas (2010) have provided empirical evidence on the effects of different types of ads, but more research is needed on this topic. Even in the case of product claim ads there could be varying degrees of brand vs. category-related information (e.g., Amaldoss and He 2009). An investigation of the most effective mix of these two types of information can guide pharmaceutical firms to strike the right informational balance in their messages, thus improving welfare effects and further reducing their advertising waste. A cross-country analysis could also shed light on the effect of each regulatory regime on pharmaceutical sales and the effectiveness of the different marketing-mix instruments. For example, a comparison among USA, Canada, and the UK, which represent the three types of regulatory regimes, liberal (USA), moderate (Canada), and strict (UK), adjusting for national characteristics and local conditions, could provide a more definitive answer on the effects of regulations. Of particular interest will be to examine whether DTP elasticities are lower in more liberal regulatory regimes, hence suggesting that DTCA is a "substitute" of DTP, or whether the introduction of DTCA contributes to an increased overall elasticity to all promotional expenditures.

In sum, research so far has focused on the economic effect of DTCA and found it to be small. Thus, from this perspective it does not appear that DTCA has a "destructive" effect as it does not boost the market power of pharmaceutical firms. Furthermore, DTP activities such as detailing are much more effective in increasing pharmaceutical sales suggesting that the physician is still in control of the decision-making process. Our empirical analysis also confirmed these findings and suggested that DTCA exhibits oversaturation effects later in the life cycle of a therapeutic class and is unlikely to be the major driver of pharmaceutical sales. On the other hand, DTP spending appears to be more influential and resistant to life cycle effects. Future research should focus more on the welfare benefits of DTCA through the analysis of individual-level databases that track information on patients as well as the physicians that treat them, in order to provide a deeper understanding of the DTCA effect on physician–patient interaction and decision-making.

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Chapter 23
Spillovers and Other Externalities in Pharmaceutical Marketing

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Abstract This chapter highlights the impact of spillovers and other externalities on the pharmaceutical manufacturer's marketing strategy. First, a spillover arises when a marketer's action affects either an unintended audience or the targeted audience in an unintended manner; an externality is defined more broadly in the sense that all spillovers are externalities, but all externalities need not be spillovers. Next, the pharmaceutical industry is characterized by three relatively unique features: (1) unlike other consumer settings, ethical drugs can be dispensed to patients only when they are prescribed by a licensed practitioner; (2) drug manufacturers have patent protection; and (3) there is variation in how marketing activities are regulated across different segments or geographical regions. These features facilitate the existence of certain types of spillovers and externalities. For instance, direct-to-consumer advertising (DTCA) is permitted in the USA but not in Canada; this suggests the possibility of a spillover—onto the unintended Canadian consumers from DTCA in the USA. For illustration, we use IMS data on nasal steroids to explore empirically both the existence of a spillover and its impact. The empirical analysis suggests that the DTCA spillover into Canada contributes around 4–6 % to the US long-term DTCA return on investment. Such results underscore the value of accounting for spillover effects in developing and evaluating marketing strategy. More generally, this chapter juxtaposes the unique features of the pharmaceutical industry with the extant work on spillovers and other relevant externalities to identify knowledge gaps that warrant research attention.

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23.1 Introduction

The competitive landscape in the pharmaceutical industry is currently littered with blockbuster drugs that have either gone or are scheduled to go off-patent: e.g., Pfizer's Lipitor, Forest Labs' Lexapro, GlaxoSmithKline's Advair, Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership's Plavix, Warner Chilcott's exclusivity for Actonel in Western Europe, and Eli Lilly's Zyprexa. Given the ensuing battle against generic manufacturers—such as Teva and Mylan, the world's number one and two generic drug manufacturers, respectively—for market share, it is increasingly valuable for pharmaceutical companies to manage their marketing resources more effectively. In that context, an issue that has received limited attention in the literature deals with spillovers and related externalities in this industry.

Consider for example (albeit briefly, since more details are given later in the chapter) how one type of spillover may arise and its possible ramifications to strategy. Much of the Canadian population lives relatively close to the US border and has access to US television broadcasts; in addition, US-based magazines—such as the Sports Illustrated—that are circulated in Canada do not have Canada-specific production-runs (see e.g., Mintzes et al. 2001). Consequently, despite the fact that Canada prohibits direct-to-consumer advertising (DTCA) of ethical drugs, a good chunk of its population is exposed to such advertising from multinational pharmaceutical companies.

This exposure will have an impact on the sales of the advertised pharmaceutical products in Canada; and while the marketing managers of the Canadian divisions of these firms are aware of this effect, they may do nothing about it—as noted by the Director of Marketing Planning at Merck Frosst Canada a few years ago: "*We are aware … but generally don't do anything differently because of it*." Accounting for the spillover, however, will likely modify the expected response from other marketing activities (such as detailing) and can impact how resources are allocated—e.g., variation in market response can affect how sales territories are designed, say for different sales reps in Canada, or how quotas are assigned for measuring and compensating sales performance. There can also be implications to assessing marketing effectiveness and determining the appropriate levels of the various marketing activities, such as detailing and DTCA levels in the USA. Clearly, accounting for such externalities will allow the pharmaceutical firms to fine tune their strategies and tactics, and help utilize their resources optimally.

23.1.1 What Is a Spillover and How Is It Related to an Externality?

Intuitively speaking, a spillover arises when an action (such as DTCA by Pfizer) generates an impact in a manner that was not explicitly intended—for example, Pfizer's DTCA raises a given consumer's awareness of the disease and makes her

approach a physician, who prescribes an Eli Lilly product which he deems more appropriate for her condition. In other words, Pfizer's marketing effort has indirectly and (in all likelihood) unintentionally, raised Lilly's sales.

A similar sentiment is echoed in De Bondt's (1996) presidential address at a meeting of the European Association for Research in Industrial Economics: "Spillovers refer to the side effect of strategy. Many business strategies have to account for spillovers on the demand and production sides. Potential sources of confusion (regarding what a spillover is) include R&D that improves competitiveness of one firm and may simultaneously reduce the profits of a rival, even though the latter receives some useful information that may allow it to reduce cost or improve quality …"

Next, a search of the literature reveals that a concrete definition of an externality is relatively hard to come by; e.g., Mas-Colell et al. (1995, p. 351) note that "a fully satisfying definition of an externality has proved somewhat elusive" and offer the following definition: *An externality is present whenever the well-being of a consumer or the production possibilities of a firm are directly affected by the actions of another agent in the economy*. The principal concern expressed by Mas-Colell et al. (1995) in coming up with a definition is that the word "directly" should be interpreted to exclude any effects that may be mediated by prices.

Keeping in mind these perspectives, we will employ the following definition for a spillover throughout the chapter:

> When a marketer's action—which is targeted at a particular audience and undertaken in the pursuit of a specific set of goals—affects either an unintended audience or the targeted audience in an unintended manner, we say that a *spillover* has occurred.

It is worth noting from Mas-Colell et al. (1995) that the definition of an externality[1] is broader than that of a spillover, in the sense that all spillovers are externalities, but all externalities need not be spillovers. Essentially, in our context, an externality accommodates both the unintended and intended impact of actions; for instance, a physician may decide which medicine should be used to treat a given patient's ailment—such decision making on behalf of the patient is viewed as an externality (on the patient) but is not a spillover since there is nothing unintentional about it. Finally, one principal reason why we distinguish between the two is that the word spillover conveys the intended meaning with apparent clarity.

Academics have long agreed, at least at a conceptual level, that these types of externalities can arise in practice (see e.g., the discussion in Gruenspecht and Lave 1989); empirical explorations of such phenomenon, however, are not as extensive as one may expect. To better understand the nature of the spillover effects, we identify why and in what settings the spillover may arise along with the nature of the consequences. Before proceeding further, it is useful to highlight three principal features that distinguish the pharmaceutical setting from other industries and markets.

[1] We subscribe to their definition of an externality throughout the chapter.

23.1.2 Unique Features of the Pharmaceutical Industry

To understand the first relatively unique feature of the pharmaceutical context, let us start with a bit of history. Through the late 1950s and early 1960s, pregnant women in Australia, Canada, Europe, and other parts of the world (not including the USA) were prescribed thalidomide during their first trimester to treat morning sickness. It was later determined that using this drug led to many birth defects in children. The US FDA at that time, despite having limited regulatory authority and only 180 days to police new drugs, had somehow prevented thalidomide from receiving government approval (Scherer 2000). This success paved the way for the US Congress to empower the FDA with considerable authority and latitude to ensure that new drugs were both safe and effective. Since then, the FDA has continued to establish and implement rigorous standards before new medicines are introduced in the US market.

Now, the Congressional Budget Office (CBO) estimates that the process from discovery to new drug launch (via preclinical, three phases of clinical trials and the approval process) takes an average of 12 years and costs 0.8 billion US dollars.[2] And only a small fraction of the new molecular entities (NMEs) that enter the process eventually make it to the product launch stage. For instance toward the end of the 1990s, the Cystic Fibrosis Foundation started to support a search for molecules that corrected defects in the CFTR protein; it is only in the first week of 2012 that regulators approved Kalydeco, produced by Vertex Pharmaceuticals (Kaiser 2012). Interestingly, while the above process is risky (because the NME can fail at any stage), time consuming and requires a huge upfront investment, it can be relatively cheap (costing as little as a few hundred thousand dollars) to reverse engineer an approved medicine and come up with say a generic substitute. This last feature is often absent in other industries because the latter entrant is forced to duplicate much of the R&D before introducing the substitute product.

Consequently, patent protection in the pharmaceutical industry is particularly stringent and prevents easy mimicking by competitors. This protection, along with a relatively inelastic demand—since consumers' costs are subsidized by insurance payments, and because the relatively wealthy segment of the population may purchase brand name drugs even when the insurance does not cover their use—leads to relatively high prices (cf. Frank and Salkever 1992). As an example, the

[2]Of course, only about one-third of new-drug applications are for NMEs. A majority of these applications are for either reformulations (or incremental modifications) of existing drugs or new "on-label" uses (see CBO 2006 and DiMasi et al. 2003). Also, generics have a simpler approval process by using an ANDA, which essentially means that they do not have to engage in clinical trials. Further, among the many available alternative strategies (see Chap. 9 in this book), pharmaceutical companies may sometimes engage in "evergreening" their original patent via either late filing the follow-on patents, developing follow-on drugs with minor modifications, or even engaging in collusive agreements with generic manufacturers. Both the 2003 Medicare Modernization Act as well as the FTC have introduced some changes (e.g., in terms of the nature of agreements between companies) to limit evergreening (see the discussion in Danzon and Keuffel 2007).

yearly cost for the twice-a-day pills of Kalydeco is $294,000! By the same token, however, when an approved drug goes off patent, the manufacturer encounters a sharp decline in revenue. When faced with that eventuality (e.g., between 2012 and 2014, over 100 products in the US market are set to lose patent protection), drug companies typically prepare diligently to counter the revenue loss, and undertake defensive strategies: e.g., they plan on marketing the OTC versions of the drug, form alliances, or acquire other firms to consolidate their NME portfolios, enter new markets, or reevaluate the R&D expenditures.[3]

The second unique feature is that in countries like the USA, UK, and Japan, consumers can obtain an ethical drug only when equipped with a script from a person licensed to prescribe that medicine (e.g., a physician, nurse practitioner, etc.). While the prescriber has professional responsibility, s/he is nevertheless cognizant of other considerations—such as the patient's insurance coverage and the associated formulary, and counter-detailing efforts from HMOs, Medicaid, or other pharmacy benefit managers (PBMs). In other words, the prescriber can be viewed as an agent (for the consumer) who may have incentives that are divergent from those of the consumer. In support of such a view are these results.

A survey by the Government Accountability Office (GAO) found that only 2–7 % of consumers, who saw DTCA, requested and ultimately received a prescription for the advertised drug (see US GAO 2006). Similarly, a 2006 survey of physicians by the Kaiser Family Foundation shows the following: When asked by a patient about a specific treatment, 50 % of the surveyed physicians said they frequently recommended lifestyle or behavioral changes, 14 % frequently recommended no treatment, 18 % recommended OTC drug, another 14 % recommended a different ethical drug, while about 5 % gave a prescription for the requested drug. This is consistent with a 2004 survey conducted by the FDA which revealed that a majority of physicians do not feel pressured to prescribe the requested medication (see also Kravitz et al. 2005).

In any case, there is agreement in the industry (established by surveying physicians) that when patients are more aware of the disease and treatment options, the health outcomes are improved; in other words, the impact of both under-diagnosis and under-treatment is attenuated via patient involvement and education (see PhRMA 2008). Academic research that accounts for this involvement exists, but is relatively rare; Ding and Eliashberg (2008), for instance, construct a joint utility

[3] Historically, as noted in CBO (2006), the pharmaceutical industry has been at the forefront in terms of the percentage of sales revenues that is devoted to R&D. While the investment continues to be significant (PhRMA reports that in 2010, the pharmaceutical industry invested US$67.10 billion toward research and development), recent news reports are suggesting that the trend in R&D spending may be changing (see Reuters, June 27, 2011). The 2010 spending level, for instance, is 3 % less than that in 2008 and 2009, and reflects a growing disillusionment with poor returns on pharmaceutical R&D. Reportedly, Pfizer has taken the most dramatic steps under its new CEO, Ian Read, to slash about a quarter of its R&D budget over the next 2 years; other companies have made smaller cuts.

function for each patient–physician pair, vary the weight placed on the input provided by the patient, and develop forecasts for the sales of ethical drugs.

The third feature that distinguishes the pharmaceutical setting is the variation in the regulation of marketing activities across different segments or even geographical regions. For instance, there is variation in how the US and Canadian regulatory authorities treat DTCA (more on this in a subsequent section). Analogously, price regulation differs across countries; some countries (such as France, Italy, and Japan) have direct price controls—i.e., they set the magnitude of the price ceiling. Other countries, such as Germany, the Netherlands, and New Zealand, however, use reference prices to set the limits on reimbursement. In this latter system, a manufacturer may charge a price above the reference price, and it is the patient (and not the government) who must pay the excess portion above the reimbursement limit (see e.g., Danzon and Keuffel 2007; Chintagunta and Desiraju 2005; Stremersch and Lemmens 2009).

Having outlined the unique features of the pharmaceutical setting, we now provide a brief summary of the research—mainly from marketing—that has examined spillovers and other related externalities. Later in the chapter we review this research in more detail, and note the role of the above unique features in highlighting spillovers that will benefit from further research attention.

23.1.3 A Brief Summary of Extant Research

Any analysis of spillovers needs to accommodate the following issues: the substantive contexts in which spillovers are likely to be relevant, the underlying (possibly theoretical) mechanisms by which spillovers arise in practice, and the consequences of spillovers, which are popularly referred to as the "spillover effects." We now summarize each of these issues in turn.

An inspection of previous research reveals that a variety of marketing settings seem conducive for spillovers to arise: (1) brand extensions either within a given product category or across different categories; (2) when a firm's marketing communications focus only on a subset of a given product's attributes; (3) organizational structure that involves multiple agents who put forth marketing efforts on behalf of that firm or a subset of its brands; (4) brand alliances, R&D alliances, and co-marketing alliances that involve partnerships among firms; (5) sequential entry of products into a given market either within a category or across categories; (6) the launch and takeoff of a product in multiple international markets; and (7) multimarket competition among brands or firms.

Given the above relatively broad assortment of settings where spillovers may arise, we find it convenient to group the extant research along three dimensions: (1) whether the focal firm (or brand) is examined in isolation or in the context of competing firms/brands; (2) whether the analysis is conducted in the context of a single category or across product categories; and (3) whether the examined products are all available concurrently or sequentially. This grouping allows us to generate (at least) a partial taxonomy—that is outlined below and consolidated in Table 23.1, which also includes citations to representative research—for the various types of spillovers.

Table 23.1 Various contexts in which spillovers and related externalities have been studied in the literature

	Within one product category		Across different product categories	
	Products available concurrently	Products available sequentially	Products available concurrently	Products available sequentially
In the context of *one firm or one brand* (e.g., in an umbrella branding setting)	*Information spillover*: Firm/brand advertises about one attribute; consumers make inferences about the unadvertised attribute(s) (Ahluwalia et al. 2001)	*Forward spillover*: Firm introduces a new product under the brand name of an established product and decides on the quality of the product (Wernerfelt 1988)	*Forward and reciprocal spillover*: Firm extends the brand name to a new category; the promotion affects the product in the old category (Erdem 1998; Erdem and Sun 2002)	*Forward and reciprocal spillover*: Firm promotes the Rx version and subsequently introduces the OTC version; the OTC version is affected by the promotion of the Rx (Ling et al. 2002)
	Multi-agent externality: One agent's efforts on behalf of the brand affects the other agent's payoff (Lal 1990)	*Reciprocal spillover*: Firm introduces and advertises a product extension; advertising also affects the parent brand (Balachander and Ghose 2003)		Firm introduces a new product under umbrella branding; information about the new product affects the umbrella brands (Sullivan 1990)
In the context of *multiple firms or competing brands* (e.g., in a brand portfolio or multi-market contact setting)	*Spillover in product or brand portfolios*: The brand equity of one product may affect the others in a firm's product portfolio (Lei et al. 2008)	*Prior perception spillover and dynamic-perception spillover*: An entrant introduces a new brand (drug) in the category served by an incumbent; the new brand benefits from the incumbent's reputation (Janakiraman et al. 2009)	*Spillover in marketing alliances*: One brand forms an alliance with another established brand; performance of the alliance affects consumers' attitude toward the partnering brands (Simonin and Ruth 1998; Suh and Park 2009)	*Counter-extension spillover*: A firm with an established brand in category X launches an extension into category Y; an incumbent serving category Y then launches a counter-extension into category X. This raises competitiveness in the original category and affects the established brand in category X (Kumar 2005)

(continued)

Table 23.1 (continued)

Within one product category		Across different product categories	
Products available concurrently	Products available sequentially	Products available concurrently	Products available sequentially
Spillover from variation in regulations: See Sect. 23.3 in this chapter	*Across-market spillover*: See Chintagunta and Desiraju (2005)	Multiple firms (e.g., Sony, McDonald's, Old Navy, and ConAgra Foods) form an alliance to promote a product (e.g., the movie *Surf's Up*); marketing effort of each partner raises the product's equity and affects the sales of other partner's products (Chennamaneni and Desiraju 2011)	
Information spillover and multi-agent externality: In R&D alliances (see Veugelers 1998)	*Across-market spillover*: Firm introduces a new product in multiple countries; the product's time to takeoff in other countries affects the takeoff in a focal country (Van Everdingen et al. 2009)	*Information spillover and multi-agent externality*: In R&D alliances (see Veugelers 1998)	
Spillover from scandals: Competitors also can get affected (Roehm and Tybout 2006)			
Across-market spillover: Brands compete in multiple markets; actions in one market affect the firms' decisions in other markets (Chintagunta and Desiraju 2005)			

Forward spillover occurs when the equity of a given firm's "parent" product (i.e., one that has been in the market longer) affects a "child" product; and reciprocal spillover occurs when efforts on behalf of the child product affect the parent product. Spillover in product or brand portfolios arises when the equity of one or more of the firm's products or brands affects the equity of the others—this is conceptually broader than the forward and reciprocal spillover noted above. Marketing alliance spillover crops up when consumers' evaluation of the alliance affects the evaluations of the partner firms or brands.

