Chapter 6
A Look to the Environment and the Impact on OPEX

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The objective of this chapter is to provide an overview about some of the driving forces on OPEX in the pharmaceutical environment. We separately look at two different perspectives:

1. *The business environment for pharmaceutical companies, and*
2. *The global dimension of today's business including the so called pharma-emerging markets*

Based on these perspectives we will derive the impact of the current developments on pharmaceutical production and pharmaceutical OPEX. We will come back to this in Part 4 of this book dealing with the future of pharmaceutical production.

The General Business Environment

With a glimpse to global stock markets, the pharmaceutical industry has performed poorly compared to other industries over the last 10 years.[1] Positive influencing factors like the strong growth in emerging markets (see Fig. 6.1), the aging population and influenza pandemics seem to be counterbalanced by other factors like increasing competition, the global financial and debt crisis, the patent cliff, an increasing complexity and a declining R&D productivity.[2]

[1] Cf. KPMG (2011), p. 2

[2] Cf. KPMG (2011), p. 2

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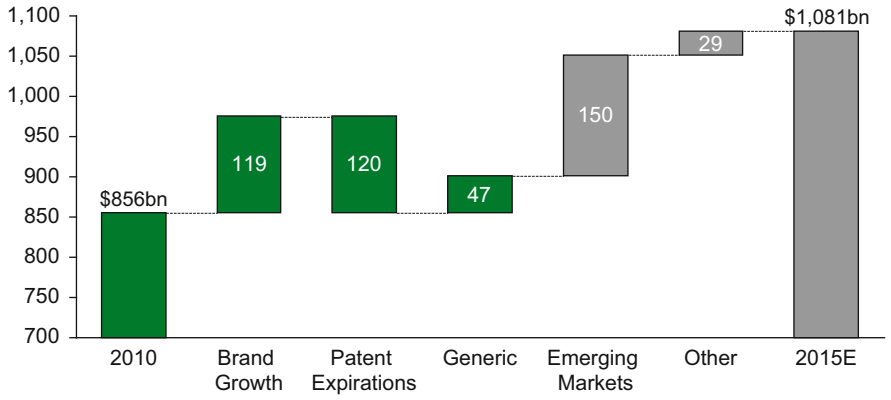

Fig. 6.1 Emerging markets are the key drivers of total spending (cf. KPMG (2011), p. 3)

We will describe some of these factors more detailed in the following parts and will derive the impact on OPEX and manufacturing at the end of this chapter.

R&D Productivity

In recent years, R&D productivity in the pharmaceutical industry has been widely discussed. There is no doubt that not only the long-term success and survival of a multitude of pharmaceutical companies, whether they are research driven or generics, depend on the output of their pipeline, but the future wealth of the entire mankind is also dependent on how successful these pharmaceutical companies are in developing new therapies for the unmet diseases and medical conditions.

Since 1950, FDA has approved about 1,350 New Molecular Entities (NMEs) (Munos 2009; EvaluatePharma 2012; FDA 2013). Of the more than 4,300 companies that are involved in drug innovation, only 6 % have registered at least one NME ever since. More than 150 companies that have delivered in total more than 600 NMEs have already disappeared from the pharmaceutical landscape, mostly through M&A activities (Munos 2009).

Productivity is typically measured as the ratio of output versus input. This, however, makes the measurement of the pure number of New Molecular Entities (NME) – although it is obviously easy to count – an imperfect measure of R&D productivity, as the mere number does not reflect changes in an increased output quality (Pammolli et al. 2011). Both input and output of the research process are influenced by various factors. The research and innovation processes lasting for several years, are determined by substantial knowledge spillovers, multiple, heterogeneous sources, and drain of knowledge due to employee turnover. Globally dispersed R&D of private and public organizations and numerous research

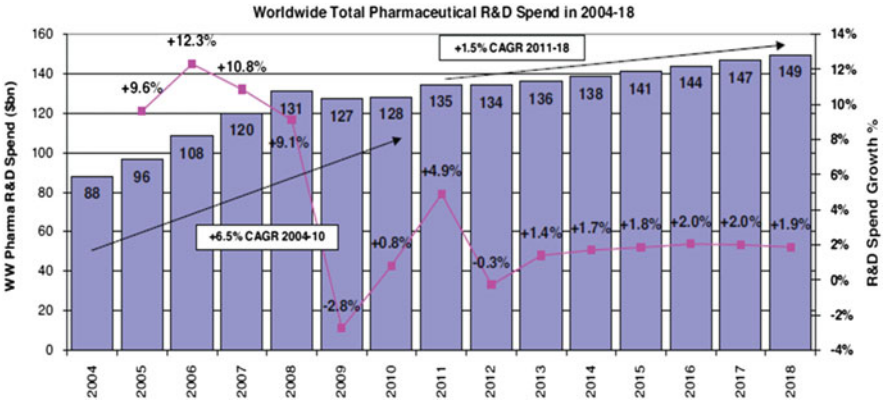

Fig. 6.2 Worldwide total pharmaceutical spend (EvaluatePharma 2012)