Information spillover occurs when consumers assess the unadvertised attributes of a firm's product from the advertised attributes. Such spillover also arises when a firm gains knowledge from the R&D efforts of a competing firm. Further, in the context of R&D partnerships and in organizational settings where the efforts of multiple agents affect the firm's performance (or the performance of a subset of its brands) or the R&D outcomes, a multi-agent externality can arise.

Next, prior-perception and dynamic-perception spillovers develop when competing products in a given category are introduced sequentially and the perceptions of the latter entrant are affected by the market's experience with the early entrant. Counter-extension spillover happens when a (focal) firm expands into an unrelated category and unintentionally brings the two categories closer in the consumers' mind; this facilitates counter-extensions by competitors into the focal firm's original category. Scandal spillover arises when firms that are not directly involved in the scandal are also affected by it (e.g., when Vioxx was voluntarily recalled by Merck, the harmful effects of Cox-II inhibitors became more salient and affected how other drugs such as Celebrex were perceived; see e.g., US FDA 2004).

An across-market spillover can occur in multi-market contact settings where competitive actions in one market affect the firms' decisions in other markets; an across-market spillover can also occur when a product is introduced in multiple (international) markets and the time to takeoff in one market affects the takeoff timing in other markets. Another setting where an across-market spillover arises is in geographically proximal markets where the governmental regulations vary—as in the case of DTCA, which is legal in the USA and not so in Canada; and such advertising done in the USA affects consumers in the Canadian market.

Now we note briefly the underlying mechanisms or key features that help explain why the various spillovers may arise: (1) the process by which consumers access information and assess its usefulness—in particular, signaling theory (e.g., Wernerfelt 1988) and the accessibility–diagnosticity framework (Feldman and Lynch 1988) are often invoked to explain spillovers; (2) inter-linkages either in the consumer demand across products/markets or in the R&D output across firms; (3) competing managers take a portfolio approach when making decisions across markets which are otherwise independent (the multi-market contact theory; e.g., Parker and Roller 1997); (4) the effect of government regulation in a given market; and (5) the variation in governmental regulations across markets.

Finally, we turn to the spillover effects, which can have either positive or negative implications for the marketer; here we provide a quick sample of the types of effects that have been documented. The multi-agent externality and marketing alliance spillover often lead to an under-investment of marketing efforts; this suboptimal behavior can be costly to the focal firm and the alliance partners. Similarly, scandal and counter-extension spillovers can have brand dilution effects. Across-market spillover, particularly those related to variation in government regulations, can lead to suboptimal resource allocation decisions when the spillover is not taken into account.

By contrast, forward and reciprocal spillover, information spillover in the context of unadvertised attributes, prior-perception spillover, and spillover in product or brand portfolios tend to benefit the marketer. For instance, the perceived linkages among the various brands in a company's portfolio may enhance the effectiveness of marketing efforts designed for each individual brand. The magnitude of enhancement, however, depends on the strength and directionality of the association among the brands (Lei et al. 2008).

It is worth reiterating that spillovers can affect competing brands. An early entrant's success, e.g., may give an opportunity to a competitor who enters later and employs a me-too strategy (Janakiraman et al. 2009). Such opportunities can arise due to prior-perception and dynamic-perception spillovers among competing ethical drugs, especially when the patients (or their de facto agents, the physicians) perceive the brands to be similar.

Overall, previous work has documented a variety of spillover effects that have valuable implications for companies in many settings. With that in mind, we organize the rest of the chapter as follows: Section 23.2 reviews the relevant academic literature dealing with the various spillover effects. Section 23.3 provides an illustrative analysis of how the effects of spillover across markets may be examined, and expands on the sketch of the example given at the beginning of this introduction. Section 23.4 concludes the chapter by identifying contexts within the pharmaceutical market where spillovers can play a significant role but have received limited research attention.

23.2 Extant Research on Spillover Effects

We now discuss a representative set of research findings on the spillover effects that arise in various market settings.

23.2.1 The Under-Investment Effect

This is an important issue that arises in the presence of an externality involving multiple firms or agents. Consider, for instance, a setting in which a franchisor (such as McDonald's) manages two franchisees in a given geographical territory.

In that setup, the efforts of a given franchisee on behalf of the franchisor will enhance, say, the equity of the brand (or franchise) name; this in turn has a positive impact on the sales of the second franchisee. The presence of this inter-linkage (and being aware of it!) gives the second franchisee an incentive to lower its efforts to enhance the brand name. Consequently, in equilibrium, both agents will lower their efforts leading to the under-investment problem. See Lal (1990) for a formal analysis on how to manage such franchisees; for other analyses of the under-investment problem in a channel context, with distributors who do not have exclusive territories, see Iyer (1998) and Desiraju (2004).

An analogous effect arises in R&D partnerships and among firms involved in a co-marketing alliance. Amaldoss et al. (2000), for example, show that in a joint product development alliance, each partner can free ride on the investments made by the other partners, thereby leading to under-investment. Other research on R&D alliances (for a review, see Veugelers 1998), too, shows that the presence of an externality among the partners leads to lower R&D investments.

Similarly, consider a co-marketing alliance such as the one Sony formed with McDonald's, Old Navy, ConAgra Foods and many other partners to promote the movie Surf's Up. In such alliances, when one of the partners, say McDonald's, puts forth effort to popularize Surf's Up, Sony enjoys a direct benefit. Now, Old Navy gains when Sony's equity is enhanced and therefore, indirectly enjoys the impact of that benefit. This latter effect can be seen, e.g., in Howard (1996) who notes that in the context of a Disney–McDonald's tie-in promotion, when the movie's popularity went up, the alliance's value to McDonald's went up; Simonin and Ruth (1998), too, document an analogous relationship in an experimental context (see also Suh and Park 2009).

Note that Yang et al. (2009) show the empirically estimated impact on a brand of joining teams with varying levels of equity. Since the equity of a team goes up from the efforts of the "other" members of the team, the entries in the table are indicative of the varying magnitude of the indirect linkage under discussion. The individual partners of an alliance typically do not account for such an inter-linkage while deciding on their levels of investment (hence we refer to it as a spillover); this in turn leads to overall under-investment in marketing efforts and affects the value of the alliance. See Chennamaneni and Desiraju (2011) for details on the relative value of alternative contractual agreements to manage such alliances.

23.2.2 Spillover Effects Under Umbrella Branding

Next, we turn to spillovers that may arise via consumers' interactions with branded products. Marketing academics have addressed several dimensions of such spillovers (e.g., Erdem 1998; Erdem and Sun 2002; Sullivan 1990; Balachander and Ghose 2003).

Spillover among products using the same "umbrella" brand name—for instance, Yoplait regular yogurt (which was introduced into the market first) and Yoplait nonfat yogurt; we'll refer to the regular product as the parent and the nonfat version as the child—may arise as follows: Yoplait's marketing efforts, such as advertising,

for the nonfat (regular) yogurt may affect the sales for the regular (nonfat) yogurt. When efforts to market the parent product affect the child product, that impact is referred to as a *forward spillover effect*; and when efforts on behalf of the child affect the parent, the corresponding impact is called a *reciprocal spillover effect*.

Now, the spillover effects (i.e., either forward or reciprocal) may be explained by invoking one of two theoretical frameworks: in the first, consumers may use available information on some products and/or brands to update their knowledge of unavailable information regarding other products and/or brands via an economies-of-information argument (e.g., the quality-signaling explanation offered in Wernerfelt 1988); the second offers a consumer memory-based explanation using the associative network theory (e.g., Anderson 1983).

Under the first approach for instance, when it is difficult for consumers to discern product quality prior to purchase, the signaling explanation suggests that a "high-quality" firm would optimally extend its established brand name only to another high-quality product—because doing otherwise would (eventually) lower consumers' perceptions of the quality of all its other products. In that context, Erdem (1998) and Erdem and Sun (2002) consider a model of consumer learning which allows quality perceptions to be correlated across products in distinct categories—they study toothpaste and toothbrush—and find empirical support for the signaling explanation: e.g., all the brands that extended to the child category were perceived to have high qualities in the parent category; further, advertising can help lower consumers' quality uncertainty over time. Other explorations of spillover under this approach include DeGraba and Sullivan (1995), Choi (1998), Andersson (2002), and Hakenes and Peitz (2008).

Also, Kumar (2005) explores how counter-extensions by competing brands may modify the positive effects of the spillover discussed above. Suppose that Samsung, which is a market leader in the TV category, extends into the computer category successfully. Then, Kumar (2005) hypothesizes that consumers will perceive the two categories (i.e., the TV and computer categories) to be now more similar to one another. Subsequently, for example Dell, which may be a leader in the computer category, has a better chance of success when extending into the TV category. The net result of such a counter-extension will likely dilute Samsung's leadership in the TV category. In other words, a brand extension may result in both a positive effect (say, due to quality signaling) and a negative effect from brand dilution. Kumar (2005) finds support for such a negative spillover effect; further, the magnitude of each of these effects is moderated by the market position of the brands under consideration.

Next, the second approach, i.e., the memory-based argument, presumes that consumers store their information about a brand as a network of nodes (or concepts) which are then connected by links (that represent associations between the concepts); further, the strength of a link represents the strength of the association between the concepts. When a node is activated above a threshold level—either by an external cue such as an advertisement or by "spreading" activation from another node—the consumer retrieves the corresponding piece of knowledge from memory. Now, the intensity of the spreading activation is assumed to go up with the strength of the link

between the "new" node and the previously activated node; so the likelihood that the new node will receive the required threshold level of activation goes up when the spreading activation arrives via a stronger link.

Focusing only on one product category (in contrast to the across category setting in Erdem 1998 and Erdem and Sun 2002), Balachander and Ghose (2003) (BG) find empirical support for the memory-based explanation. They argue first that the parent product can be expected to be associated strongly with the brand name (node) in consumers' memory; consequently, when exposed to say the advertising for the child product, the activation of the umbrella brand will likely spread to the parent product (because of the strong link between the two). The ensuing retrieval of the parent will lead to a positive, reciprocal spillover effect. By contrast, exposure to advertising for the parent product is not likely to trigger the child product since the strength of association between the child and the umbrella brand is not significant. BG find that the reciprocal spillover effect of advertising is stronger than the parent product's own advertising effect, and the difference in the magnitudes of these effects is the highest when the child product has been introduced relatively recently into the market (and goes down with time).

23.2.3 Spillover Effects in Other Contexts

The theory underlying BG's hypotheses falls under the broader Feldman and Lynch's (1988) accessibility–diagnosticity framework; BG's focus is mainly on the accessibility (i.e., how different nodes and the associated information may be triggered by spreading activation) part of the framework. More recent research on spillovers considers the diagnosticity dimension of the accessed information as well.

For instance, Roehm and Tybout (2006) consider the spillover effects of a scandal within a given product category: either the competitors of the scandalized brand might be deemed guilty by association, or the scandal might be interpreted as unique to the scandalized brand, thus possibly benefiting its competitors. In other words, assuming that the relevant information for the various brands can be accessed, if the information about the scandalized brand is perceived as being informative about (and diagnostic for) the competing brand, then the former prediction would arise. In an analogous spirit, Lei et al. (2008) also note that the strength of the linkage between two nodes will depend on the direction of the activation.

Also drawing on the accessibility–diagnosticity framework, Janakiraman et al. (2009) examine whether spillover effects can arise between direct competitors in a given product category (cf. Kumar 2005). They argue that since competitors may enter the market sequentially, consumers' perceptions of the earlier entrant(s) can spillover onto the later entrant(s). Using marketing communications and prescription choice data from a panel of physicians, they find support for two types of spillovers: the first is a prior-perception spillover, in which the physician draws upon the quality perceptions from an existing brand to form the prior perception of quality for a new entrant (before any patients experience the new brand); the second is a dynamic-perception

spillover that takes place over time as a result of patients' ongoing experience with competing brands. Interestingly, both these spillovers arise empirically only when the new entrant brands are similar to the previously existing brands.

Researchers have also reported spillover effects in other contexts such as the selective interpretation of product attributes not mentioned in ads (Ahluwalia et al. 2001). Further, Ling et al. (2002) (LBK) empirically estimate brand-level spillover effects of ads for prescription drugs (in the antiulcer and heartburn categories) on the corresponding OTC versions. LBK's focus is on the (temporal) forward spillover effect of ads for established prescription drug brands on the corresponding OTC versions that are subsequently introduced in the same market.

We conclude this section by highlighting the effects of another set of spillovers that can arise across countries. For instance, Van Everdingen et al. (2009) examine how a new product's "takeoff" in one country affects the takeoff timing in another country (see also Verniers et al. 2011). Their study employs data from eight high technology products (e.g., DVD players, video cameras), from 1977 to 2004, across 55 countries. Using a relatively general econometric specification that allows for asymmetric effects for a given pair of countries, they find that the new product takeoff timing is prone to an across-market (cross-country) spillover effect inasmuch as the country is poorer, the higher the number of tourists it receives, and the higher its population density compared to the other countries. Further, the time to takeoff in a given country is affected by the corresponding takeoff time (and not the time of introduction) in a foreign country. The intercountry influence depends on their geographical and economic proximity, but not on their cultural similarity. The influence on a foreign country's time to takeoff is positively related to a given country's physical size, economic wealth, and the number of exports.

By contrast (in terms of the number of product categories considered), Chintagunta and Desiraju (2005) econometrically examine the (supply-side) interactions among three competitors within a product sub-category across several geographical markets. They use quarterly data from 1988 to the end of 1999 on the sales, prices, and detailing levels of Prozac, Zoloft, and Paxil (which belong to the SSRI antidepressants subcategory) in the USA, the United Kingdom, Germany, France, and Italy. These authors postulate that the levels of the marketing variables (i.e., prices and detailing) in a given market will depend on three factors: the within-market response to each variable, along with the nature of the interfirm strategic interactions both within that market and across markets.

In particular, an across-market "spillover" strategic interaction may arise because: (a) the local market affiliate and a global pricing team can set prices jointly; (b) order of entry into the category can matter across countries, since some European governments practice cross-country reference pricing; and (c) the threat of aggressive actions in one market can result in possible punishment by rivals in the other markets (the multi-market contact effect). Chintagunta and Desiraju (2005) employ an econometric specification that allows for a general pattern of across-market spillover interactions and helps in identifying which interactions affect prices and detailing levels in a given market. Their results indicate that all the three factors

mentioned in the previous paragraph are significant in this category, and underscore the importance of considering across-market spillover interactions in developing multi-market strategy.

23.3 Sample Analysis: Impact of Spillover from a Variation in Regulation

DTCA of prescription drugs has been at the center of much attention and debate over the last decade or so. In this section, we elaborate on the example given at the beginning of this chapter and address these two issues[4]: Does DTCA in the USA influence sales in Canada due to spillover from a variation in government regulation? In case it does, what is the magnitude of return from such spillover?

This type of an externality can be important when markets that are geographically close to one another have different sets of regulations governing them. In marked contrast to FDA's policy, Canada's Food and Cosmetics Act expressly prohibits advertisements for prescription drugs. Several medical and consumer groups (the Canadian Medical Association, the Canadian Pharmacists Association, and the Consumers' Association of Canada) are strongly opposed to DTCA in Canada. Further, despite heavy lobbying by Canadian pharmaceutical industry groups to legitimize DTCA, Health Canada has not moved in that direction. DTCA remains a widely debated issue in Canada.[5]

Turning now to the US market, during the 1970s and 1980s, the FDA authority to regulate the promotion of prescription drugs was restricted to messages aimed at doctors and healthcare professionals. Nevertheless, a few pharmaceutical products began targeting ads directly at customers. In response, FDA requested a voluntary moratorium on DTCA during 1983. However, this moratorium was subsequently lifted in a 1985 ruling (Palumbo and Daniel Mullins 2002). In other words, FDA gravitated toward a policy that allowed DTCA as long as it satisfied the same legal requirements for physician-directed ads (i.e., fair balance in benefit and risk information, and "brief summary" of risk information to be included).

An exception was made for electronic ads where the "brief summary" could be substituted by a "major statement" of risks in audio alone or in audio plus video. Furthermore, the ad had to make "adequate provision" to enable the viewer to easily obtain full information about prescription medications, including the risks involved.

[4]This section draws on the analysis in a working paper by one of the authors (see Desiraju et al. 2004a).

[5]More generally, DTCA garners much discussion and review in many countries, and currently remains legal only in the US and New Zealand (Coney 2002). Europe and Australia, for example, are in various stages of active consideration of DTCA for prescription medications.

This requirement made it virtually impossible to create TV DTCA, because the required risk information could not be packed into such a limited exposure interval.

Overall therefore, the 1985 ruling encouraged pharmaceutical firms to advertise their prescription medications more aggressively and more broadly in print media until the early 1990s. Around this time, a few firms took the lead in sponsoring non-product-specific advertising on commercial TV (e.g., "help-seeking" ads that describe disease symptoms without mentioning a specific product; "reminder" ads that encourage patients to consult their doctor, or that mention a drug's name without stating its indications—see Pines 1999). FDA considered such commercials potentially confusing to consumers.

At the same time, though, FDA faced an increasing demand from consumers for more information and clarity about prescription drugs. To investigate policy options, FDA announced a public hearing about DTCA in 1995. Following extensive deliberations in 1996, FDA issued a "draft guidance" document in August 1997 that was targeted at the pharmaceutical industry. This document specifically allowed product-specific TV advertising for prescription drugs. It clarified that, in a product-specific TV ad, the "adequate provision" standard could be met with a reference to one or more of the following sources that provide additional information: a toll-free number, a website address, or a print ad running simultaneously. The TV DTCA also had to contain a "major statement" of risks. In August 1999, the FDA issued a "final guidance" on TV DTCA that reaffirmed the provisions in the draft guidance. As a result, DTCA is "here to stay" (Pines 1999, p. 518). Even though the FDA launched a DTCA policy review in 2003, its broad goal remains stable, i.e., to encourage the flow of accurate information about prescription drugs to consumers to assure their active participation in decisions relating to their own treatment.

The following factors point to a spillover of DTCA from the USA into Canada. Generally, consumers are highly involved with DTCA because it is a tool that empowers them on important healthcare matters. This involvement is exacerbated for Canadian consumers because they face an information vacuum that is artificially mandated by regulations banning DTCA. Further, researchers share the view that it is difficult for Canada to effectively enforce this ban. And, several US-based magazines that are circulated in Canada do not have Canada-specific production-runs (see Mintzes et al. 2001). As a result, consumers from both the USA and Canada are exposed to the same print DTCA. In addition, US-based TV broadcast signals are carried into Canada regularly (Papp 1997). With this setup in mind, we now illustrate a possible approach to empirically explore the impact of this type of spillover.

23.3.1 Overview of the Data

For this illustration, we use data for a specific ethical drug subcategory—nasal steroids. This category was launched at the same time in the US and Canadian markets and experienced significant DTCA since 1997 when the laws governing

DTCA changed in the USA. For both the US and Canadian markets, the data contain monthly information for the period of January 1997 through June 2002. In each country, the data set tracks the total prescriptions written, the average price of the prescription, detailing expenditures, DTCA expenditures (in TV and magazines) in the US market, and other marketing efforts (denoted as "ome") such as professional journal advertising, meetings, and events. IMS Health Canada provided the Canadian data, while the US data on sales, prices, detailing, and ome are from Verispan, and data on DTCA expenditures are from TNS Media Intelligence-CMR (www.tnsmi-cmr.com).

23.3.2 The Model

Here, monthly category sales denote the total number of prescriptions for nasal steroid medications in that time period. Category sales depend on the prices, detailing, DTCA, and other marketing activities of all brands in the category; further, sales are also influenced by seasonality. As marketing variables such as detailing, DTCA, and ome can have carryover effects, we allow for such effects in the specification. The category sales relationships are captured via country-specific linear regression models. The DTCA expenditures via TV and magazines are combined together (and denoted "dtc"); this allows us to compare our analysis of the US data with extant research on DTCA effects that has investigated only the combined effects of all DTCA. In period t and country j, category sales, S_{jt}, are defined by:

$$\begin{aligned}\mathrm{Ln}(S_{jt}) = \alpha_{0j} + \alpha_{1j}\mathrm{SD}_1 + \alpha_{2j}\mathrm{SD}_2 + \alpha_{3j}\mathrm{SD}_3 + \alpha_{4j}P_{jt} + \\ \alpha_{5j}D_{jt} + \alpha_{6j}\mathrm{OME}_{jt} + \alpha_{7j}\mathrm{DTC}_{\mathrm{US},t} + e_{jt}\end{aligned} \tag{23.1}$$

where SD_k ($k = 1, 2, 3$) refers to the seasonal dummy variable, P_{jt} the share-weighted category price in the country under consideration,[6] D_{jt} the goodwill level associated with detailing (det), OME_{jt} the goodwill associated with other marketing efforts (ome), and $\mathrm{DTC}_{\mathrm{US},t}$ the goodwill arising from the combined (i.e., TV and magazines dtc) expenditures. The goodwill terms will reflect carryover effects of marketing activities (see below). Notice that DTCA expenditures are incurred only in the USA. However, they affect sales in both countries, and our specification allows the impact of these expenditures to vary across countries, as indicated by the subscript j. The α's are the estimated country-specific parameters, and e_{jt} is the mean-zero random error term.

[6] A log–log formulation for price is another possible specification that can be employed here; we use the current approach to allow for easier comparison with some of the other empirical explorations of DTCA.

To capture goodwill, we employ the standard Nerlove–Arrow exponential decay model (see Nerlove and Arrow 1962; Lilien et al. 1992, p. 280). Let det_{jt} and ome_{jt} represent the category levels of detailing and other marketing efforts, respectively, in period t. Then the goodwill stocks in period t (i.e., D_{jt}, OME_{jt}, and DTC_{jt}) are given by:

$$D_{jt} = \theta_{j\text{D}} D_{j,t-1} + \sqrt{\text{det}_{jt}}; \tag{23.2}$$

$$\text{OME}_{jt} = \theta_{j\text{O}} \text{OME}_{j,t-1} + \sqrt{\text{ome}_{jt}}; \tag{23.3}$$

$$\text{DTC}_{jt} = \theta_{j\text{DTC}} \text{DTC}_{j,t-1} + \sqrt{\text{dtc}_{jt}} \tag{23.4}$$

where, $\theta_{j\text{D}}$, $\theta_{j\text{O}}$, and $\theta_{j\text{DTC}}$ are the country-specific carryover coefficients for detailing, other marketing efforts, and DTCA combined expenditures, respectively. The square root captures diminishing effects (Erickson 1992) and allows for zero values for variables.

Detailing expenditures are deflated using the wage series for all workers. DTCA spending was deflated using PPIs for advertising, while prices and other expenditures were deflated using the Consumer Price Index (CPI) for all urban consumers. The CPI and wage series were obtained from the Bureau of Labor Statistics (BLS) for the USA, and from two websites (Statistics Canada and the Bank of Canada) for Canada. The quarterly data in the latter series was transformed into monthly series using the SAS CONVERT utility, in line with other studies (e.g., Ling et al. 2002). Descriptive statistics for the data are in Table 23.2. The average retail price in Canada is about one-half of that in the USA for the same time period. Further, the Canadian market is about a tenth of the size of the US market in terms of the total number of prescriptions written in this category.

The carryover parameters $\theta_{j\text{D}}$, $\theta_{j\text{O}}$, and $\theta_{j\text{DTC}}$ are determined via a grid search procedure (see Neslin 2001 and Rizzo 1999 for similar applications). We obtained the following carryover parameters for (23.2), (23.3), and (23.4): 84, 0, and 55 % for detailing, OME and combined DTCA, respectively. Even though we allowed for the two countries to have different carryover parameters, the above values gave the best results. For our estimation, we fixed the carryover rates at these values.

Our interest here is to explore whether DTCA spillover exists. It is possible, however, that other types of (unobserved) spillovers may also be present; or, some common demand shocks—such as due to the release of a new scientific study on drug efficacy—may be present. Consequently, the error terms in the category demand functions for the USA and Canada (given in (23.1)) may be related. Therefore, we use the seemingly unrelated regression estimation (SURE) procedure. We also obtained estimates from the OLS procedure. The SURE and OLS results did not differ significantly.[7]

[7]One potential concern is the endogeneity of marketing instruments, especially that of DTCA (see e.g., Kremer et al. 2008).

Table 23.2 Descriptive statistics on monthly time series variables

	US					Canada				
Variable	*N*	Minimum	Maximum	Mean	Std. dev.	*N*	Minimum	Maximum	Mean	Std. dev.
Rx scripts (number)	66	1,670,000.00	3,359,000.00	2,426,909.09	387,575.49	66	161,131.00	303,138.00	230,001.50	34,142.22
Share-weighted price ($)	66	31.12	40.97	37.89	1.47	66	17.77	21.34	19.46	0.99
Detailing expend ($)	66	5,102,000	14,283,000	8,736,000	2,265,000	66	77,000	1,064,200	590,800	284,300
OME expend ($)	66	236,700	4,198,600	1,960,600	1,099,900	66	0.00	168,120	58,180	38,970
TV DTCA expend ($)	66	0.00	19,703,000	4,745,000	4,757,000					
Mags DTCA expend ($)	66	0.00	4,689,000	1,646,800	1,446,200					

Note: Information about price, detailing, OME, and DTCA have been adjusted for inflation (with 1992 as the base year) and are reported in US$ for both countries. The reported analysis combines the TV and magazine DTCA expenditures

Table 23.3 Regression results

	Dependent variable	
	USA	Canada
	Log(category Rx total)	Log(category Rx totals)
Independent variable	Model 1	Model 2
Intercept	14.259214***	12.070408***
Quarterly sales dummy 1 (SD1)	0.045223**	0.045618*
Quarterly sales dummy 2 (SD2)	–0.108323***	–0.018122
Quarterly sales dummy 3 (SD3)	–0.085629***	–0.047146*
Share-weighted country-specific price	–0.001767	–0.003712
Goodwill from country-specific detailing	0.000017***	0.000054***
Goodwill from country-specific OME	0.000058**	–0.000089
Goodwill from combined US DTCA (TV + magazines)	0.000034***	0.000029***
R-square	0.9040	0.8520
N	66	66

*$p<0.10$; **$p<0.05$; ***$p<0.01$

23.3.3 Results and Discussion

We begin with the results for the parameters of the category demand function. Subsequently, short-run and long-run elasticities for detailing and DTCA, and single- and multi-period return-on-investment (ROI) measures for detailing and DTCA are discussed, in that order.

23.3.3.1 Parameters of the Category Level Demand

Table 23.3 shows the SURE parameter estimates for the category sales models (we estimate (23.1) for each of the countries). We refer to the US results as Model 1 and the corresponding results for Canada as Model 2. The models fit the data well, as judged by the high R^2 values. We find that after controlling for the seasonal effects, the goodwill measures associated with detailing and DTCA have statistically significant coefficients and the correct (positive) sign for both countries.

The significant DTCA terms in the Canada regression (Model 2) showcases the spillover effect. Price is not statistically significant, but has the correct (negative) sign. OME has the right sign and is statistically significant in the USA. However, it does not have a statistically significant effect in Canada. At least two of the three seasonal dummies have significant effects, reflecting seasonality in the category.

23.3.3.2 Short-Run and Long-Run Elasticities

We report the short and long-run elasticities for DTCA and detailing in Table 23.4 (the long-run elasticity is computed as in previous studies; see e.g., Narayanan et al. 2004).

Table 23.4 Short-run and long-run elasticities for detailing and combined direct-to-consumer advertising (DTCA)

Expenditure	Period	USA	Canada
Detailing	Short-run	0.0251	0.0208
	Long-run	0.1570	0.1297
OME	Short-run	0.0406	–
DTCA	Short-run	0.0430	0.0367
	Long-run	0.0955	0.0815

Note: Here and in the rest of the tables, OME has no long-run results since its carryover is zero

Begin by noting that the detailing elasticity is higher in the USA than in Canada. One underlying reason is that the elasticity estimate depends on the regression coefficient as well as the spending level. Therefore, while Canada has a higher regression coefficient (compared to the USA), it can be seen from the descriptive statistics that the level of spending is considerably lower (than in the USA).

Next, we find that long-run elasticities are larger than the corresponding short-run elasticities. This is consistent with the positive carryover effects of the corresponding marketing activities. Essentially, the larger is the carryover coefficient, the larger will be the long-run elasticity (compared to the short-run estimate). This feature explains why the long-run elasticity of detailing (with a carryover coefficient of 84 %) is roughly 6 times the short-run elasticity, while the corresponding DTCA (with a carryover coefficient of 55 %) long-run elasticity is only around twice the short-run elasticity.

Finally, and most interestingly, we note that the DTCA elasticities are fairly similar across the two countries.[8] This suggests that spillover has the potential for significantly enhancing US pharmaceutical firms' revenues. We must note, however, that ROI estimate for each of the two countries will depend on the corresponding revenue base in that country. Therefore, it is possible that ROIs may differ for the two countries; these are reported below.

23.3.3.3 Return-on-Investment Measures

Our interest here centers on the marginal revenue product for each marketing investment at the category level. Using brand-level data, Neslin (2001) observed that up to one-half of the ultimate ROI from a marketing investment occurs within the first

[8]It is worth noting that our advertising elasticity estimates discussed here are consistent with the advertising elasticities reported in Sethuraman et al. (2011): the average short-term elasticity (over 751 elasticities from 56 studies published between 1960 and 2008) is 0.12; the mean long-term elasticity is 0.24.

Table 23.5 ROI for detailing and combined DTCA (i.e., TV DTCA + Magazine DTCA)

For every marginal $ spent on	Period	Additional revenue of ($)		
		USA only	Canada only	USA + Canada
Detailing	Current-period	0.2881	0.1784	No spillover
	Multi-period (current + future periods)	1.5847	0.9825	
OME	Current-period	2.0750	–	No spillover
DTCA	Current-period	0.6737	0.0291	0.7028
	Multi-period	1.4925	0.0647	1.5572

month of expenditure, and that it may take at least a year for most of this impact to be realized (see also Mizik and Jacobson 2004). In that spirit, we focus below on both the short-term (i.e., current-period) ROI and the long-term (multi-period) ROI.

Short-term or current-period ROI. Suppose X is one such investment in the USA; then due to spillovers, a measure of the short-term return on investment (ROI) in period t is:

$$\mathrm{ROI}_t^X = \left(P_{\mathrm{USA},t} \frac{\delta S_{\mathrm{USA},t}}{\delta G_{\mathrm{USA},t}} \frac{\delta G_{\mathrm{USA},t}}{\delta X_{\mathrm{USA},t}} \right) + \left(P_{\mathrm{Canada},t} \frac{\delta S_{\mathrm{Canada},t}}{\delta G_{\mathrm{Canada},t}} \frac{\delta G_{\mathrm{Canada},t}}{\delta X_{\mathrm{Canada},t}} \right) \tag{23.5}$$

where G is the goodwill associated with X. For detailing and OME, the spillover term in (23.1) is eliminated. These results appear in Table 23.5.

Short-term ROIs for US detailing are smaller than short-term ROIs for US DTCA; though, the US estimates are larger than the corresponding Canadian detailing ROI. Next, turning to the impact of spillover on ROI, we note that it accounts for about 4 % of total US ROI. Current-period ROIs, however, ignore the fact that the effects of marketing investments last more than one period. When a firm raises its promotional expenditure by a dollar, that dollar affects not only the goodwill for the current period but also the goodwill in future periods. Indeed, in our specification, there is a carryover of 84 and 55 % for detailing and DTCA, respectively. Due to this inter-temporal linkage, we now turn to the multi-period ROI.

Long-term or multi-period ROI. Here, for a given set of values of all the independent variables, we compute the expected-value of the dependent variables (shares, category sales, and consequently, revenues). Then, we raise a given promotional expenditure for a single focal period by a dollar and compute the new revenues in the current and subsequent periods. We repeat this procedure and report the multi-period ROI as the change in the sum of revenues for the current and 11 subsequent periods for every additional dollar spent on that promotional activity in the current period. That is, multi-period ROI represents the change in revenues for a year from the period when the promotional activity is changed.

These long-term ROIs are also reported in Table 23.5 for both detailing and DTCA. Note that these long-term ROIs are significantly higher than the corresponding current-period ROIs. And, the DTCA spillover effect into Canada contributes around 4–6 % to the US long-term DTCA ROI.[9]

Finally, it is interesting that even though DTCA elasticities are comparable, the difference in the DTCA ROIs from the two countries is fairly large. First, this may be explained by noting (e.g., in Table 23.2) that the average number of prescriptions in Canada is significantly smaller than in the USA. In other words, the revenue base is considerably smaller in Canada than in the USA. Consequently, it is not surprising that the ROIs vary significantly across the two countries. With a higher revenue base, Canadian ROIs would have been larger. Therefore, spillover has the potential to make a significant impact on revenues. Pharmaceutical companies should find such observations useful.[10]

23.4 Research Gaps

Begin by recalling our discussion from Sect. 23.2 about the under-investment problem due to spillovers. It is noteworthy that both R&D and co-marketing alliances can be observed widely in the pharmaceutical industry; e.g., Teva and P&G have recently announced an alliance—combining P&G's marketing abilities with Teva's global footprint and expertise in drug manufacturing—to target key OTC markets such as those in Germany, Russia, and Brazil. In a similar vein, The Wall Street Journal (2011) reports that according to the Elsevier's Strategic Transaction Database, the pharmaceutical industry has witnessed roughly 780 alliances from 2007 to 2011! So, while the broad considerations outlined earlier regarding externalities in R&D and co-marketing alliances will apply here, there seems to be room to fine tune our understanding.

[9]Previous research has computed *brand*-level ROI measures. Neslin (2001) examined pharmaceutical brands with at least $25 million in annual revenues (a total of 391 brands and 127 generics were analyzed over the 1995–1999 period). His study reports median brand ROI estimates for detailing and DTCA at $1.72 and $0.19 respectively with DTCA ROI as high as $1.37 for recently launched brands with high revenues. Wittink (2002) reports the following estimates for brands with annual revenues between $100 and $500 million in 1998–2000: detailing ROI in the $1.8–2.6 range (average is $2.1), and DTCA ROI in the $0.1–0.4 range (average $0.1). More analyses by specific therapeutic classes revealed differences across classes in the range of Detailing ROI estimates ($2.8–3.3 for hypertension; $1.7–2.2 for arthritis; $1.2–1.8 for asthma) but no differences emerge for DTCA ROI (the range is $0.0–0.2 for all three classes).

[10]From a resource allocation perspective, e.g., Mantrala et al. (1992) show that improvements in sales and profits are more sensitive to improvements in resource *allocation* rules rather than just increases in investment levels.

For instance, the pharmaceutical industry has been a leader (across a wide-variety of industry groups) in terms of investments in R&D as a percentage of sales; so, under what circumstances is there likely to be an under-investment problem in this industry? In that sense, replicating the empirical/theoretical findings from non-pharmaceutical contexts seems valuable. In particular, given the structure of the NME approval process, spillovers may be more of a problem in some settings than in others.