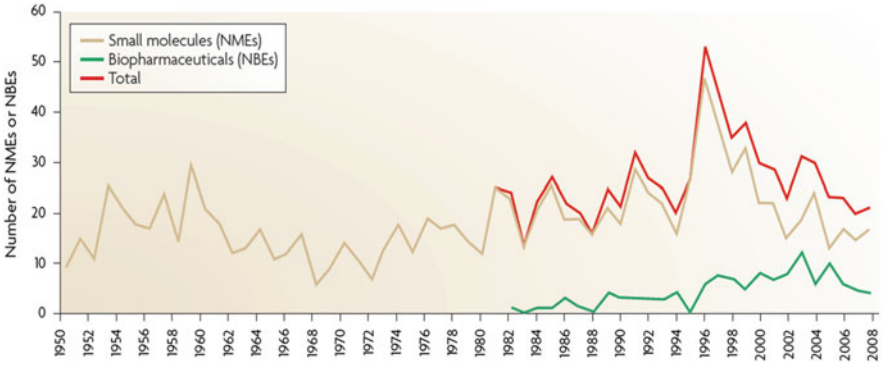

Fig. 6.3 Timeline of approvals of new molecular entities (NMEs) and new biological entities (NBEs) by the US food and drug administration (FDA) between 1950 and 2008 (Source: Munos 2009)

collaborations exacerbate a correct measurement of R&D productivity (Orsenigo et al. 2001; Owen-Smith et al. 2002; Pammolli et al. 2011).

However, it is widely acknowledged that R&D productivity in the pharmaceutical industry seems to be decreasing for the last couple of years (Paul et al. 2010). Although R&D investments have increased significantly during the years (see Fig. 6.2), the industry lacks an appropriate growth in its final output (see Fig. 6.3), the approval of new drugs as therapeutic innovations (Pammolli et al. 2011). Thus, one can arrive at a conclusion that therapeutic innovation in the pharmaceutical industry has become increasingly challenging. And, not to mince words, without an increase in productivity, the industry's survival and growth prospects are at an indisputable risk (Paul et al. 2010).

Several reasons for a declining R&D productivity can be found listed by practitioners and scientists. A growing complexity in science, pressures on pricing,

market access and tougher competition, as well as the hurdles on unmet needs, tighter regulation (Tollman et al. 2011) and market consolidation due to continuing M&A activities (LaMattina 2011) are some of those determining factors. R&D managers with sometimes inadequate leadership training, insufficient scientific medical expertise or even no profound experience in R&D, partially tend to over-manage or even micro-manage the R&D process, thus contributing to the industry's concerns. Moreover, the short-term goals of business-driven organizations and their sometimes aspirational objectives impede medical opportunism and scientific creativity (Paul et al. 2010). The introduction of new technologies and the continuous improvement of R&D processes have led to higher efficiency levels of certain process steps. Nevertheless, these efforts have not been able to overcome the forces mentioned above (Tollman et al. 2011).

In contrast, countries that maintain even more demanding regulations have promoted the innovativeness and competitiveness of their pharmaceutical sector. Recent studies show that companies operating in countries under the auspices of an exacting regulatory apparatus are more selective in the compounds which they pursue for future development. As such, R&D investment and thereby the emergence of the pharmaceutical industry have been positively simulated by making pharmaceutical research more risky and implementing rigorous regulatory requirements (Munos 2009).

Considering the pure number of truly innovative NMEs, opinions are quite consistent. Some argue that the number of NMEs has been stable for the last 5-6 years but the proportion of true revenue-generating drugs as a percentage of R&D expenditures has decreased significantly (Paul et al. 2010). Others even dramatize the picture distinguishing the past 5 years from the period between 1996 and 2004 when FDA has approved an average of 36 NME per annum (Oliver Wyman 2011). However, considering the historical average of around 31 launches per year since 1950 (see Fig. 6.2), the industry's current performance is not as dramatic as often thought. But we agree that a decline in the average 5th-year sale of nearly 15% between 1996 and 2004 and the period from 2005 till present (Oliver Wyman 2011) put an undeniably hard pressure on the industry. Additionally, the probability of about 21 % that a new drug will once achieve a blockbuster status has not changed for the last 20 years. This, unfortunately, does not apply for the investment in order to maintain such a formidable success rate (Munos 2009). As such, some clearly state that the pharmaceutical industry needs a significant increase in its R&D productivity in order to compensate the revenue loss due to patent expirations (Paul et al. 2010).

An outlook into pharma's future shows that growth of the global pipeline is currently stagnating. In 2009 the number of research projects from preclinical to Phase III had reached its peak with a total of 7,709 compounds, excluding biosimilars and reformulations, and shrunk down to 7,408 since (Berggren et al. 2012). The pipeline for preclinical compounds declined by 11 % between 2009 and 2011; in the same period also the pipeline for Phase I and II projects has shrunk. In contrast, the number of late-stage Phase III compounds has a yearly average growth rate of almost 9 % since 2009. Despite this observed slowdown, the status of the pipeline is promising. Currently it is still larger than it was during the