A related issue is that richer countries can afford higher market prices for new drugs, and allow companies to recoup their R&D investments. By contrast, poorer countries exhibit a lower willingness to pay and limit the return on investment. In practice, new drugs are introduced in both types of countries (usually with a delay; see e.g., Desiraju et al. 2004b). However, parallel trade can diminish the drug firms' ability to price discriminate among countries (Danzon and Keuffel 2007). Further, empirical research has shown—see Narayanan et al. (2004)—that DTCA by competing firms raises consumer awareness and expands category demand, while detailing affects market shares; by contrast Fischer and Albers (2010) find across a wide variety of categories that DTCA and detailing have quite the opposite effects. It will help to understand the extent to which competing firms may take into account such externalities in category demand in determining equilibrium investments in DTCA and detailing.

In order to extend the revenue stream from approved NMEs, drug companies often explore alternative indications that may be treated by each NME. We highlight a potentially important spillover in that context (that is worthy of research attention) via three examples:

1. In October 2010, Botox (manufactured by Allergan Inc.) received approval for chronic migraine. However, for sales to ramp up, Allergan needs a sufficiently large group of physicians that are trained to use the product and believe that it will benefit their patients. In other words, physicians' perception of Botox (from its earlier approval) will likely play an important role in affecting their response to the newer detailing efforts. Although the company has a large proportion of its sales staff dedicated to this end, Botox for headache probably will not have enough momentum in the short-run.
2. Next, Bristol-Myers Squibb's Abilify (anticipated sales of $2.9 billion) is indicated for Schizophrenia in adults; but it can also be used in the treatment for Bipolar Disorder (Manic or Mixed), and helps as an add-on for treating depression. However, if word were to spread about the side-effects from Abilify when used to treat one of the indications (e.g., see Andy Behrman's video on You Tube), then there can be an unintended spillover onto the use of Abilify for the other indications.
3. Similar is the point with respect to Revlimid (from Celgene Corporation); this drug's approved indication (by the FDA) is relapsed or refractory myeloma. It is also being considered for maintenance therapy after chemo; however, the results from a drug trial in France observed heightened reoccurrences in patients who received a maintenance level dosage of Revlimid. These results can have ramifications for Revlimid inasmuch as, e.g., how physicians (and educated patients)

react to them. Assessing the impact from such spillovers can be instructive to drug companies in evaluating the strategy (cf. the analysis of scandals in Roehm and Tybout 2006).

Another possible externality is linked to the dyadic decision making (see Ding and Eliashberg 2008) feature of pharmaceuticals.[11] Drug use by other patients conveys information about a given drug's efficacy and safety to either the physician or/and the patient, and can lead to herd behavior. In such a setting, a particular drug—which is not necessarily the most efficacious or safest for that matter while meeting FDA approval guidelines—can reach a dominant position in the market, at least in the short-run, despite the availability of substitutes (see e.g., Berndt et al. 2003). In other words, aggregate usage affects brand evaluation and can impact, e.g., the drug's rate of penetration in the market.

Next consider an unintended consequence from US government regulation that Scherer (2000) describes in some detail: By the early 1990s, HMOs and PBMs became significant players in the industry, and started establishing lists of drugs (aka formularies) that are suitable to treat a given illness. Once physicians began to comply with the formulary guidelines (i.e., physicians were now "forced" to consider the patient's insurance and the associated formulary prior to selecting the appropriate drug to prescribe), the HMOs and PBMs had a bargaining chip to negotiate with the drug manufacturers. In other words, drug companies that sold substitutable products (that were still under patent protection) were played off against each other by the HMOs and PBMs to obtain significant price discounts—varying from 20 % to more than 50 %—to include those drugs in the formularies.

At about the same time as the above events were unfolding, the US government passed laws that required drug manufacturers to give the governmental agencies (that were reimbursing prescription drug purchases of patients covered by Medicaid) price discounts equal to the higher of either 15.1 % or the best deal offered to any nongovernmental buyer of any prescription medication. So, the manufacturers faced with the deep-discount demands of the HMOs and/or PBMs realized that such discounts will have to be extended to the government organizations as well; since Medicaid purchases constituted a significant portion of the manufacturer's revenue, these discounts would end up being too costly. Consequently, Scherer (2000) and the studies cited therein note that there have been substantial reductions in the discounts offered by the manufacturers. More recent studies of this phenomenon can be useful in establishing the spillover effect of government regulation (see Verniers et al. 2011 for a valuable effort in that direction).

The presence of spillover from a given marketing action has the potential to affect the response from other marketing actions; for instance, suppose that DTCA and effort from the pharmaceutical sales force (aka detailing) has a synergistic effect. Recalling the analysis from Sect. 23.3, we note that the market response from

[11] The dyadic decision making aspect can moderate the effects of all of the spillovers being discussed here.

detailing in Canada can be higher in the presence of spillover. Consequently, managers who are carving out distinct territories for different sales reps, or setting quotas, will benefit by accounting for spillover.

Such analysis can have implications, for instance, to the costs from re-importing pharmaceutical drugs into the USA. Essentially, US drug manufacturers argue that reimportation of their drugs into the US market cuts into their profitability (see Senate Bill S319, introduced in 2011 for more details on alternative perspectives on reimportation). However, if spillover effects are generating a positive ROI (that has been hereto unaccounted), then the net cost from reimportation may be attenuated to some degree. In any case, these types of analyses underscore the importance of addressing the cross-border issues more completely.

Our goal in this chapter has been to highlight the importance of accounting for spillover effects of marketing activities in the pharmaceutical industry. It is noteworthy that extant research has examined a variety of market settings and has employed both analytical and econometric approaches, as well as experiments to examine the impact of spillovers and externalities. We hope our discussion here will spark further research on this important topic.

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Chapter 24
Closing the Marketing Strategy-Tactics Gap: An Institutional Theory Analysis of Pharmaceutical Value Chain

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Abstract This chapter identifies a strategy-tactics gap in most previous studies of pharmaceutical marketing, and addresses it by systematically analyzing the marketing strategies used in practice with the help of a unique dataset of court discovery documents unsealed in a recent litigation. Adopting an institutional theory perspective, we examine the dominant logic that underlies pharmaceutical marketing strategies, and contrast it with the organizing logics of the value chain partners. Four distinct marketing strategies with carefully crafted interdependencies emerge from our analysis: (1) market penetration strategy involving a focus on segmentation and penetration, (2) evidence-based strategy involving production of science, (3) medical education strategy involving development and dissemination of standards of care, and (4) surrogate selling strategy involving leverage of peer-to-peer influence among target physicians. Together, the strategies uncovered in our analysis provide coherence to the observed marketing tactics and show that they are largely consistent with the logic of consequences which conflicts with the logic of appropriateness guiding the actions of the value chain partners. The institutional theory analysis shows that: (1) pharmaceutical value chain is characterized by conflicted logics, (2) that are amplified by pharmaceutical marketing strategies thereby, (3) inviting regulatory intervention to constrain and restrict pharmaceutical marketing efforts. We propose an open systems framework that elaborates on value chain interdependencies and compare it with the economic framework that characterizes most current research. We close the chapter with an agenda for future research into the theory and practice of pharmaceutical marketing.

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24.1 Introduction

Scholarly research in pharmaceutical marketing has disproportionately focused on the *tactical* issues of optimizing the ROI of pharmaceutical promotion spend,[1] paying scarce attention to the marketing *strategies* that underlie these tactics. In an integrative review of the literature, Manchanda and Chintagunta (2004, p. 143) articulate marketing literature's emphasis well by observing that much research aims to identify "ways in which these [pharmaceutical] firms can increase the amount of prescriptions (i.e., increase revenues) or reduce the number of salesperson calls (i.e., lower costs) via a more efficient allocation of [promotion] effort." Enhancing the effectiveness and efficiency of pharmaceutical promotion tactics is the dominant theme in a diverse and rich body of marketing literature (Venkataraman and Stremersch 2007; Manchanda and Chintagunta 2004; Narayanan et al. 2004; Mizik and Jacobson 2004; Oliver and Van Horn 2004; Wittink 2002; Gönül et al. 2001). By contrast, studies of the nature and scope of pharmaceutical marketing strategies are negligible. Strategy is a firm's organizing scheme for competitive advantage and provides coherence to a firm's diverse tactical choices. Moreover, strategy operationalizes the dominant logic of the firm's management for achieving its goals and objectives by blueprinting the underlying logic that gives meaning to organizational action (why are we doing this? why are we doing this way, and not some other way?) (Prahalad and Bettis 1986; Porac et al. 1989). In the integrative review cited above, mention, much less consideration, of strategy is largely absent while the diverse perspectives and findings related to detailing tactics and practices are thoroughly reviewed (Manchanda and Honka 2005). Without consideration of strategy, a tactical focus is as myopic as studying action without cognition, and analyzing *what* and *how* without understanding *why*.

Curiously, inattention to pharmaceutical marketing strategy and the resultant strategy-tactics gap has persisted despite surprisingly vigorous, and often unflattering, analysis of pharmaceutical marketing strategies among medical practitioners and public alike (DeAngelis 2006; Angell 2005; Brennan and Mello 2007; Heuvel 2007). For instance, medical scholars express uneasiness at the "[pharmaceutical industry's] sophisticated and wide-reaching marketing *strategies*," (Moncrieff et al. 2005, p. 84), and their ire appears focused on the "marketing *strategies* masquerading as evidence-based medicine," (Eichacker et al. 2006, p. 1642). Concerned that "physicians have been the central target of marketing *strategies*" (Studdert et al. 2004, p. 1891), several studies find this trend "at best very troubling" (Steinbrook

[1]The promotion spend by the pharmaceutical industry in the United States is estimated to be between $27.7 and 57.5 billion (Gagnon and Lexchin 2008). Pharmaceutical promotion practices include detailing (where salespeople visit with physicians to update them on recent therapeutic advances and encourage them to write prescriptions that favor the firm's products), sampling (where samples of company's drugs are provided to encourage trial) and physician meetings (where educational meetings are convened to show efficacy evidence of company's drugs) among other related practices.

2008, p. 1062) and propose a "firewall between marketing and science" (Antonuccio et al. 2003, p. 1028). Several books by medical practitioners claiming to unveil industry strategies paint a dark picture of an industry focused on maximizing profits at any cost (Petersen 2003; Angell 2005; Murray 2010). Swayed by this publicity, the pharmaceutical industry has seen its public standing fall from a 50 % (1998) to less than 12 % (2010) favorable rating in a *Harris survey of public trust*,[2] with 46 % favoring more governmental regulation, and its index of drug stocks decline by 25 % over the last 5 years (Collis and Smith 2007). Angelmar (2005, p. 1) summarizes this trend by noting that the pharmaceutical industry's "business model has come undone."

Given such aversive response, the strategy-tactics gap in the pharmaceutical marketing literature is inexplicable.[3] Lack of systematic studies of pharmaceutical marketing strategies lends an impression of uncontested validity to the mostly hostile studies reported in the medical literature. Thus, the strategy-tactics gap warrants attention from researchers interested in pharmaceutical marketing. In particular, two questions are germane to our study:

1. What specific marketing strategies do pharmaceutical companies use to engage medical practitioners, and how do these strategies relate to particular tactics?
2. Under what conditions and why do pharmaceutical marketing strategies amplify (or diminish) the aversive (approving) response from its value chain partners?

This chapter aims to address the preceding questions by making three contributions. First, we aim to conduct a systematic analysis of a pharmaceutical company's marketing strategies and relating them to specific tactics deployed to engage medical practitioners. Our theoretical lens is institutional theory which is well suited for examining the organizing logics that underlie strategy (Oliver 1991; DiMaggio and Powell 1983; Scott 1987). Our premise is that understanding value chain implications of organizational strategy requires an explicit consideration of legitimacy, not just profitability, outcomes. No previous study has utilized institutional theory to examine pharmaceutical marketing strategies or its value chain implications (see, however, Singh and Jayanti 2013).

Second, this chapter empirically examines the dynamics of value chain's response to pharmaceutical marketing strategies using the concept of institutional logics. The institutional view conceives "logics" as socially constructed mental models that groups of individuals hold as shared cognitions of socialized routines for action that

[2]The *Harris Interactive* survey is a longitudinal study of public trust across a range of industries and asks the following question, "Do you think each of the following does a good or bad job of serving its customers?" The results reported here are from a report in the *Economist* titled, "Prescription for Change," published June 16, 2005.

[3]To some extent, this neglect is indicative of lack of access to data on pharmaceutical strategy making, much of which is proprietary. By contrast, data on promotion spend has been made relatively accessible by research agencies such as IMS, Wolters Kluver and Verispan.

are "essential" to facilitate communication, order interactions, and promote learning among market actors (Denzau and North 1994, pp. 4–5; March and Olsen 1998; Scott 2001). In this sense, logics provide mental maps for constructing market action (e.g., strategies) and interpreting it (e.g., by physicians), as well as guide subsequent response (e.g., physicians' response toward pharmaceutical marketing). Specifically, our conceptualization develops three interrelated ideas: (1) pharmaceutical marketing strategies are rooted largely in the *logics of consequences*, (2) physicians' interactions with their patients are rooted largely in the *logics of appropriateness*, and (3) a value chain with members rooted in disparate logics of consequences and appropriateness is inherently conflicted. Building on this conceptualization, we examine the ebbs and flows of the conflicted logics in the pharmaceutical value chain.

Third, using the empirical analyses as a foundation, we outline a conceptual framework grounded in an open systems view for future research on pharmaceutical marketing strategies. Our framework emphasizes an embedded analysis of pharmaceutical marketing, where studies of pharmaceutical marketing are incomplete and likely misleading without consideration of value chain dynamics. Specifically, we weave our framework around three key assertions: (1) systems (e.g., value chains) with disparate logics are prone to entropy due to inherent conflicts in their dominant logics, (2) managerial action focused on internal logics enhances value chain conflict and results in counterintuitive effects, and (3) a focus on organizational legitimacy can seed coordinated exchanges among value chain partners to potentially overcome system conflict. We show that our theorizing can explain current trends that are particularly averse to pharmaceutical marketing despite increasing knowledge of its efficiency and effectiveness. We close by outlining an agenda for future research on pharmaceutical marketing.

24.2 An Institutional Theory Analysis of Pharmaceutical Value Chain

The institutional perspective provides an embedded view of market exchanges where regulatory institutions, public and private firms, and consumers are linked through market interactions (Oliver 1991; Dimaggio and Powell 1983; Scott 1987). Generally viewed as one of the leading perspectives for analysis of market action and evolution, institutional theory gives privileged status to the notion of logics and the institutions that create, maintain, and disrupt them (Heugens and Lander 2009; Lawrence and Suddaby 2006; DiMaggio and Powell 1991; Grewal and Dharwadkar 2002; McFarland et al. 2008). Neo-institutional scholars construe logics as socially constructed mental models that market actors hold as shared cognitions for socialized routines of action. For instance, Scott (2001, p. 57) defines logics as collective "frames" and navigational guides for market decision making (Caronna 2004).

Collective frames for corporate decision making are conceptualized as a "dominant logic" in the strategy literature (Prahalad and Bettis 1986; Porac et al.

1989; Lampel and Shamsie 2000). Prahalad and Bettis (1986, p. 490) define dominant logic as "the way in which managers conceptualize the business and make critical resource allocation decisions." From an institutional lens, dominant logic provides a mental model of a common set of assumptions and beliefs about organizational purpose and goals that guide managerial decision making and strategic choices. Thus, pharmaceutical marketing strategies are located at the intersection of strategy and institutional theory literatures within the dominant logic framework of shared cognitions that underpin strategic choices by pharmaceutical managers.

We develop the dominant logic at this intersection for pharmaceutical marketing strategy next. Thereafter, we take this theorizing forward by conceptualizing the dominant logic underlying physician–patient exchanges. In the final section, we join these developments to highlight the conflicted action implications of disparate logics in the pharmaceutical value chain.

24.2.1 Pharmaceutical Marketing Strategy and Logics of Consequences

The dominant logic of pharmaceutical marketing conforms to the institutional theory conception of the logic of consequences (March 1996; March and Olsen 1998), which asserts that an orderly and stable system of market relationships arises as a result of exchanges among market actors pursuing self-interested gains. The logic of consequences is reminiscent of Adam Smith's merchant logic, manifested through assumptions of market mechanisms and goal of maximizing ROI. Heide and Wathne (2006) note that the logic of consequences is common to several theories of inter-firm relationships including transaction cost, agency, and game theories. For instance, in a supply chain, self-interested manufacturers and distributors may coordinate their actions and trust each other because the long term payoffs from coordination and restrained opportunism exceed short term benefits from unilateral opportunism (Barney and Hansen 1994).

Past research provides evidence supporting the foundation of pharmaceutical marketing on the bedrock of the logic of consequences. In their review, Manchanda and Honka (2005) note that much pharmaceutical marketing effort is directed at physicians and consumers with the goal of facilitating market exchanges that optimize the company's return on marketing investments (Narayanan et al. 2004; Ahearne et al. 1999). Consider, for example, physician detailing, a wide spread practice of using sales representatives to reach physicians. Detailing efforts are guided by a consequential logic to deploy selling skills to slant physicians' preferences and "utility functions" in favor of the company's products (Narayanan et al. 2005). Consistent with this, research examines whether the amount of detailing is "optimal" from a ROI perspective (Narayanan et al. 2004). Manchanda and Honka (2005, p. 785) note that it is an "important" goal of research to "establish that detailing [has] significant effect on physician prescription behavior" and to "improve the efficiency and effectiveness of detailing practices."

The logic of consequences is also evident in other pharmaceutical marketing practices. For instance, direct-to-consumer marketing is intended to enhance awareness and provide information about product benefits to indirectly stimulate demand by provoking consumers to consult their physicians for prescriptions. Although pharmaceutical companies assert the importance of patient welfare and product information, they openly acknowledge their motive to maximize return on shareholder investments. It is well known that return on investments of pharmaceutical companies (estimated at 15 %) have consistently exceeded normal market returns (Fagan and Hayes 1998).

However, absent systematic studies of pharmaceutical marketing strategy, it is premature to unequivocally assert the logic of consequences as its underlying dominant logic. Unfortunately, such studies pose nontrivial challenges because significant aspects of strategy practice are "invisible" as they are either proprietary or hold competitive advantage only if they remain obscure. As a result, most commercially available data on pharmaceutical marketing practices (e.g., IMS, Verispan/Scott-Levin) include instruments that illuminate only those aspects of the strategic practice that the organizations wish to make "visible." Nevertheless, we believe that it is critical to call for studies that shed light on the heretofore "invisible" practice of pharmaceutical marketing strategy to understand its dominant logic and address the strategy-tactic gap.