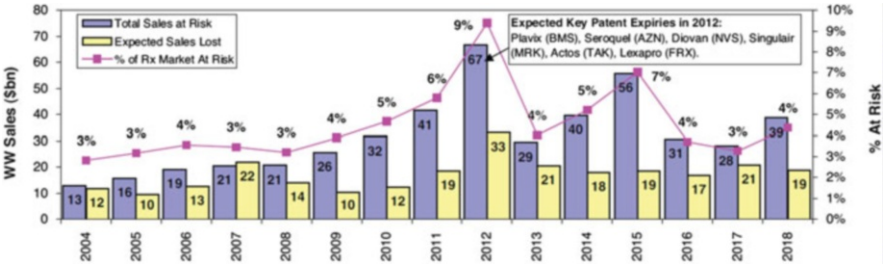

Fig. 6.4 Worldwide sales at risk from patent expiration (EvaluatePharma 2012)[3]

previous 5 years to 2011 (Berggren et al. 2012) when it brought nearly 31 NMEs per year to market (EvaluatePharma 2012). On an even optimistic assumption based on a stable success rate of 8.3 % from Phase I to launch, Berggren et al. (2012) estimate an average output of the pharmaceutical research pipeline of 35 launches per year until 2016.

The Patent Cliff

Beginning in 2010, the pharmaceutical industry has faced a historical high wave in drug patent expiration. This phenomenon is widely known as the "patent cliff" (DeRuiter and Holston 2012). With a significant number of top-selling drugs, like Pfizer's Lipitor® to treat and lower blood cholesterol, Bristol-Myers Squibb's Plavix® preventing platelets from coagulating, GlaxoSmithKline's Advair® for a treatment of asthma patients, or AstraZeneca's drug to treat schizophrenia and symptoms of bipolar disorder, Seroquel®, big pharma has experienced painful patent expirations, paving the way for their lower-priced generic substitutes. As such, the patent cliff is the result and aggregation of several successful products that have reached the end of their patent life and hence put substantial sales at risk (Fig. 6.4). The industry's tumble from the expiry of lots of patents is even intensified by the continued global economic crisis, which has health care payers in advanced countries in a state of disarray (Mullin 2012). It is noteworthy that the cliff that peaked in 2012 was mainly caused by drugs that have been discovered in the late 1980s (EvaluatePharma 2012). This, however, provided the concerned organizations with plenty of time to prepare them for the approaching sales drop. As eventually most pharmaceutical companies face similar situations, the industry put substantial effort in finding appropriate solutions to cope with these challenges

[3] (Patent analysis: 'Total Sales at Risk' represents the worldwide product sales in the year prior to patent expiry but allocated to the year of expiry. E.g. Plavix had sales of $7.1bn in 2011, this is shown above as 'At Risk' in 2012 (EvaluatePharma 2012)).

PROTECTION EXPIRY YEAR	US		JAPAN	UK	FRANCE	GERMANY
2012	Plavix® Seroquel® Singulair® Actos® Lexapro®	Diovan® Diovan HCT® Geodon® Boniva®	Nu Lotan Myslee® Preminent Haigou Seroquel®	Lipitor® Amias Seroquel® Aricept® Singulair®	Tahor Singulair® Pariet® Ixprim Aprovel	Seroquel® Atacand® Atacand® Plus Sortis® Aricept®
2013	Oxycontin® Aciphex® Zometa®	Xeloda® Opana®ER Asacol®	Diovan® Plavix® Livalo® Elplat®	Viagra® Xeloda®	Seretide® Coaprovel Xeloda® Micardis® Viagra®	Viani® Zometa® Atmadisc® Coaprovel Viagra®
2014	Nexium® Cymbalta® Celebrex® Symbicort®	Lunesta® Restasis® Evista® Sandostatin® LAR Actonel®	Prograf® Glivec® Abilify®	Abilify® Cipralex® Risperdal® Consta®	Seroplex® Abilify® Ebixa® Risperdal® Consta® LP	Axura Risperdal® Consta® Blopress Plus®
2015	Abilify® Copaxone® Gleevec® Namenda®	Provigil® Combivent® Zyvox® Prezista® Avodart®	Zyprexa® Adoair® Alimta® Spiriva® Symbicort®	Spiriva® Cymbalta® Alimta®	Alimta® Spiriva® Copaxone® Protelos® Cymbalta®	Spiriva® Copaxone® Alimta® Cymbalta®
2016	Crestor® Benicar® Benicar HCT® Cubicin®		Blopress Baraclude®	Glivec® Vfend®	Glivec® Cancidas® Vfend®	Glivec® Zyvoxid Vfend®

Fig. 6.5 Major protection expiries by country and year (Source: IMS 2012)

and to mitigate expected losses (Mullin 2012). Unfortunately, pharmaceutical companies do not yet have a good model at hand to get through such transitions (Jimenez 2012).

Due to substantial patent expiration, the pharmaceutical industry is losing its financial cushion (Fig. 6.5). Since 2006, patent expiry cost the industry an estimated $60 billion in sales. Even more, by 2015, market prognosis project this figure to raise up to $160 billion (Bloom 2012), with its heaviest burden in 2012 and 2013 (Jimenez 2012).

However, the patent cliff is mostly associated with research driven pharmaceutical manufacturers, expiry of their patents and the subsequent loss of sales. Especially for the reason that shortly after the generic substitutes have been launched, prices decline by an average of 40 % and lead in some cases to drastic reduction in sales of nearly 80 % (Denoon and Vollebregt 2010, see also Grabowski and Vernon 1992; Hemphill and Sampat 2011). Actually, in the short term, generic manufacturers will benefit from the patent cliff, as they rapidly acquire market share once branded products lose their IP protection. Starting in 2015, the generic industry is expected to also experience a slowdown in revenue growth as fewer branded blockbuster drugs will be coming off patent (DeRuiter and Holston 2012).

From Fig. 6.4 it is apparent that the pharmaceutical industry is approaching another patent cliff in 2015. With a predicted $33.5 billion sales at risk, this cliff nearly equals that in 2012 (see Table 6.1). However, there are some important differences worth considering. Many of these branded blockbusters that will come off patent are biologic drugs. And with biological drugs, it is expected that sales will not immediately fall of the cliff, unlike the small-molecule blockbusters did back in 2012 (EP Vantage 2013). The basic reason for this is that biosimilars, in contrast to generic small molecule drugs, may differ substantially from their original counterpart and therefore may require costly and long-lasting approval procedures (Frey et al. 2009).

Table 6.1 Top products going off-patent in 2015 (EP Vantage 2013)

Rank	Product	Company	US annual sales ($m) in 2014 (year before patent expiry)
1	Lantus	Sanofi	4,791
2	Abilify	Otsuka Holdings	3,876
3	Rituxan	Roche	3,610
4	Neulasta	Amgen	3,441
5	Copaxone	Teva Pharmaceutical Industries	2,678
6	Gleevec	Novartis	2,002
7	Namenda	Forest Laboratories	1,575
8	Lovaza	GlaxoSmithKline	882
9	Treanda	Teva Pharmaceutical Industries	746
10	Combivent	Boehringer Ingelheim	694
Other			9,320
Total			33,524

The End of the Blockbuster Era

For pharmaceutical companies nothing is quite as exciting as having a promising new molecule in their pipeline that – in the best case – targets some major unmet human health problem (Booz&Co 2012). In the past decades, the pharmaceutical industry continuously adapted its business model towards the development of *the* single drug that solves a common medical problem of tens of millions of people. Relying upon those annual blockbusters to drive a company's profits, the pharmaceutical industry applied this "one size fits all" approach ignoring a patient's unique biology (Jørgensen 2008). The model at present is based on high uncertainties as well as highly skewed distributions of revenue and profit; and shows several similarities with the production of cultural products like movies and their instability of profits (Collier 2011; Hannigan et al. 2013).

In 1987, Glaxo's Zantac® was the first global drug surpassing US$1 billion in annual sales (Rickwood 2012) introducing a new era in pharmaceutical history: the era of blockbusters. A decade later, six blockbuster drugs accounted for 12 % of annual sales in the United States (Aitken et al. 2009), the by far biggest pharmaceutical market at that time. In the following years, the number of blockbusters increased to 51 in 2001, contributing some 25 % to global sales and jumped to 116 blockbuster drugs since, providing 36 % of the global pharmaceutical market's value (Rickwood 2012). However, when the term "blockbuster" was coined in the late 1980s, a drug having that status accounted for about 0.74 % of the global annual pharmaceutical market (see Fig. 6.6). Due to inflation and overall market growth which nowadays provides products an increased number of opportunities for generating sales and to reach this former elite level of US$ 1 billion, the value of a drug that has reached the blockbuster status has significantly diminished by nearly 85–0.12 % of global market value (Rickwood 2012).

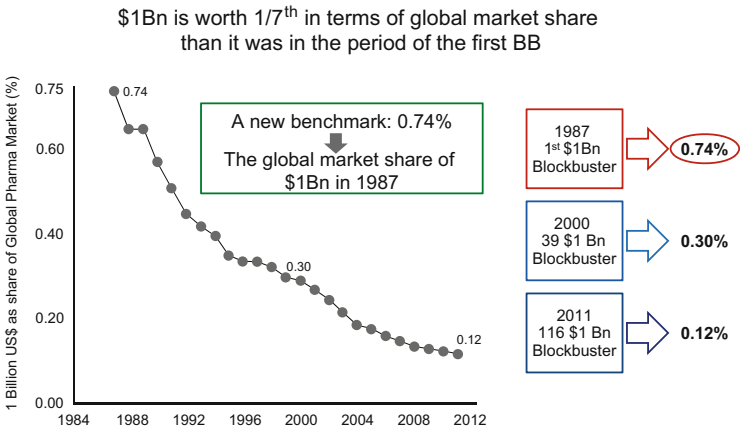

Fig. 6.6 The total value of a blockbuster 1987–2011

Furthermore, since their first emergence, the characteristics and identity of blockbusters have changed. Originally and predominantly applied in primary care, during the past decade the blockbuster model has shifted toward specialty therapies (Aitken et al. 2009; Rickwood 2012; Oliver Wyman 2011). According to Rickwood (2012) in 2002, 70 % of those drugs, traditionally defined as blockbusters were assigned to the group of primary care products. Five years later, the proportion of global drug spending that incurred for primary care drugs has diminished to 55 %. Thereof, 22 % amounted for the five top-selling therapeutic classes which comprised acid pump inhibitors, antidepressants, oral antidiabetics, lipid regulators, and respiratory agents. In contrast, specialist drug therapeutic classes like anti-epileptics, antipsychotics, autoimmune agents, erythropoetins, oncologics, etc. already accounted for 45 % of global drug spending (Aitken et al. 2009). Recently in 2011, the drug distribution was inversely rated with only 44 % of all blockbusters being primary care drugs (Rickwood 2012).