24.2.2 Physician–Patient Exchanges and Logic of Appropriateness

The logic of appropriateness provides a theoretical foundation for conceptualizing physician–patient exchanges that are governed by institutionalized norms of fiduciary responsibility and rule driven cooperative behaviors even when such behaviors may undermine individual pay-offs (March 1996). Patients rely on the professional expertise of physicians to obtain prescription regimens that help cure diseases and enhance well-being. From an economics perspective, such professional-mediated exchanges are problematic because of "hidden information"—not knowing how to distinguish credible professionals, and "hidden action"—not knowing whether the professional, once engaged, will shirk from acting to safeguard patient interest, among other agency problems (Arrow 1985).

Sociological studies of the medical profession in particular, and professionals in general (e.g., lawyers, auditors), show that institutionalizing the logics of appropriateness is a mechanism for solving the agency problems (Parsons 1968; Starr 1982; Freidson 2001). Shapiro (1987, 2005) formalizes these arguments by positing that professionals may be viewed as "agents" who are bound by fiduciary responsibility to serve the interests of "principals" (e.g., patients) such that there is an expectation that the agent will put the principal's interests above self-interest (Boatright 1992). Actors resolve choice dilemmas by following a set of prescribed rules paying less attention to the personal gains from their decisions (March and Olsen 1998).

Grayson et al. (2008) note that in some industries (e.g., banking), professional organizations codify expectations for members' actions that foster a "climate of trust" to draw and reassure customers. Such rules are not instrumental, but essential to the evoked role identity. A banker is rule-bound to limit exposure of consumer deposits to risky investments, even though such practice may enhance payoffs, because doing so without consumer consent violates the norms of a "trusted banker" who upholds consumers' best interests *no matter what*. Here, the principle of trust is essential to the identity of the banker; without trust one cannot claim to be a credible banker. Recent Wall Street excesses that precipitated the worst financial crisis that eroded the financial industry's legitimacy reaffirm the role of trust in fiduciary relationships.

Institutionalized norms of fiduciary responsibility commit professionals to follow codes of conduct or an oath of service (e.g., the Hippocratic Oath) that build trust and curb opportunism. Consequently, an effective and stable system of market relationships, here involving physicians and patients, emerges when market agents (i.e., physicians) behave in accord with institutionalized norms of fiduciary responsibility that are "socially constructed, publicly known, anticipated, and accepted" (March and Olsen 1998, p. 952).

24.2.3 Conflicted Logics in a Pharmaceutical Value Chain

Our preceding analysis suggests that different market actors (i.e., pharmaceutical companies and physicians) in a pharmaceutical value chain are embedded in their own distinct logic. Collectively, industry–physician and physician–patient exchanges coexist as an interdependent market system. Viewing the logics of consequences and appropriateness as coexistent requires theorizing their potential conflict and its consequences for the value chain (March and Olsen 1998). This potential for inherent conflict is centered on physicians who are engaged in consequential logic-based exchanges with the pharmaceutical industry on one side of the value chain, and in appropriateness logic-based relationships with patients on the other side.

Coexistent logics need not *necessarily* lead to conflicted logics. Many physicians' actions that are guided by consequential logic, such as the pursuit of a reputation for conducting controversial and influential studies, earning a decent income, and quality of life commensurate with their status, need not compromise physicians' fiduciary responsibility in patient relationships. Likewise, while it may be commonly understood that detail salespeople work for pharmaceutical organizations that primarily follow a consequential logic, they are not necessarily restrained from acting as a trustworthy source of unbiased information. Only when actions implied by a particular logic directly or indirectly constrain or suppress possible actions that are implied by the second logic does a problem of conflicted logics exist (Carson 2004).

The institutionalized frame of professionalized medicine holds that its members give priority to fiduciary responsibility and forgo self-interested gains. In other words, professions address conflict of logics problems by legislating norms that mandate the priority of the logic of appropriateness (e.g., American Medical Association's *Ethics Opinion* at http://www.ama-assn.org/ama/pub/

physician-resources/medical-ethics/code-medical-ethics.page, and U.K. Medical Council's *Good Medical Practice* at http://www.gmc-uk.org/guidance/good_medical_practice.asp). Thus, pharmaceutical marketing efforts directed at building close relationships with physicians may amplify the problem of conflicted logics. Moore et al. (2006, p. 11) note that "doctors are loath to admit" that conflict of logics "slant" their professional judgments even as they are "succumbing" to them and "*believe* that their biased advice is unbiased."

Insights are needed to map how the conflicted logics of the pharmaceutical value chain unfold over time, and what factors amplify or diminish the underlying conflict. Although the logics of pharmaceutical marketing and physician practice are *theoretically* conflicted, in *practice* the logics may coexist without posing impediments to collaborative relationships in the value chain. For instance, the pharmaceutical industry may pursue its consequential goals indirectly or passively while directly or actively focusing on value creation by emphasizing its products and therapies that serve appropriateness goals of the value chain. The nature and degree of conflict in practice will vary by pharmaceutical industry's choices of strategy content, and the dynamics they engender. Thus, we conduct a systematic and comprehensive examination of pharmaceutical promotion practices and thereafter intersect the findings with the discourse in academic medicine to examine the nature and degree of conflict between the logics and its evolution over time.

24.3 Study Data and Analytical Approach

A particularly useful source for unadulterated view of the industry's strategies is publicly available court documents generated as part of discovery in a litigation involving industry marketing practices. The laws governing public access to court records provide detailed, authenticated, and otherwise proprietary data for review and analysis. Court records include internal memos, contractual arrangements, internal/consultant reports, strategy and tactics, financial/accounting analyses, and other related materials that are "discovered" during the process of case filing and research. Discovery materials do *not* inherently indicate illegal practices. Many materials represent business as usual, and are used to provide the background for developing the court's arguments and evidence.

A careful, comprehensive, and thorough analysis of these discovery documents can provide a unique insight into industry practices that are neither illegal nor unconventional and are otherwise not available for public scrutiny. Moreover, triangulating these insights with those available from the professional medicine and popular press literature is likely to bolster the confidence in the obtained insights and mitigate the risk that stems from analyzing a single case that may be idiosyncratic or atypical. Recent research has increasingly used court documents to obtain insights into pharmaceutical marketing (Ross et al. 2008; Psaty and Kronmal 2008; Healy and Cattell 2003). Nevertheless, court cases are subject to biases of small (e.g., $N=1$) and unrepresentative samples, and caution is warranted in generalizing from such analyses.

We analyzed over 5,827 pages of discovery documents from a recent court case that involved marketing practices related to Neurontin® (gabapentin). Details of the case, *United States of America ex. rel David Franklin vs. Pfizer Inc, and Parke-Davis, Division of Warner-Lambert Company* (Steinman et al. 2006) settled on May 13, 2004, and our analytical procedures are in the Appendix. In order to keep the discussion focused, we elaborate on the nature and scope of strategies revealed in our analysis, and the underlying logics reflected in these strategies. We supplement our analysis with reviews of professional medicine and popular press literature. To the extent professional medicine and popular press are voices of the industry's downstream value-chain members, this supplementary review is of material significance in understanding conflicted logics of pharmaceutical value chain.

24.4 Results

Our data analysis revealed (a) four distinct strategies used by the pharmaceutical company to communicate with physicians, and (b) systematic interdependencies among the four strategies that we categorize as either expertise- or promotion-based for the discussion that follows. Figure 24.1 displays the strategies and their interdependencies. Table 24.1 summarizes each of the four strategies providing links to relevant

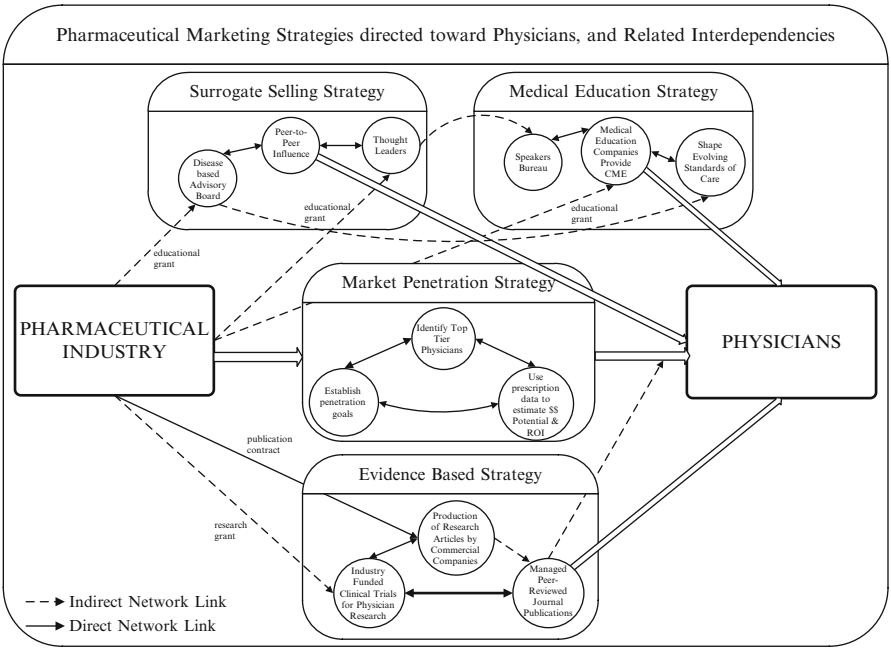

Fig. 24.1 Pharmaceutical marketing strategies and their interdependencies as extracted from court documents

Table 24.1 The logic of consequences and pharmaceutical marketing practices

Strategy (%budget)	Marketing tactics	External validity
Market penetration strategy (6.6%)	Target centers of influence based on (1) availability of neurology, geriatric, psychiatric, cardiology and internal medicine programs, (2) number of residencies and fellowships, and (3) out patient visit volume (Exhibit 34, phase 1)	Neurometrix instituted a "customer referral program" in which physicians receive credits for steering other doctors to Neurometrix (Abelson 2006)
Marketing objectives Increase the accessibility of the Parke-Davis portfolio to all major teaching institutions		
An epilepsy and pain educational program that is targeted at (1) neurology specialists including general neurologists and neurosurgeons, and (2) primary care physicians whose practice includes a significant number of patients with epilepsy or chronic pain (Exhibit 51)	PPS (Professional Postgraduate Services) developed a Home Study Program (HSP) supervised by Parke-Davis representatives to be distributed to about 10,000 target physicians in April 1996 (Exhibit 51)	Urorad Health care aggressively targets urologists for marketing IMRT (intensely modulated radiation therapy), a procedure for radiation therapy in patients with prostate cancer (Saul 2006)
Evidence-based strategy (53.6%)	Clinical trial program to financially support research studies and publish them sequentially in reputable journals to promote a "life cycle planning" of Neurontin® market performance (Exhibits 72 and 57)	Sleeping pill manufacturers orchestrated publications to undermine a competing generic drug—Trazodone—which is considerably cheaper than manufacturer branded drugs such as Lunesta and Ambien (Carlat 2006)
Marketing objectives "Execute publications, educational activities, and promotional plan to expand Neurontin® monotherapy usage"		
To seed the idea in physicians' minds that Neurontin® can and should be used earlier in the treatment armamentarium." (verbatim from 1998 Situation Analysis Report; Exhibit 57)	"MES (Medical Education Systems, Inc.) will Work with medical faculty (chosen at the discretion of Parke-Davis) to draft approximately twelve scientific articles on the topic of AED therapy" budgeted $160,500 in grant money for these articles (Exhibits 65 and 66)	Mathews (2005) reports widespread practice of "ghost writing" research articles for publication in medical journals that are written by professional writers on behalf of physicians and funded by pharmaceutical companies at the cost of "$30,000 per article or more"
To increase the titration level of Neurontin® dosage (1,200 mg/day to 1,800 mg/day) (Exhibit 39)	Promotional campaign using detailing, direct mail, and journal advertising to promote the use of Neurontin® earlier and titration at higher doses (Exhibit 39)	

(continued)

Table 24.1 (continued)

Strategy (%budget)	Marketing tactics	External validity
Medical education strategy (27.8%)	"Unrestricted" educational grant to Medical education companies to prepare programs accredited by ACCME with Parke-Davis representatives shaping the content and following attendance counts to support a "growth opportunity" in off-label uses (1997 situation analysis)	Cephalon funded doctors' participation in seminars at which paid speakers promoted off-label uses (Carreyrou 2006)
Marketing objectives To develop or support educational programs consistent with Parke-Davis's marketing To increase Neurontin new prescriptions by educating non-prescribers to begin prescribing and current prescribers to increase prescription behavior	Educational seminars and teleconferences to increase Neurontin® new prescriptions (Exhibit 79)	
"Surrogate selling" strategy (11.9%)	Recruit physicians qualified as high prescribers of AED's by providing incentives to entice participation (Exhibit 76)	Dr. Gleason was arrested for promoting Xyrem for off label uses and acknowledged receiving more than $100,000 from Jazz Pharmaceuticals (Berenson 2006)
Marketing objectives "Maximize relationship with key epileptologists to expand Neurontin usage with residents/fellows, office based neurologists and selected PCPs"	"Make influencers aware of availability of research opportunities in clinical trials"	AstraZeneca provided 400 physicians financial inducements as consultant's fees to prescribe Zoladex (Petersen 2003)
Use peer influence to give non-users reassurance of Neurontin®'s efficacy and tolerability Gain 100% access for Neurontin®	"Emerging thought leaders will be paired with existing thought leaders to meet others supportive of Parke-Davis and its products." (Exhibit 45) Disease-based Advisory Boards (e.g., AIDS Neuropathy, Child Neurology, Migraine)	

documents that provide evidence of individual strategies. Included in Table 24.1 are marketing objectives and tactics established for each strategy as extracted from internal company documents (see columns, "Strategy" and "Marketing Tactics"). Verbatim comments are included from internal documents and sworn testimonies. In addition, Table 24.1 also includes references to additional popular sources to provide evidence

of broader industry use of the identified strategy (see last column titled "External Validity"). We also supplement this evidence with reports from the literature in academic medicine. We use this evidence to mitigate the concern that the identified strategies are idiosyncratic to the pharmaceutical company involved in the focal court case. Below, we discuss each of our results and refer to actual court documents and verbatim notes (and quotes) to illustrate our findings.

24.4.1 Pharmaceutical Marketing Strategies and Associated Tactics

The four distinct strategies identified in our analysis to influence physician decision making include: (1) market penetration strategy involving a focus on segmentation and penetration, (2) evidence-based strategy involving production of science, (3) medical education strategy involving developing and disseminating standards of care, and (4) surrogate selling strategy involving promoting and leveraging peer-to-peer influence among target physicians. We discuss each in turn and the tactics associated with each strategy.

The *market penetration strategy* involved (a) identifying and profiling high-potential physicians; (b) estimating each physician's market potential; and (c) establishing penetration goals for each segment to achieve maximal consequential impact (first row Table 24.1; Fig. 24.1). High potential physicians were identified using data from health information companies (e.g., IMS Health, Verispan) providing records of each physician's prescription writing (identified by license number) which is linked to physician demographic profile obtained from the American Medical Association (Steinbrook 2006). This unique data allows segmenting the market to identify "high prescribers" and tracking their prescription writing over time. Market potential was calculated by categorizing prescription writing patterns into deciles—higher deciles indicate higher market potential (e.g., market potential of tenth decile physicians estimated at $309,517 (Exhibit 35[4])). Using the decile information, Parke-Davis set penetration goals for sales people by emphasizing that it takes "17 decile-7 physicians to bring the same business as 1 decile-10 physician," (Exhibit 35). To enhance salespeople credibility with decile-10 physicians, Parke Davis implemented a Medical Liaison Program where highly qualified scientists (often with Ph.D.s) were partnered with salespeople to address scientific questions about efficacy of drugs in physician interactions. For instance, a Parke Davis territory manager explains the difficulty in gaining access to a decile-10 physician and the role of medical (clinical) liaisons to overcome it:

> Dr. X was decile 10 …. doesn't see anybody. And the door was opened by bringing the clinical liaison in … I think it's an ego trip for the physician, (Exhibit A).

[4]Referred exhibits pertain to materials included in the court documents related to *United States ex rel. David Franklin vs. Parke-Davis, 147F. Supp.2d 39* and available at http://dida.library.ucsf.edu.

Similar indication of market penetration strategy is evident as common industry practice in the secondary data we collected to examine the validity of our findings (last column of Table 24.1). Datamonitor (2001) reports that physician profiling through prescription tracking improves profit margins by as much as 3 % and the initial uptake of innovative drugs by 30 %. Research suggests that profiling dates back to 1940s when the American Medical Association collaborated with pharmaceutical companies to help assemble physician profiles (Greene 2007), and prescription writing data, and making both open to industry access (Grande 2007).

The *evidence-based strategy* involved a three pronged approach: (a) industry funding of clinical trials through research grants; (b) generating publications from clinical trials with a bias for positive results; and (c) contractual arrangements with commercial companies to write, process, and orchestrate publications in referred journals without explicitly exposing their role (second row Table 24.1; Fig. 24.1). Internal documents noted that research grants to physicians were intended to encourage clinical trials that induce familiarity with higher doses of Neurontin (Exhibit 39). The objective of the evidence-based strategy was to favor publishing articles with positive findings that "increase sales" (Exhibit 21), and return on investment estimates were explicitly calculated to target disease indications with the greatest revenue potential. The company entered into formal contracts with commercial companies to develop a coordinated effort for executing publications by "life cycle planning" (Exhibit 72) that involved a time-based program of sequentially publishing scientific articles in peer-reviewed journals (Exhibit 57) in order to create a "drumbeat in the literature," (Exhibit 63; Table 24.1). Company managers routinely tracked the status of manuscripts processed for publication by contract companies to coordinate their promotional efforts, as they also reviewed problems in keeping the publications on track. For instance, AMM Adelphi, a commercial provider contracted for evidence-based strategy, reported to a Parke Davis manager as follows:

> … these physicians [designated authors] are clinicians rather than academicians or researchers, making them less accessible than scientific authors. Thus, these papers require more time and management than is usual… We anticipate that by year's end, you will have several manuscripts submitted to journals as well as either a paper or poster accepted for the AAN, (Exhibit 64).

Parke-Davis internal documents reveal that the company contracted with Medical Education Systems, Inc. to ghost write articles (e.g., failure to include an individual as author who has made substantial contributions to research or writing of the manuscript) for $13,375–18,000 per article and to include physicians as guest authors (e.g., include an individual as author who does not meet authorship criteria) for an honorarium of $1,000 (Table 24.1).

Our secondary data reveals that several companies including Scientific Therapeutics Information and Health Sciences Communication openly advertise their commercial intent to contract for publishing scientific articles for the pharmaceutical industry. Moreover, ghost writing and guest authorship in peer-reviewed journals remains a common practice (Ross et al. 2008). In a recent survey of six peer

reviewed medical journals, ghost writing was demonstrated in 13 % of research articles, 10 % of review articles, 6 % of editorials, and 11 % of Cochrane reviews. Guest authorship was even more prevalent, and found in 16 % of research articles, 26 % of review articles, 21 % of editorials, and 41 % of Cochrane reviews (Flanagin et al. 1998; Mowatt et al. 2002).

The *medical education strategy* involved: (a) shaping standards of care; (b) actively managing a Speakers' bureau; and (c) contracting with medical education companies providing continuing medical education (CME) to physicians (third row Table 24.1; Fig. 24.1). Parke-Davis marketing efforts focused on influencing standards of care to position Neurontin as a first choice in treatment regimens. This goal was achieved through scheduling presentations by influential thought leaders who are favorable to Neurontin at various CME events. In some instances, Parke-Davis paid physicians to attend these events, act as part of the audience, and plant leading questions intended to portray Neurontin in a positive light (Exhibit 79). Parke Davis managed a Speakers Bureau, a data base of key influencers and thought leaders who were paid to present at educational symposia. Parke-Davis encouraged sales representatives to "identify and train strong Neurontin advocates and users to speak locally for Neurontin," (Exhibit 19). Our review of Parke-Davis' documents suggests that the company granted unrestricted educational grants to medical education companies ostensibly for educational purposes; however, company managers provided input in shaping conference content, suggesting thought leaders as speakers, and in tracking participating physicians' pre- and post-seminar prescribing behavior. Territory managers evaluated unrestricted educational grant proposals as illustrated below:

> I am forwarding two budget proposals… One is the satellite symposium alone and one includes a highlights proceedings.. with the satellite. Please review.. so that we can move forward with the grant request through Dannemiller[commercial provider], (Exhibit D).

Similar examples of industry efforts to leverage physician education efforts for consequential gains abound in medical literature (Table 24.1). For instance, studies show that industry sponsored CME programs "preferentially highlighted" the sponsors' drugs and positively affected physician prescription habits after attendance (Bowman and Pearle 1988; Wazana 2000; Relman 2001). Drug companies provided 65 % of total revenue of CME programs organized by commercial providers, providing a financial incentive to create educational programs that cast a favorable light on the companies' products (Steinman and Baron 2007). Choudhry et al. (2002) found that 59 % of authors responsible for updating or developing clinical practice guidelines had financial relationships with companies whose products they considered or included in the guidelines.

Finally, Parke-Davis used a *surrogate selling strategy* by (a) promoting contagion effects through "Neurontin® Champions," (b) recruiting thought leaders; and (c) managing disease-based advisory boards (last row Table 24.1; Fig. 24.1). Promotion of contagion effects involved a "pyramid of influence," where Neurontin® Champions, influential and favorably disposed epileptologists recruited from large

teaching hospitals, reassured their peers about Neurontin's efficacy. The company invited these champions to disease-based advisory boards for discussing diagnostic criteria and appropriate treatment plans for specific diseases (e.g., neuropathy, migraine) that promoted Neurontin as a first choice in standard treatment plans. The key goal of the surrogate selling strategy was to "increase Neurontin new prescriptions by convincing non-prescribers to begin prescribing and current prescribers to increase their prescription behavior" (Exhibits 78 and 79). Medical liaisons encouraged Neurontin champions to publicize their feelings:

> In fact, John had met with somebody… who had asked about restless leg… told her exactly what he's doing. And, she's using it like crazy now. That zip code that Dr. X is in like up to a fifteen percent curve on the market share, (Exhibit A).

The medical literature provides corroborating evidence on surrogate selling. For instance, Henry et al. (2005) report in their study involving Australian physicians that 23 % of their sample was on industry advisory panels and 16 % acted as expert speakers for specific pharmaceutical products. Surrogate selling influence has been examined in seeding trials where the pharmaceutical company awards drug-trial grants to physician investigators with the intent to encourage the physicians to advocate the drug to their colleagues. For instance, internal documents pertaining to Merck's ADVANTAGE (Assessment of Differences between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness) seeding trial revealed that Merck designed the study with a quest to engage future prescribers with Vioxx (Hill et al. 2008). Additionally, the appropriateness of physician membership in speakers' bureau and advisory boards and their role in surrogate selling have been questioned by a number of medical researchers (Brennan et al. 2006; Angell 2008; Jampol et al. 2009; Insel 2010). In a national survey of department chairs in the 125 accredited medical schools and 15 largest independent teaching hospitals, Campbell et al. (2007) found that 27 % of department chairs surveyed had a consulting relationship with the industry and 14 % served on the speakers' bureau.

24.4.2 Strategic Interdependencies

Our analysis indicates that Parke-Davis structured deliberate interdependencies among the four strategies outlined above, which we broadly classify as *expertise* or *promotion* based interdependencies. The goal of these interdependencies was to link strategies so that they collectively exert a synergistic influence on a physician's decision to write prescriptions that favor the company's products. Expertise based interdependencies focus on leveraging knowledge (e.g., scientific evidence) and knowledgeable physicians (e.g., thought leaders) to support Parke Davis' objectives for Neurontin. Promotion based interdependencies focus on leveraging data (e.g., prescription writing) and networks (e.g., Neurontin champions) to bolster the sales efforts in direct interactions with targeted physicians. These interdependencies are

shown in Fig. 24.1 as direct or indirect linkages corresponding to promotion or expertise based interdependencies respectively. Promotion based interdependencies are direct linkages because they largely involve sales people employed by the company, while expertise based interdependencies mostly involve independent physicians. We discuss the findings related to expertise- and promotion based interdependences in order.

Expertise based interdependencies. Our analysis reveals that Parke Davis leveraged expertise in several forms of interdependencies. For instance, the expertise of lead investigators funded by Parke Davis as part of evidence-based strategy was leveraged by inviting them to participate in CME initiatives as part of the education strategy. The CME initiatives by favorably pre-disposed physician scientists assured standards of care in favor of Neurontin. A sworn testimony of an expert witness illustrates these interdependencies:

> A continuing medical education monograph … was supported by an unrestricted educational grant from Parke-Davis… [to]the author of the monograph and narrator of the accompanying audio tape … Dr. X [name withheld], President of the International Headache Society… (Exhibit N).

In another form of interdependency, the speaker's bureau constituted as part of the education strategy was systematically culled to solicit physician scientists favorable toward Neurontin for disease advisory boards (Exhibit 69) and encouraged to disseminate the emergent knowledge from their recently "published" research as part of surrogate influence strategy (Exhibit 34). To broaden the reach of surrogate influence, teleconferences were used to connect Neurontin "champions" with over 1,000 physicians and facilitate the creation of 100 "Pain CME Case Study Groups" to promote education as part of Parke Davis efforts to increase Neurontin's off-label use for pain. In an expert testimony, this interdependence is noted as follows:

> Dr. X [name withheld] sponsored through an unrestricted educational grant discloses participation on the speakers bureau for Parke-Davis [among other affiliations], writes in a CME monograph that it is important not to under dose gabapentin when managing PHN, (Exhibit P).

Parke Davis structured interdependencies between evidence and surrogate selling strategies by routinely rewarding physicians who were Neurontin champions with privileged research grants. For instance, in a major phase IV trial, STEPS (**S**tudy of Neurontin: **T**itration to **E**ffectiveness and **P**rofile of **S**afety) recruited more than 700 physicians with payments of $300 for each patient enrolled, a strategy that resulted in a 20 % increase in new patients and 3 % increase in market share (Exhibit 72). Although Parke Davis limited the number of patients that physicians could recruit for the study to 10, it allowed leading physicians at large teaching hospitals or centers of influence (who had potential to sway a large number of their colleagues) to recruit up to 50 patients each. Grants made to these thought leaders were to further Neurontin sales within the hospital and to use these physicians in surrogate selling programs (Exhibit 34). For instance, a request by Dr. X [name withheld] was approved because he was a "great Neurontin believer," (Exhibit 85) as noted in the following excerpt from an expert testimony:

> Parke-Davis considered Dr. X [name withheld] a "key influencer" at one of Boston's "centers of influence" with the potential not only to increase his own Neurontin prescriptions, but to influence his peers' Neurontin prescribing at New England Medical Center. Dr. X was offered money to conduct a study on Neurontin's use for restless leg. After the payment was made, Dr. X placed more than 160 patients (non-study patients) on Neurontin, (Exhibit 85).

Promotion based interdependencies. Parke Davis regularly analyzed and tracked market research data on physicians' prescription behaviors and patients' prescription filling to bolster the sales efforts in direct interactions with targeted physicians (Exhibit 132). For instance, Parke Davis used consultant and dinner meetings to wine and dine high decile doctors to provide them with information about off-label uses of Neurontin. Internal documents revealed that the invitation to attend these meetings was based solely on high rates of prescribing (Exhibit 17) and attendees were provided a "hard hitting message about Neurontin," (Exhibit 69). One such meeting at the Jupiter Beach, Florida was set up to expose 100 physicians with the "greatest potential" to prescribe Neurontin," (Exhibits 49 and 53). Area business managers were provided with trending work sheets to track the pre- and post-meeting prescription writing by participants (Exhibit 54). The Neurontin Marketing team monitored the attendance and provided attendee names to territory managers for follow-up. The following memo to area business managers illustrates the penetration-surrogate interdependencies.

> Attached is the Trending Worksheet for the recent Neurontin Consultants Program in Jupiter Beach, Florida. The attendees from your district are listed. This tool is very valuable in tracking the value of participating in this program, (Exhibit 54).

In another form of promotion interdependence, Parke Davis targeted thought leaders from large teaching hospitals who have the greatest potential to write Neurontin prescriptions. Sales people were reminded that "the key influencers should be …kept aware of the availability of research opportunities in clinical trials," (Exhibit 24). Territory managers and medical liaisons used published evidence garnered from such grants to persuade targeted physicians to write prescriptions favoring the company. A territory manager from Parke Davis explains thus:

> Medical liaison A [name withheld] and I went to see Dr. X [name withheld] last July… and we brought Y's data with us on restless leg. We showed him that… right after we talked to him, he began to try Neurontin on patients that he just started on, (Exhibit A).

Internal documents also illuminate the interdependence between penetration and education strategies. For instance, Exhibit 39 states that "medical education supports the Neurontin promotional campaign and supplements field sales efforts providing physicians with the opportunity to share their experiences and to learn from key thought leaders how to successfully use Neurontin in clinical practice." As noted above, Parke-Davis used commercial companies to monitor pre and post prescription behavior of attendants to Educational Teleconferences using a Promo Trak methodology (Exhibit 79). This data was provided to sales people to find new

prospects as well as fine tune current market penetration efforts. An expert testimony describes how the penetration-education interdependencies were carried out:

> An unrestricted educational grant for $303,740 was granted to Handbooks in Health Care Co. for the production of 75,000 copies of an epilepsy handbook. Approximately 96,000 high prescribers of anticonvulsant agents were identified as targets for this book and territory managers were instructed to introduce the book to high prescribers in their territory, (Exhibits B and 90).

24.4.3 Marketing Strategies and Conflicted Logics in the Pharmaceutical Value Chain

Our analysis reveals that the marketing strategies and the deliberate structuring of interdependencies conflate the logics of appropriateness and consequences escalating the problem of conflicted logics within the value chain. As depicted in Fig. 24.1, this conflation occurs because pharmaceutical marketing strategies and the interdependencies built among them exploit the logic of appropriateness for consequential gains. For instance, our analyses reveals that the industry provides "unrestricted" funds to produce favorable "research" that is published in peer-reviewed journals through ghost writing. Upon publication, the "research" is disseminated using a "medical education" strategy involving "grants" for continuing education and "surrogate selling" strategy involving "contracted" thought leaders. Moreover, "thought leaders" identified through prescription tracking are awarded research grants for clinical trials, and subsequently invited to populate speakers' bureau and disease advisory boards to sway their peers through medical education and surrogate selling strategies. Although we do not fully develop organizational role in instantiating such complex strategies and interdependencies, in a separate analysis we have theorized and empirically examined this issue (Singh and Jayanti 2013). Our analysis shows that, the conflicted logics of the pharmaceutical value chain does not constrain organizational action. Rather, organizations deliberately internalize conflicted logics to direct their sales professionals to display appropriateness-like roles that cleverly camouflage consequences related goals.

As long as the industry's efforts to camouflage its conflation are successful, the strategy produces consequential results. Grants are considered a contribution to science not marketing, research is viewed with credibility not tainted by commercial intent, and thought leader's recommendations carry legitimate weight of an expert, not a contracted spokesperson. However, these strategies undermine the very mechanisms (e.g., CME and Journal Publications) of interpersonal trust that are crucial to the legitimacy of the medical profession. As a result, the more successful the pharmaceutical marketing strategies are in achieving their objectives, the more likely are they to amplify the conflicted logics of the value chain with one caveat; the growing conflict is latent and inert as long as the industry's deliberate conflation of logics remains undetected.

Once detected, however, the conflict rises to the surface and invites swift and strong response. For instance, the industry's evidence-based strategy prompted the *Journal of American Medical Association*, along with *International Committee of Medical Journal Editors* to require all authors to include an explicit disclosure of conflict of interests and, for industry sponsored research, ask authors to conduct independent statistical analysis as a condition for publication (DeAngelis 2006). Noting that "over 50 % of articles" in top journals may be "ghost-written," the U.K. House of Commons (Health Committee 2005, p. 53) stressed that regulatory guidelines should "leave no room for ghost-writing." Additionally, the Accrediting Council for Continuing Medical Education has enforced strict policies against faculty recommendations and CME content reviews by commercial sponsors. The American Medical Association and the American Psychiatry Association have followed suit by restricting industry involvement in CME activities. In March 2009, the *Journal of the American Medical Association* (*JAMA*) called on all professional medical associations to end drug company relationships. Academic medical centers including Yale, Harvard, Duke, Stanford, University of Pennsylvania, Henry Ford Health System, and UCLA have banned physicians from receiving monetary or non-monetary gifts, however small, and prohibited drug samples and detailers from patient care areas (Croasdale 2006).

Rising public aversion to industry's deliberate conflation of logics in its marketing strategies has also invited regulatory intervention. The recent healthcare reform in the United States includes the Physician Payment Sunshine Act, a mandate for transparency in the financial relationships between pharmaceutical industry and physicians. Additionally, prosecutors and professional agencies have imposed monitoring and oversight restraints on pharmaceutical industry-physician interactions. Recently, ProPublica has provided open access to a searchable database called "dollars for docs" for public to uncover industry payments to local physicians.

24.5 Open Systems Framework for Pharmaceutical Marketing Strategies: Directions for Future Research and Practice

Our comprehensive analysis of pharmaceutical marketing strategies and tactics unveils new insights and calls for new directions for research and practice. First, our analysis provides evidence that pharmaceutical marketing strategies are largely driven by an economic model to maximize ROI and maintain focus on consequential gains. More significantly, our analysis lays bare the intricate and carefully crafted interdependencies among a diverse set of tactical moves that pharmaceutical marketing managers construct as strategy to influence physician decision making. What makes these strategies aversive to physicians and public alike is not so much as they are driven by an economic imperative of "self-interest without guile" but the systematic and sustained effort to cloak the economic self-interest within a logic of

appropriateness to appear as benevolence acts in the interest of enhancing physician knowledge and public health. By ignoring strategies that underlie pharmaceutical marketing tactics, most past research in marketing misses both the intricate interdependencies among tactics and willful effort to obscure these interdependencies from scrutiny by physicians and public. As a result, extant research in marketing is of limited use to anticipate or explain the increasingly unfavorable response to pharmaceutical marketing tactics, and regulatory effort to contain and constrain their reach. Thus, a new direction is needed to break free from the myopia of past research.

Second, our analysis indicates that an institutional theory perspective is well suited for studying pharmaceutical marketing strategies within a broader, value chain perspective. Our institutional theory-based development considers both the logics of consequences that govern pharmaceutical marketing efforts and the logics of appropriateness that frame physicians' medical decision making. Joint consideration of industry and physician logics allows us to explicitly analyze the conflict that actions rooted in these disparate logics entail. Our analysis highlights that conflicted logics become institutionalized and rationalized as normative routines making the system less flexible and susceptible to market failure. More significantly, our analysis shows that this conflict is amplified over time, perhaps inadvertently, by self-centered actions of market actors who are narrowly focused on their own logics and unable to grasp a system view—in a way, *missing the forest for the trees*. Past studies have generally given scant attention to the disparate logics that characterize pharmaceutical industry–physician relationships, and hesitated in adopting a value chain perspective. New frameworks for studying pharmaceutical marketing strategies are needed that consider: (1) interdependencies among pharmaceutical value chain partners motivated by disparate logics, (2) embeddedness of market actors, and (3) temporal evolution of the nature and intensity of system conflict. Absent these considerations, we risk incomplete, if not misleading, understanding of pharmaceutical marketing strategies and its consequences.