Along with the shift from primary care to specialist drugs a change of pharmaceutical companies' business model seems to be apparent. Several augur the end of the blockbuster era (Hill and Chui 2009; Collier 2011; Thomas Reuters 2011; Cooksey and Buffery 2012) and question, if pharma companies can actually survive, if they pursue their current business model without adaptations (Booz&Co 2012). Thus, following Porter's (1998) generic strategies, many pharmaceutical manufacturers are currently changing their focus from the once dominating mass markets toward smaller, vacant niche markets (Collier 2011). This becomes evident with the latest trends in orphan drugs (Sharma et al. 2010; Unknown 2010; Thomas Reuters 2011) and personalized medicine (Jørgensen 2008; Bates 2010). In accordance with such growing diversity and manifold demand in specialized medicine, traditional blockbusters are not exclusively reserved for the mass markets, but also drugs targeting at smaller patient populations start increasingly to exceed the billion dollar hurdle (Rickwood 2012). This is in line with Jeff Kindler's (former CEO of

Pfizer) statement "[...] we're changing the way we do business [...] we are still pursuing blockbusters, but we are also focusing on addressing many specialized needs of many smaller groups of people" (Kindler 2010).

The Debt Crises and Healthcare System Cost Reduction Programs

Unlike automotive, construction, semiconductor or machinery, the pharmaceutical industry is hardly marked by cyclic fluctuations. With the beginning of the financial crisis in 2008 – emanating from the United States and Europe – several thought that a non-cyclic industry as pharmaceuticals was immune to turmoil and recession, but the global economic crisis and the following downturn disabused them fast (Pharma 2012). In fact, although several countries were hit severely by the economic crisis, only a few of these suffered a considerable decline in pharmaceutical consumption. On a regional consideration, between beginning of 2008 and the end of 2009 South East Asia's consumption increased by nearly +28 %, the American region grew by some +12 % – only Europe had to recover from a −3 % decline, reached in the third quarter of 2009, to a marginal +2 % gain of pharmaceutical consumption by the end of 2009 (Buysse 2010). Recent investigations of the IMS Institute for Healthcare Informatics report a drop of the nominal US drug spending by 1 % in 2012 to US$ 325.8 billion (IMS 2013).

As a reaction of the global downturn, the subsequent sovereign debt issues, and reduced government budgets, beginning in 2010, many European countries imposed a multitude of cost-containment measures (Miller 2011; Vogler et al. 2011; Coker 2012). Besides, since that time, all countries appear to be permanently optimizing their pharmaceutical system (Vogler et al. 2011). The most commonly applied cost-containment were price reductions of pharmaceutical products (Vogler et al. 2011; Coker 2012), followed by changes in copayments, which most of the time led to increasing costs for patients to compensate lower reimbursement rates, adaptions of reference pricing systems, and policy changes that affected reimbursement procedures (Vogler et al. 2011). Moreover, several already weakened economies that suffered low demand, little tax revenues as well as high unemployment, were hit twice by initiated government austerity programs and reserved bank lending. Reduced government spending, higher interest rates, and difficulties in private-sector credits negatively affect those countries' overall economic activity (Miller 2011).

Pharmaceutical companies, heavily relying on the European market had to manage considerable effects on their financial performance due to pressures from the European deficit-led pricing as well as from above mentioned influences (Coker 2012). This, however, involved pharmaceutical companies of all business types. Tighter budgets at research driven companies led to reduced spending in R&D, putting depleting pipelines under additional pressure and forcing R&D leaders to

continuously justifying their investments (Deloitte 2011). Furthermore, the rising cost pressure in the health care industry induces governments to allow an earlier generic entry (Jimenez 2012). Pharmaceutical contract manufacturing organizations (CMOs) that supply the European market – which is dominated by national healthcare systems as the primary buyer and distributor of pharmaceutical products – have to put up with the deterioration of their operational performance as volume and price reduction evoke a sharp decline of drug expenditures (Miller 2011).

The Increased Competition

Macroeconomic and regulatory changes determine the competitive and operational environment of pharmaceutical manufacturers and their managers' tactical and strategic decisions (Rossetti et al. 2010). Prior to 1984, the pharmaceutical industry was dominated by research driven companies that barely felt the competition from generic product imitations. This came from costly requirements set by the Food and Drug Administration (FDA) that had to be met by generic drugs these days (Grabowski and Vernon 1992). Since September 1984 the Hatch-Waxman Act (formally known as Drug Price Competition and Patent Term Restoration Act) regulates the entry of generic drugs in the US, the world's largest pharma market (Grabowski and Kyle 2007). Most significantly, with the law becoming effective, an abbreviated process (Abbreviated New Drug Application (ANDA)) has been introduced to shorten the time for generic drugs to receive FDA approval. The law enables generic manufacturers to legally conduct the necessary tests of bioequivalence and to apply for FDA approval before the respective patent expiration (Frank 2007). Under certain circumstances, FDA approves a 180-day exclusive right for the first generic manufacturer that has filed an entitled ANDA. This exclusivity allows a generic manufacturer to compete solely with the patent owner before other generic competitors enter the market (Hemphill and Sampat 2011). Today those patent challenges occur increasingly earlier in a branded drug's life cycle than before (Grabowski and Kyle 2007). In the European market, generic drugs are often favored by government drug policy and as such their prescription is encouraged or has even become mandatory not to overtax drug budgets (Kanavos et al. 2008).