We propose one such framework that draws from open system theories of organizational action (Stern and Barley 1996; Katz and Kahn 1966). Our proposed framework has several distinct aspects that together constitute a theoretically useful foundation including: (1) focus on a system of market relationships that characterize the pharmaceutical value chain, (2) emphasis on organizational and system legitimacy, and (3) linking *macro*-level system logics and *micro*-level actions of individual market actors as they negotiate an order from emergent contests of competing logics. Table 24.2 outlines the key elements of this proposed framework—referred to as "open systems framework"—and compares it with current economic framework that characterizes most studies of pharmaceutical marketing. Specifically, the nine elements in Table 24.2 are organized around three discussion points relating to foundations (what are the basic theoretical and conceptual building blocks?), premises (what are its assumptions and axioms?) and key questions and mechanisms (what are its proposed hypothesis and processes?). These elements are best viewed as building blocks of a theory rather

Table 24.2 Comparative analysis of frameworks rooted in consequential and open systems based view of institutional logics for pharmaceutical marketing

	Elements	Economic framework	Open systems framework
Foundational elements	Fundamental objective	Return on marketing investments	System and organizational (subsystem) legitimacy gains from marketing investments
	Focal phenomenon	Consummation of market exchanges	Interdependence and interconnectedness of market relationships
	Foundational logics	Logics of consequences	Logics of consequences *and* appropriateness
	Market mechanisms	Creating and extracting value	Balancing value extraction and legitimacy gains
Premises	Agency	Managerial actions are sufficient to assert control to structure and shape market exchanges in the value chain	Managerial actions are insufficient to unilaterally structure market exchanges in the value chain; instead, outcomes of managerial actions are influenced by system interdependence
	Market state	Orderly movement toward stability and equilibrium	Disorderly movement toward less differentiated structures and possible dissolution
Key questions and mechanisms	Guiding questions	How, when and why do market-mix instruments influence value chain partners, and how to optimize return on these instruments	How, when and why do market actions enhance or diminish system and organizational legitimacy, and how to enhance the effectiveness of market actions
	Market concepts	Detailing, sampling, advertising, and networks that are critical to extracting value from market exchanges	Contested logics, differentiation, progressive mechanization, market dilemmas, and equifinality that are critical to enhancing system and organizational legitimacy
	Market order	Emerges through top-down processes supported by market-mix instruments that the market actors deploy to align market exchanges with their favored logics	Emerges in bottom-up, self-organizing processes that characterize interactions among market actors guided by disparate and usually conflicted logics making the process nonlinear, path dependent, and unpredictable

than a fleshed out theory itself. We believe that outlining the elements of a theory with a focus on comparative analysis will likely provoke debate and discourse essential to guiding future theoretical efforts. We develop the elements in Table 24.2 in more detail below, and outline the key propositions resulting from it in Table 24.3 to guide future research.

Table 24.3 Propositions for a research agenda of an open systems study of pharmaceutical marketing

Foundational elements
Market exchanges between value chain partners with disparate organizing logics are prone to conflict when fiduciary responsibility is central to one, but not both, of those logics
Organizational legitimacy is a key mediator for the influence of marketing strategy on long term (a) sustainability, and (b) profitability
Marketing strategies centered exclusively on a firm's own internal logics will (a) enhance value chain conflict and (b) lower organizational legitimacy
An organization is likely to be perceived as more legitimate, the more it is perceived by its value chain partners and customers to (a) deliver something that adds value to exchange relationships in the system (pragmatic legitimacy), (b) be a trustworthy partner that can be relied upon to protect the best interests of its downstream customers and curb opportunism (moral legitimacy), and (c) engage in activities that are meaningful and desirable for society (cognitive legitimacy)
In the long term, marketing strategies centered exclusively on pragmatic legitimacy will undermine (a) moral legitimacy, and (b) cognitive legitimacy
The higher the organization's legitimacy, the greater its effectiveness in (a) securing scarce societal resources, (b) long term sustainability, and (c) overcoming market threats (e.g., due to unfavorable information, shocks, crisis)
Greater the persistence of unresolved conflict among value chain partners, lower the organizational legitimacy for one or both partners
Premises
Greater the marketing incentives to physicians with the objective of influencing their prescription writing (a) higher the system conflict and (b) lower the organizational legitimacy
Greater the effectiveness and efficiency of marketing strategies rooted in consequential logic, (a) higher the system conflict and (b) lower the organizational legitimacy
Greater the focus of value chain partners on the stability of their own internal dominant logic, greater the intensity of system conflict
Key questions and mechanisms
The more a value chain is characterized by persistent system conflict, the more likely are retaliatory actions by value chain partner(s) to safeguard their own legitimacy
Managerial actions with a strong (weak) focus on consequential logic will result in increasing (decreasing) unilateral actions by value chain partners to safeguard their legitimacy by (a) erecting firewalls and (b) maintaining arms length relationships
Collaborative actions among value chain partners are likely to be more effective, the more they are organized as open, bottom-up, self-organizing systems (rather than structured, top-down, regulated systems)
Over time, value chains will have an increasing tendency toward mechanisms that provide efficiency gains and reduce complexity (progressive mechanization)
Greater the system's success in progressive mechanization, lower its capacity to effectively resolve emergent system conflicts

24.5.1 Foundational Elements

Whereas an economic framework directs managerial attention to the objective of maximizing ROI, the open systems framework directs managerial focus to organizational and system legitimacy. We assert that legitimacy is a stronger predictor of

organizational effectiveness in value-chains characterized by conflicted logics, and where fiduciary obligations are relevant. Suchman (1995, p. 574) defines legitimacy as a "generalized perception that the actions of an entity are desirable, proper or appropriate within some socially constructed system of norms, beliefs and definitions."[5] That is, legitimacy is not an abstract, monolithic or enduring evaluation; rather, it is socially constructed by an organization's value chain partners based on a multidimensional evaluation including (1) pragmatic legitimacy or the degree to which it delivers something that adds *value* to the system, (2) moral legitimacy or the degree to which it employs means and procedures that are *trustworthy*, and (3) cognitive legitimacy or the degree to which its activities are *meaningful* and desirable for the use and distribution of societal resources (Scott 1987; Suchman 1995). As such, a legitimacy objective draws attention not only to value creation but also on *how* (using trustworthy means?), *what* (using meaningful activities?) and *for whom* (fair allocation of benefits).

A particularly foundational element in the open systems framework is that interdependencies assume special importance in systems where value chain partners are embedded in institutionally disparate logics. Unlike an economic framework that achieves its coherence by its assertion of a unitary logic of consequences, an open systems framework problematizes coherence by consideration of dualistic logics. In our study, we have noted that the pharmaceutical value chain involves partners that are beholden to different logics. An open systems framework argues that pharmaceutical industry embrace the dualistic logics of the value chain in designing its strategies and tactics. Singular focus on its own logics ignores the interdependence of the value chain as a system. Consequently, while the economic framework focuses on the mechanisms of creating and extracting value, the open systems framework requires focus on mechanisms that balance the organizational need to extract value with the objective of gaining legitimacy (Table 24.2).

To balance value extraction with legitimacy gains does not necessarily imply accepting tradeoffs. Rather, an open systems framework suggests that organizational effectiveness is likely to be enhanced (compromised) when strategic actions in pursuit of consequential logics also bolster (undermine) the social codes and norms implied by the appropriateness logic of value chain partner. In studying hospital survival rates from 1945 to 1990, Ruef and Scott (1998) found that, after controlling for organizational and environmental factors, top-rated hospitals (with greater legitimacy) improved their survival rates by factors of 2–5 over average-rated hospitals (with lower legitimacy). Likewise, Arthur (2003) showed that Fortune 500 organizations that gained (moral) legitimacy by investing in work family initiatives during 1971 and 1996 posted "excess" shareholder returns to enhance firm's financial resources. Consistent with this, Rao et al. (2008) demonstrate that US biotechnology firms derived greater stock market returns from innovations if

[5] Deephouse and Carter (2005) note that legitimacy claims are distinct from reputational claims. Organizational reputation is a qualitative assessment based on social comparison among a set of, possibly legitimate, firms. However, legitimacy is about social acceptance based on conforming to social norms.

they were perceived to possess greater legitimacy by their value-chain partners. Thus value extraction and legitimacy are not inherently incompatible goals.

Nevertheless, our position is not that an open systems framework is universally appropriate, and legitimacy objective necessarily relevant for all organizations. Value chains organized around a singular, coherent logic commonly shared by its members may be well described by an economic framework rendering an open systems framework less meaningful. Consider, for instance, the oil industry value chain. One may be appalled by the windfall profits of oil companies at times of rising gas prices, but one accepts it as business practice. As such, while legitimacy is important (e.g., oil companies resist perceptions of price gouging), its role in organizational effectiveness is not overtly enhanced. The American Petroleum Institute's chief economist, John Felmy, recently provided details of industry costing to assert that industry "profits are not much higher than those of large industrial companies" and, in fact, some refiners are "losing money" (Esch 2008).

Our position is that open systems framework is more appropriate, and legitimacy risk more relevant for organizations that are embedded in value chains characterized by conflicted logics. In such value chains, market action motivated by singular economic objective of creating and extracting value is likely to exacerbate the conflict of logics, and diminish organizational legitimacy. For instance, in our study, we show that pharmaceutical marketing strategies escalate system conflict within the value chain because they exploit mechanisms that physicians have institutionalized to preserve impersonal trust necessary for the legitimacy of the medical profession (Mello and Messing 2011; Fugh-Berman 2008; Orentlicher 2010). For instance, the stated motivation for the AAMC task force for prescribing industry-profession interactions is "all real or perceived conflicts of interest" concerns that stem from "increasingly dependent" relationships between the physicians and pharmaceutical industry (AAMC 2008, p. iii.). Likewise, the American Medical Association responded to numerous complaints by physicians troubled by aggressive tactics of drug sales representatives to implement an "opt-out" program for physicians to remove their data from the Physician Master file used by the industry to target and track physicians' prescribing patterns (O'Reilley 2006). A Gallup survey of physicians who opted-out of the Masterfile program indicated that 60 % would be willing to change their mind if they were assured that the prescribing data was used to support public good, not marketing practices (O'Reilley 2006). Thus, legitimacy risks can escalate with increasing intensity of conflicted logics, and undermine long term gains usually flowing from collaborative relationships with value chain partners (Bansal and Clelland 2004).

From the standpoint of managerial practice, it is appropriate to question if legitimacy is resistant to direct managerial intervention because it is conceptually nebulous and pragmatically resilient to managerial control. After all, legitimacy, like reputation, is earned not manufactured or acquired. As such, the relevant organizational challenge is not how to manipulate legitimacy assessments of its value chain partners, but to understand how managerial action builds or depletes legitimacy

assessments, and how to repair legitimacy breeches. For instance, Suchman (1995) notes that legitimacy response is a strategic issue and mending legitimacy breeches may require managers to decouple or disassociate from offending activities, institute credible monitoring controls, restructure market arrangements, or engage in aggressive damage control. Whether such managerial action mends or exacerbates legitimacy breeches within the value chain is an important line for theorizing and empirical work. The proposed open systems framework offers several lines of inquiry for exploring the preceding issues as noted in Table 24.3.

24.5.2 Premises

The economic and open systems frameworks differ in their underlying premises. Specifically, in contrast to economic framework's premise of autonomous managerial action (March 1996), the proposed open systems framework is premised on the notion of action-system interdependence. Rooted in the notion of a "rational man," the economic framework holds that individual managers largely hold agency for action, and their collective actions are the key to understanding how institutional systems are structured and shaped over time, and how these system dynamics, in turn, influence organizational outcomes. Indeed, the economic framework does not assert that institutional systems are swayed by any single manager. Rather, it posits that managers in an industry often share common schemas of their institutional environments and, as common patterns of managerial action emerge, their collective actions are powerful forces in influencing organizational, value chain, and institutional outcomes (George et al. 2006).

By contrast, the open systems framework adopts a constrained role for managerial agency while emphasizing the role of action-system interdependence. Sidestepping both the agency vs. structure debate and paradox of embedded agency (Heugens and Lander 2009), an open systems perspective recognizes that managers hold agency in shaping institutional structures and processes; however, it does not accord agency the status of taken for granted as per the economic framework. Rather, an open system framework views managerial actions to be just as empowered as they are constrained by the institutional structures and processes that embed their actions. This open systems view of managerial action, empowered *and* constrained, is referred to as action-system interdependence. Dating back to action theory (Parsons 1956), action-system interdependence implies that individuals construct actions from repertoires available in the institutional system; yet, actions are interpreted or are effective in catalyzing change depends on processes of sensemaking and response by other actors in the system.

The pharmaceutical value chain is a prototypical instance of such interdependence. Fiduciary responsibility requires subordinating self-interest in the service of external constituencies (e.g., pubic, society), enlarging the scope of the system and exposing it to external scrutiny. Considerable evidence exists to suggest that market actors in such systems are often blind sighted by implications of action-system

interdependence and fall prey to its counterintuitive dynamics when they become overly focused on their internal logics. Notable instances of such blind sighting include Arthur Anderson in the auditing scandal, Student Loan Xpress in the student loan disaster, Lincoln Savings and Loan in the S&L crisis, and AIG insurance and Prudential in the insurance industry debacle.

The two frameworks also differ in their premise for the equilibrium state of the market (or lack thereof). Market equilibrium is a premise of the economic framework, such that market actors are assumed to exercise agency to move markets toward a stable, steady state. An equilibrium state is thought to be more likely when the value chain is aligned with a singular institutional logic by design, default or managerial agency. By contrast, an open system is agnostic to market state and is inherently antithetical to stable, orderly and equilibrating processes of market evolution and shift. Consistent with its foundations in conflicted logics, an open systems framework is more compatible with the premise of disorderly movement where markets become arenas of contested logics that risk negative system spirals and are marked by increased conflict, aggressive retaliation, and eroding cooperation among value chain partners.

It is important to note that the open systems framework is not premised on inevitable negative spirals. Just that this *could* and *does* happen. The fundamental point is that system dynamics evolve in response to interactions among market actors, often resulting in emergence of new types of actors, relations, and networks (Katz and Kahn 1966). As per systems theory, order and structure emerge in a bottom-up, self-organizing way from the micro-interactions among market actors making the process nonlinear, path dependent, and unpredictable. The emerging order and structure are not necessarily conducive for the survival and growth of individual market actors. Nevertheless, managerial intuition and instruments of "planning and strategic action" rooted in autonomous action may be problematic because they promote system run downs (Wilkinson and Young 2007, p. 372). For survival and growth, actors "must move to arrest the entropic process" by drawing energy (negative entropy) from its environments through interdependent action that recognizes system as the unit of analysis, co-learning and collaboration as key system processes, and legitimacy as the desired outcome (March 1996). These possibilities are captured in our research propositions presented in Table 24.3.

24.5.3 Key Questions and Mechanisms

The open systems and economic systems offer contrasting pathways for inquiry and practice. Representing the current state of the literature, the economic framework focuses research inquiry on understanding how, when and why do market-mix instruments influence physician decision making, and in developing models for optimizing the return on market-mix investments. Such inquiry is especially powerful when it can identify the unique and synergistic effects of clearly defined market mix instruments. Much past research has used this framework to study effects of

diverse instruments such as detailing, sampling and advertising. Consistent with its premises, the economic framework asserts that managers can use the evidence of market mix effects to make top-down decisions that set up incentives to structure market exchanges in way that is favorable to the organization.

The open systems framework shifts inquiry and practice attention away from ROI of market mix instruments and toward market action and its legitimacy implications. By using market action as the unit of analysis, the open systems approach places more emphasis on strategies that underlie market action, and in understanding how market action is interpreted to construct legitimacy judgments. Because market action is centered on the actor and legitimacy on the partners and observers who interact with or are exposed to the actor, the open systems adopts a more holistic view in understanding how, when and why market action is effective.

Moreover, the open systems approach offers novel concepts for understanding value chain system dynamics. For instance, consider the concepts of conflicted logics and market dilemmas. The notion of contested logics focuses on system mechanisms triggered by ongoing contests among market actors rooted in the conflicted logics of the value chain. In some decisions, the contests may favor a consequential logic while for others the logic of appropriateness may hold sway. Outcome patterns of such contests over time and decisions shape the ebb and flow of system dynamics. Patterns that are heavily weighed by consequential logic may erode moral legitimacy, just as patterns tilted heavily by logic of appropriateness may exact a price in terms of pragmatic legitimacy. Although speculative, the notion of conflicted logics as games of trust-value tradeoffs in micro-level managerial decisions provides a novel way of examining system dynamics. When tradeoffs persist as interactional routines that are reinforced over time, a market dilemma exists. Such dilemmas may require policy intervention to set new ground rules for market exchanges that favor resolution of conflicts through market self-regulation. Likewise, when actors are sensitive to market dilemmas, they may be motivated to overcome path dependencies to stem further legitimacy losses and avoid regulatory intervention. The systems theory notions of equifinality—many different paths leading to the same outcomes, and entropy—progressive mechanization can be mitigated by arresting energy from the system, provide a foundation for understanding processes of contested logics and the resultant market dilemmas that open new windows for future research.

Recent work in coevolutionary game theory offers useful directions (Bergstrom and Lachmann 2003; Lewin and Volberda 1999). Drawing on biological principles of mutualistic interaction between two or more species that are embedded in a large milieu of a biological system, evolutionary game theorists examine questions such as what keeps the interaction from breaking down as individual species succumb to their own consequential logic, disorderly movement toward less differentiated structures and possible dissolution, how they allocate benefits of cooperation to avoid interaction breeches (e.g., market failure), why certain routines get replicated and reinforced and what makes certain species or systems to break away from their path dependencies to be more flexible and adaptable (Lewin and Volberda 1999).

Future research can build on this stream of work to more fully articulate the coevolutionary processes involved in an open systems theory of interdependence.

Viewing pharmaceutical value chain as an open system centers attention on the recursive relationships among market actors (DiMaggio 1997; Giddens 1990). For instance, Moore et al. (2006) discuss the implications of interdependencies within the context of accounting organizations. Faced with legitimacy threats from persistent conflicts between their auditing and consulting functions, accounting firms aggressively pursued "cosmetic changes" that improved the appearance of auditor independence and "skillfully masked rent seeking in the rhetoric of the public good," till the excesses of one organization (Enron) wrought a political and public backlash for a new institutional order (Moore et al. 2006, p. 20).

A particularly provocative insight from an open systems perspective is that the dominant coordinating logic at any given point is not necessarily conducive for preserving legitimacy. System theorists note that, akin to biological evolution, socio-economic systems move in the direction of more differentiated mechanisms that initially allow nuanced, flexible and contingent resolution of conflicted logics but later tend to be drawn into progressive mechanization as dominant market actors assert "fixed arrangements" to gain efficiency and reduce complexity in market interactions. However, progressive mechanization also tends to "gradually diminish and eventually abolish the equipotentiality" of the system as a whole thereby inhibiting its capacity to solve emergent problems rooted in system conflict (von Bertalanffy 1968; Katz and Kahn 1966). Thus, an open system perspective broadens current conceptualizations to include the dynamics of recursive relationships among market actors and opens several avenues for future research as outlined in Table 24.3.