This said, it is quite obvious why Grabowski and Vernon (1992) could not provide evidence for any significant entry barriers into the generic market that has seen an explosive growth, from a market share of hardly 20 % in the mid-1980s, to about 70 % today (Frank 2007; Kanavos et al. 2008; Engelberg et al. 2009; Hemphill and Sampat 2011) and experienced intensified competition since (Saha et al. 2006; Grabowski and Kyle 2007). This fierce competition also unfolds to the biotech sector whose low entry barriers and companies with normally only a few products in the pipeline are considerably vulnerable towards competitors (Guo et al. 2004).

As mentioned earlier, such fierce price competition from generic substitutes and the effect of generic market entry constitute a real challenge for branded drugs and curtail the profits that are vital to fund their innovative activity (Frank 2007).

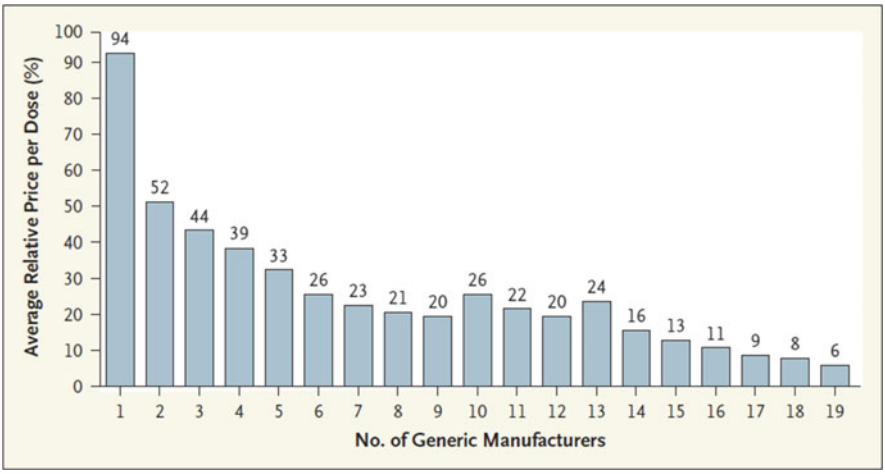

Fig. 6.7 Change in a drug's average relative price as the number of generic substitutes increases (Source: Frank 2007)

Yet generic entry does not only impact the branded drug business but also leads to increased price rivalry among generic companies themselves. The effect on average relative prices of drugs and such initiated fierce competition among generic manufacturer is illustrated in Fig. 6.7.

With the on-going market entry of generic manufacturers, increasing rivalry and competition between branded drug manufacturers and generic manufacturers is sure to ensue as competition shifts from monopoly-like markets towards competition based on price (Epperly 2013). This, in contrast to many other industries, tightens the challenges for research driven manufacturers such as the pharmaceutical industry, where the person who is consuming the product is not necessarily the person choosing and paying for it. In addition, decision making and payment are more complex within the pharmaceutical industry (Guha et al. 2008). In order to mitigate the rivalry from generics, some research driven pharma companies built up their own generic brand products or cooperate with generic manufacturers and thus try to utilize the 6-month exclusivity period by an authorized generic version of their own brand name drug. Besides, brand manufacturers participate in the price competition among others through different kind of promotions e.g. free samples or rebates. The latter often depend on a drug's sales volume that may decrease after generic entry. Guha et al. (2008) argue that volume-dependent reduction of free samples and lower rebates may result in considerable price increases as soon as generics have entered the market. Hence it might displease brand name drug manufactures that brand loyalty is rather low within the industry (MarketLine 2012). Additionally, to make matters worse, the US and European countries try to control cost, making future growth come by harder in the developed markets (Herper 2012).

With the rise of the emerging markets most pharma companies seek to participate at these new engines of pharmaceutical growth. The Agreement on Trade

Related Aspects of Intellectual Property Rights (TRIPS) regulates the protection of intellectual property (IP) at a minimum standard for all WTO members[4] (WTO 2013). Thus, research driven pharmaceutical manufacturers can make use of their patents also in countries apart of the advanced and familiar markets. Unfortunately, as latest events evidenced, TRIPS does not provide a full guarantee for fully granted patent protection in certain markets (Economist 2013). Besides some adventurous IP protection, emerging markets challenge pharmaceutical companies with a lack of reimbursement, deficient healthcare infrastructure, and the affordability of drugs due to a widely spread out-of-the-pocket spending (Bhattacharjya and Sapra 2008; Anderson et al. 2009; Booz&Co 2013). This leaves band name pharma in a state of uncertainty and further, unavoidable competition in markets that a dominated by generic manufacturers (Anderson et al. 2009; Campell and Maag 2010).

The Increasing Complexity

Pharmaceutical companies are more and more exposed to growing complexity. As such, they have to continue to find appropriate ways to handle these most diverse influencing factors. These external drivers of complexity are among the most challenging ones for pharma and are predominately characterized by economic volatility, varying customer behavior, or changes in technologies and the competitor base (Simplicity 2012). The increasing globalization and dynamic environment induce companies to expand and to accelerate their operations (Fockenbrock 2011). Beyond the unpredictable nature of pharmaceutical manufacturing, pharma companies are confronted with a high number and variety of consumption points and market intermediaries along the entire supply chain, thus leaving these organization in a muddle of interdependencies, contingencies, and uncertainties (Goetschalckx et al. 2002; Rossetti et al. 2010). In addition, the latest economic crisis intensified the already existing challenges pharma had to cope with, and brought evidence that flexible and agile companies handle these external shocks better than their sedate competitors (Fockenbrock 2011). With a number of drugs coming off patent and the drying up of steady revenues from blockbusters, many pharmaceutical companies avert from highly standardized products towards customized and low volume specialized solutions.

Only a few pharmaceutical manufactures solely rely on branded drugs. Most companies have expanded into other sectors like generics, biosimilars, diagnostics, consumer health, nutrition, or wellness (Booz&Co 2012). Thus, increasing customer demand for individually adapted products leads to the expansion of pharma's product

[4] WTO members can make use of different periods of time to delay the application of the provisions listed by TRIPS. For developed countries the period ended at 1 January 1996, for developing countries and countries in transition the period ended on 1 January 2000, for least-developed countries with regard to pharmaceutical patents the period will end on 1 January 2016. Country classifications are according to the United Nations (WTO 2013).

ranges. Without transparency of real cost allocation, marketing-fads and highly advertised drugs – often being a worst case scenario for manufacturing – are cross-subsidized by top-selling products and thus weathering revenues. High customer proximity affects a company's entire process of value creation; frequent customer interaction leads by trend to larger product portfolios and an increased complexity. Low similarities within the portfolio impede the utilization of economies of scale and deteriorate organization's efficiency (Friedli and Bellm 2012).

However, blind complexity reduction of e.g. SKUs will most likely not lead to the achieved target (see Chap. 19). Pharmaceutical manufacturers need to evaluate their right degree of complexity by balancing ultimate flexibility versus inability of supply. There are examples in the literature where companies rather preferred to increase their complexity than simplifying it down, while focusing on their core competences. Others however overestimate the added value of mergers and acquisitions and end up drowning in complexity due to poor organizational coordination and strategic misalignment of the newly built organization (Simplicity 2012).

Recent Quality Issues and Drug Shortages

In late 2007, the heparin case shocked the pharmaceutical community, when the contaminated product led to at least 81 deaths and hundreds of serious adverse events in various countries since (Briones 2008). Several established pharma companies had to also recall several batches of drug. Following these recalls, FDA officials traced the supply chain ending up at a Chinese facility that supplied the poor quality heparin active ingredient (Hedlund et al. 2012). As a matter of fact, quality issues have spread in global manufacturing despite the request of Article 2 of the WHO Constitution for setting global standards as to "develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products" (WHO 2007, p. 1).

Unfortunately, the described heparin case, even though it might be the worst one, not the only one of a kind, the pharmaceutical industry suffers from. Actually, there are far too many of these quality lapses within the industry over the past few years that have compromised public health (Eglovitch 2013).

Thus, poor product quality and numerous compliance issues brought the pharmaceutical industry easily additional costs exceeding US$ 700 million in fines since 2001 and billions more due to lost sales (McKinsey 2007). This might result from the pharmaceutical industry's legacy to apply science rather to the discovery of NMEs and rely on inspection of final product quality, than working on scientifically mastered manufacturing processes (see Chap. 29). However, it is quite reasonable that a knowledge-intense industry as pharma has recognized its shortages and trends like transparency in manufacturing and several beneficial business practices became requirements for pharmaceutical companies (Pharmtech 2009). Unfortunately, do not all pharma companies continuously strive for changing to a science-driven approach to pharmaceutical manufacturing; still

Table 6.2 Drug GMP warning letters by category from 2005 to 2012 (Source: Eglovitch 2013)

	FY 05	FY 06	FY 07	FY 08	FY 09	FY 10	FY 11	FY 12
Oral solid		6	2	4	7	16	9	7
API	2		1	3	7	8	17	8
Oral liquid	1	1	1		3	6	4	
Topical	2	1	2	3	4	6	6	6
Miscellaneous	3	4	1		6	5	4	9
Injectable	2	3	6	2	3	4	13	9
Inhalable	2		1					
Repacker	3	1	1	1	2	2		
Testing lab						1		
Veterinary	2	4	2	1	1	1		1
Biologics	1		2	1	1			
Total	18	20	19	15	34	49	53	40

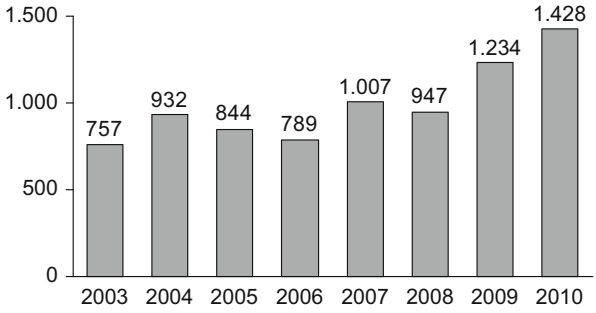

Fig. 6.8 FDA's foreign drug inspection accomplishments (FDA 2011)

too many companies are lacking behind in implementing outstanding practices and seem to hardly feel an imperative for changing their behavior until a significant compliance issue occurs (McKinsey 2007). This reluctance for change is partially reflected in Table 6.2, illustrating the development of drug GMP warning letters issued by FDA.