24.6 Concluding Notes

This chapter is motivated by the strategy-tactics gap in the extant pharmaceutical marketing literature. Much previous research appears preoccupied by modeling the ROI of diverse marketing mix instruments while largely neglecting to study the strategies that underlie these tactics. Using the aversive discourse of pharmaceutical marketing strategies in the medical literature and public press as a point of departure, the chapter aims to systematically analyze the marketing strategies used in practice by pharmaceutical industry using a unique data involving court discovery documents unsealed in a recent litigation. Moreover, we adopt an institutional theory perspective to analyze the disparate logics that characterize the value chain of pharmaceutical markets. Lacking institutional and system perspectives, current approaches are hard pressed to anticipate, much less explain, the persistent and increasingly unfavorable assessments of pharmaceutical marketing by its value chain partners including professional medicine and consumers. Our analysis suggests that the pharmaceutical value chain evidences dynamics consistent with several aspects of institutional theory: (1) system conflict due to coexistence of competing logics, (2) institutional failure in resolving conflict of logics that are

amplified by pharmaceutical marketing practices, and (3) continued escalation of conflicts of logics that invite regulatory intervention which constrains and restricts marketing efforts.

Building on our insights, we develop an open systems view of the pharmaceutical value chain and contrast it with an economic framework that guides much current research. We do not propose that the current approaches are flawed and need to be abandoned. Current approaches have produced useful insights to guide managerial action. Our point is that these approaches miss a systems view that provides action guidelines that differ or counter those resulting from current approaches. Using current approaches and system view as two sides of the coin, and conjoining them when possible, can be effective.

Going forward, conceptualizing and operationalizing legitimacy dimensions require a shift in focus from organization-centric calculus to a system-centric orientation. For instance, instead of focusing on value *extracted* from its value chain (e.g., ROI), pragmatic legitimacy attends to value *added* to its value chain. This does not imply that value extraction is ignored. Rather, value added is given greater significance in pragmatic legitimacy considerations. Likewise, moral and cognitive legitimacy are system-centric, requiring focus on evaluations of value chain partners and downstream customers. However, value chain partners are usually dispersed and are not easily accessible, making legitimacy assessment less tractable than ROI calculations. Institutional theorists have provided useful conceptual and operational advances for assessing organizational legitimacy which can be leveraged for developing legitimacy constructs appropriate for marketing contexts (Suchman 1995). For instance, Tyler (2006) suggests that justice theory concepts of distributive, interactional, and procedural fairness may be bootstrapped to assess pragmatic, moral and cognitive dimensions of organizational legitimacy.

In closing, we note that our study holds broader relevance to other markets characterized by conflicted logics and market actors bound by fiduciary responsibility. Such markets abound in modern civil societies and tend to suffer legitimacy setbacks with alarming regularity, incurring substantial societal, organizational, and human costs. We hope that our study highlights the dilemma of such markets and provides the guiding impetus for future research that provides insights for managerial action with foresight to navigate legitimacy dilemmas.

24.7 Appendix: Background Note on Analysis of Court Documents for Mapping PM Strategies

Data background. Several key litigations involving pharmaceutical marketing practices have been processed in US and international courts including: (a) TAP Pharmaceuticals who settled its nationwide class action lawsuit by paying $885 million to consumers and insurers, (b) AstraZeneca who pled guilty and paid $335 million for promoting Zoladex, (c) Eli Lilly who was charged for marketing practices involving Evista and paid $36 million dollars to the US government, and (d)

Schering-Plough Corporation who paid $435 million dollars as part of their plea agreement to settle charges for marketing drugs. In fact, six out of the top ten pharmaceutical companies[6] in 2007 have faced recent or current litigation due to their marketing tactics.

The case we selected, *United States of America ex. rel David Franklin vs. Pfizer Inc, and Parke-Davis, Division of Warner-Lambert Company,* involved marketing practices related to Neurontin® (chemically known as gabapentin) which was marketed in over 100 countries, used by over 12 million patients and was generating revenue of over $2.7 billion. The FDA initially approved gabapentin in 1993 for adjunctive treatment of partial complex seizures in adults older than 12 years in age and for dosages not exceeding 1,800 mg/day. However, by the mid-nineties, gabapentin experienced its highest growth in off-label treatment of pain syndromes (e.g., neuropathic pain, migraine) and psychiatric disorders (e.g., social phobia, bipolar disorders). Parke-Davis admitted that it used marketing and promotion strategies for unapproved, off-label uses. Under current United States law, it is neither illegal nor unethical for physicians to prescribe a drug for purposes unrelated to its FDA approved uses. Physicians are privileged by law to prescribe a drug for treatments for which they believe there is sufficient evidence of efficacy based on scientific evidence in peer reviewed journals and expert recommendations. Pharmaceutical companies are legally restrained from directly marketing and promoting a drug for off-label uses. As such, the marketing practices used are not illegal per se. They are illegal only if they are used to *directly* promote off-label uses.

Data characteristics and analysis. The court documents were obtained directly from the attorneys, and supplemented with archived data from a website of all pertaining documents housed at the University of California, San Francisco (http://dida.library.ucsf.edu). The documents included internal correspondence, details of sponsored activities and programs, exchanges between drug companies and physicians, and sworn depositions from key individuals. In analyzing these documents, we adopted an inductive approach with multiple coders. Two teams, each involving a lead researcher and a student, were constituted. The first team initially combed the materials to extract the key strategies and associated networks that had a direct or indirect bearing on the company's relationships with physicians. The second team then independently extracted the key strategies and networks, and met with the first team to resolve differences and integrate extracted strategies. Further, to ensure that the inductively derived descriptive patterns are not idiosyncratic to the gabapentin case but reflect broader industry practices, we supplemented this analysis with review of secondary materials including: (1) media reports and articles (e.g., *Business Week*, *The Wall Street Journal, CBS News*), (2) industry (e.g., PhRMA)

[6]The top 10 pharmaceuticals based on revenues (http://www.contractpharma.com/articles/2007/07/2007-top-20-pharmaceutical-companies-report) are: Pfizer, GlaxoSmithKline, Sanofi-Aventis, AstraZeneca, Novartis, Merck, Johnson & Johnson, Roche, Wyeth, and Eli Lilly and Co. The companies that were taken to trial and successfully convicted are Pfizer, AstraZeneca, Merck, Johnson & Johnson, Wyeth, and Eli Lilly and Co.

and association (e.g., AMA) reports and materials, (3) federal sources (e.g., FDA), and (4) scientific journal articles, books, and editorials. This supplementary evidence is also summarized in Table 24.1.

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Her research in Pharmaceutical Marketing has been focused on understanding individual physician's decision making and how company's Marketing activities could influence those decisions. Her projects have studied individual-level targeting, cross-category effects of Marketing activities, effects of sampling, physician learning process, as well as comparative detailing visits. Her studies have been published at *Journal of Marketing Research*, *Quantitative Marketing and Economics*, and *Marketing Letters*.

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He has co-edited the books, Handbooks in Operations Research and Management Science: Marketing (with G. L. Lilien) and Managing Business Interfaces: Marketing, Engineering, and Manufacturing Perspectives (with Amiya K. Chakravarty). Professor Eliashberg has held various editorial positions in leading professional journals including: the Marketing Departmental Editor in Management Science, an Editorial Board member for Marketing Science, the European Journal of Operational Research, Marketing Letter, and Senior Editor for Manufacturing and Service Operations Management. He is currently the Series Editor of Springer's International Series in Quantitative Marketing and the Editor-in-Chief of Foundations and Trends in Marketing. He was elected a Fellow of the INFORMS Society for Marketing Science for his contributions to the field in June 2010. His other professional services have included membership on the advisory boards of the National Science Foundation, the American Councils for International Education, and the academic liaison committee of the CMO Council.

Professor Eliashberg has been teaching the following courses at Wharton: Marketing Research; Models for Marketing Strategy; New Product Management; Design, Manufacturing, and Marketing Integration; and Analysis of the Media and Entertainment Industries. Prior to joining academia, he was employed for a number of years as an electronic engineer and marketing. He has participated extensively in various executive education programs. His executive education and consulting activities include AccentHealth, AstraZeneca, AT&T, Booz, Allen & Hamilton, Bell Atlantic, Campbell Soup, Cheil Communications, CTV Television Network (Canada), Domino's Pizza, Franklin Mint, General Motors, Givaudan, HBO, IBM, Independence Blue Cross, Inmar, Janssen Pharmaceutica Inc., Johnson & Johnson, L G Electronics, Lucent Technologies, Multimedia Development Corp. (Malaysia), Pathe Cinema (Holland), Philip Morris, Pfizer, The Siam Cement Group (Thailand), Sirius Satellite Radio, Warner Home Video, Weave Innovations Inc., Woodside Travel Trust, and Wyeth Pharmaceuticals.

Marc Fischer (Ph.D., University of Mannheim) holds the Chair for Marketing and Market Research at the University of Cologne. He has been working with pharmaceutical companies for almost 20 years. His expertise includes the measurement and management of marketing performance, brand management, and the optimization of the marketing mix. His articles have appeared in *Journal of Marketing Research*, *Marketing Science*, *Quantitative Marketing and Economics*, *Interfaces*, and other academic journals. He won the 2009–2010 ISMS-MSI Practice Prize with a work on optimizing the allocation of marketing expenditures at Bayer. He was finalist for the 2010 Franz Edelman Award competition on achievements in operations research.

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As a member of the Merck Millipore Technology Council and the Innovation Steering Committee of the Merck Group, Michael Gerards looks back on 20 years of experience in R&D, innovation, and business development. He was responsible for strategic projects in the specialty chemicals business, for instance, on the field of renewable energy, printable electronics, and nanotechnology R&D cooperation in Asia.

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Rama K. Jayanti is Professor of Marketing at Cleveland State University and is a Fulbright Scholar scheduled to teach and research at Indian Institute of Management, Bangalore, in India during spring of 2013. Her research focuses on pharmaceutical marketing, sustainability, consumer learning in online communities, customer satisfaction, and advertising opportunities in networked communities. Her research has been published in Journal of Consumer Research, Journal of the Academy of Marketing Science, Journal of Advertising Research, and Journal of Public Policy & Marketing. Her recent research on virtual health communities was featured in Crain's Cleveland Business and in Medill's News of Chicago (A newsletter of Medill's School of Medicine, Northwestern University). She has received the prestigious McGraw Hill Steven J. Shaw Best Paper Award at the Society for Marketing Advances Conference in 2006. Dr. Jayanti serves on the Editorial Review Board of Journal of Advertising Research, Journal of Services Marketing, Journal of Marketing Theory and Practice and is an ad hoc reviewer for Journal of Consumer Psychology and Journal of the Academy of Marketing Science. Dr. Jayanti teaches doctoral, MBA, and undergraduate courses in Consumer Psychology, Marketing Strategy, Sustainability, and Advertising and Promotion Management. She is actively involved with several non-profit groups such as Playhouse Square and Habitat for Humanity and is an ardent champion of sustainability initiatives at the business college and the university.

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Specializing in advertising, diffusion of new products, and pharmaceutical marketing, Ceren develops new models and methods to improve managerial decisions and marketing applications in practice, by helping managers better understand how marketing affects performance. Her work in the pharmaceutical industry encompasses several critical areas including understanding the impact of governmental regulations on strategic planning and effectiveness of DTC advertising, diffusion of highly anticipated blockbuster drugs, the role of physician and patient-directed advertising on the adoption of prescription pharmaceuticals. In addition to pharmaceutical marketing, Ceren works on the design and evaluation of integrated marketing communications campaigns, media selection and scheduling, marketing budgeting, and development of advertising creative strategies.

Ceren's work has been published in prestigious journals such as Journal of Marketing Research and International Journal of Research in Marketing. She has presented her research at UC Davis, Northwestern University, Erasmus University, Tilburg University, as well as national and international conferences in Australia, Belgium, the USA, the Netherlands, Germany, and Turkey.

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He has taught undergraduate, M.B.A., Ph.D., and executive-level courses in Marketing Management, Marketing Research Consumer Behavior, and International Marketing.

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He has authored or coauthored 20 books including "Mathematical Models in Marketing" (Stenfert Kroese, Leiden, 1974) with Philippe A. Naert, "Building implementable Marketing Models" (Martinus Nijhoff, The Hague/Boston, 1987) and with Dick Wittink, Michel Wedel, and Philippe Naert "Building Models for Marketing Decisions" (2000).

Other examples of his published work can be found, inter alia, in *Applied Economics*, *The Journal of Marketing*, *The Journal of Marketing Research*, *The International Journal of Research in Marketing*, *Management Science*, *Marketing Science*, *Quantitative Marketing and Economics*, *The Journal of Economic Psychology*, *The International Journal of Forecasting and the Journal of Econometrics*.

In 1978–1979 he was President and from 1981to1990 Vice-President of the European Marketing Academy.

In 1990 and 2003 he was Visiting Professor of Marketing at the University of California at Los Angeles (Anderson Graduate School of Management). He has also taught Ph.D. courses in Alicante, Helsinki, Vienna, Innsbruck, and St. Gallen.

In 1999 he became a member of the Royal Netherlands Academy of Arts and Sciences.

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Talya Miron-Shatz is the founding director of the Center for Medical Decision Making, Ono Academic College, and CEO of CureMyWay, a start-up company that combines patient decision making with digital health.

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He holds a Doctorate of Pharmacy from Lyon University, France, a Masters in Business Law from the Lyon Law School, and a MBA from ESSEC, France. He is also an alumnus of INSEAD, IMD, and MCE executive programs.

Pierre Morgon has over 25 years of experience with blockbuster products in diverse markets (primary care, specialty care, hospital, vaccines, and biotechnology), geographies (US, Europe, Japan, China, India, Emerging Markets), and organizations.

His experiences include marketing and operations positions at ICI-Pharma as Product Manager, then at Synthelabo (a division of L'Oreal) as International Group Product Manager and International Marketing Director, and then at Aventis Pasteur as Vice President Marketing. Then he has been leading operations in diversified contexts, first at Yamanouchi Pharma France as General Manager, at BMS France as Vice President, Hospital Operations, at Schering-Plough as Director of the Primary Care business unit in France, and at BioAlliance Pharma as Chief Operating Officer and Member of the Management Board.

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Elina Petrova, Assistant Professor at Washington State University, conducts research on innovation and entrepreneurship, marketing of prescription and nonprescription drugs, and household purchase behavior. She has a Ph.D. in Industrial Administration (Marketing) from Carnegie Mellon University, a Master's degree in Interdisciplinary Mathematics from the University of Warwick, UK, and a Master's degree in Electronic Engineering from the Technical University in Sofia, Bulgaria. She has also spent 4 years as a manager of two small international companies, getting the experience and the inside perspective of complex business decision-making from the trenches.

Her multi-track background and avid interests in technology and business alike, along with her training in both exact and applied sciences, motivate her to do research on issues spanning diverse knowledge domains. Her papers on consumer learning and valuation of OTC drugs and on promotion of prescription drugs, published in *Marketing Science* and *Journal of Marketing*, were among the first in their respective areas. This work, combined with Dr. Petrova's current focus on innovation, prompted her to focus her review for this volume on the complex and multifaceted process of drug discovery and development. In her chapter on innovation in the pharmaceutical industry she presents a systematic overview of the existing knowledge on this topic from a business and academic perspective.

Innovation in the pharmaceutical industry is intrinsically linked to scientific breakthroughs, cutting edge technology, painstaking research, and evolving organizational modes. Discovering and developing new drugs is a rather unique process: rooted in complex inter-organizational arrangements and codependencies, heavily influenced by externalities, and operating under stringent regulations. Yet, as a research area it remains relatively underexplored despite its vast practical importance. Integrating analytical frameworks and research methodologies from various business disciplines can assist in identifying systematic dependencies and key patterns of impact. Modeling the interplay between rather involved strategic decisions and firm performance can lead to more profound and holistic understanding of the complex mechanisms related to innovation in the pharmaceutical industry. Future research in this domain would not only provide for a fascinating array of interdisciplinary work but may also pinpoint new pathways for optimization of the innovation process that are applicable to other industries, too.

Priya Raghubir joined New York University Stern School of Business as a Professor of Marketing and Mary C. Jacoby Faculty Fellow in July 2008.

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Professor Raghubir's teaching interests are in the areas of marketing research, consumer behavior, and marketing strategy, and her research interests are in the areas of consumer psychology, including survey methods, psychological aspects of prices and money; risk perceptions; and visual information processing. She has published more than 40 articles in such journals as the *Journal of Marketing Research*, *Journal of Consumer Research*, *Journal of Consumer Psychology*, and *Marketing Science*. She is on the editorial boards of six journals, and has delivered more than 100 presentations of her research at major universities, symposia, and conferences around the world.

Additionally, Professor Raghubir has consulted with Acufocus, Adobe, BioRad, Boston Scientific, Daimler-Chrysler, Google, PayCycle, University of California at San Francisco, and the Centre for Executive Development at the Haas School of Business. She has also worked in the financial industry with Jardine Fleming and Citibank in Hong Kong and India.

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Her research interests include innovation diffusion models, marketing variables, pharma marketing, and educational innovation. Her research has appeared in such journals as *European Journal of Innovation Management*, *Higher Education*, Journal für Betriebswirtschaft and *Marketing ZFP-Journal of Research and Management*.

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Shankar has consulting or executive training experience with organizations such as Allstate, Cap Gemini Ernst & Young, Colgate Palmolive, GlaxoSmithKline, Hewlett Packard, HSBC, IBM, Intel, Lockheed Martin, Lucent Technologies, Marriott International, Medtronic, Northrop Grumman, PepsiCo, Philips, and Volvo. He has made several appearances on CNN, C-SPAN, and Voice of America. He has been on many advisory boards, including IBM's e-Business Conference Advisory Committee, European e-Business Center, ESSEC, France, and Ingenium Corporation. He has served as an expert witness in legal cases.

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His work in the field of industrial statistics has been published in, amongst others, the Journal of Chemometrics and Quality and Reliability Engineering International. His publications in marketing include articles in Journal of Marketing, Journal of Marketing Research, International Journal of Research in Marketing, Journal of Product Innovation Management, Marketing Letters, Applied Economics, Journal of Service Research, and International Journal of Forecasting. The main focus of his current research is on pharmaceutical marketing, marketing model building, time series analysis, diffusion modeling, marketing analytics, and statistical quality control. He is particularly interested in modeling dynamic phenomena in the pharmaceutical market.

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