No doubt, the increase of warning letters sent by FDA is surely influenced by the agency's increasing number of site inspections that are no longer focused on domestic manufacturing facilities only but continuously expanding to foreign locations as illustrated in Fig. 6.8 (Eglovitch 2013).

Yet, more frequent site inspections should not be seen as scapegoats for the industry's shortcomings and an increased submission of warning letters or 483 s in the worst case. Many pharma companies still have to learn the application of latest manufacturing practices and the capability to manufacture quality rather than controlling it. This goes in line with Eglovitch (2013, p. 1) quoting an industry observer that the recent decrease of warning letters by 23 % from 2011 to 2012 is "more of a 'statistical anomaly' than an actual indication of waning enforcement."

Therefore, regulatory agencies like FDA adjusted their focus to no longer simply monitor the outputs of inspected manufacturing sites but also their processes and systems (McKinsey 2007).

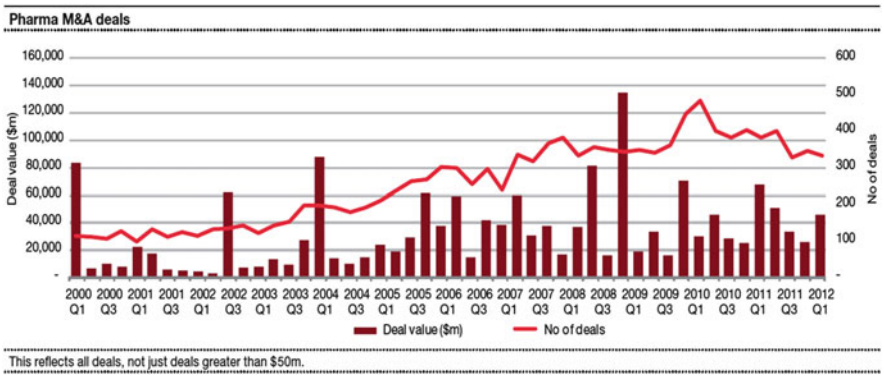

Fig. 6.9 Global M&A deals from 2000 to 2012 (Source: PwC 2012)

As long as the market does not reward quality and e.g. generic competition is predominantly based on prices (Woodcock and Wosinska 2013), it is reasonable that quality problems will continue or even become more frequent especially on a global scale. With the industry's shift to emerging markets, evidence brought by several studies that such problems are more common at pharma's offshore operations (Staton 2011), and the same problems surfacing year after year, it is – unfortunately – apparent that we will see more quality issues if global pharma stays on its current track.

Mergers & Acquisitions

For many years, technology intense industries like the pharmaceutical industry have been characterized by ample merger and acquisition (M&A) activities. Several studies reveal the effects of industry structure and characteristics on M&A deals and document evidence that such deals are driven by industry-wide shocks like deregulation or technological advances (Mitchell and Mulherin (1996); Hall (1999); Andrade et al.(2001); Andrade and Stafford(2004); and Harford (2005)). As a matter of fact, most of today's big pharma companies are the result of at least one major M&A deal (Duflos and Pfister 2007)

In the pharmaceutical industry M&A intensity grew in the mid-1980s strongly influenced by the threat of upcoming patent expirations. Due to a rising competition from generic manufacturers and potential declines in sales, some research-driven pharma companies seek to cut costs by merging their efforts for R&D, manufacturing, marketing etc. (Ramrattan and Szenberg 2006). Others pursue an increase of their product portfolio, access to certain markets or a filling of their pipeline gaps (Duflos and Pfister 2007; Collier 2011; PwC 2012). As Fig. 6.9 depicts the pharmaceutical industry has seen an almost constantly increase in both value and number of M&A deals for the past decade.

However, the rising number of deals that the industry has already witnessed and is still facing, has left its marks. The decline in the total number of big pharma companies has led to an increasingly concentrated market especially among those companies that are considered as the engines of pharmaceutical R&D (LaMattina 2011; Comanor and Scherer 2011; Bruce 2012). And such consolidation does not spare the generic market either (DeArment 2012). In accordance with a shrinking number of research-driven companies, the industry sees fewer parallel research efforts which lead to a reduced rate of pharmaceutical innovation (Comanor and Scherer 2011). With the emergence of few big, and simultaneously the vanishing of plenty of small and agile companies, the danger rises that the industry's pace would slow down due to inert companies and their slow decision-making processes (Bruce 2012). Furthermore, those vertical and horizontal integrations threat to transform the industry into an oligopoly (Gagnon 2013). From a different point of view (McKinsey 2011) argue that rumors about market consolidations are most likely conventional wisdom and that the industry over the years has become even more fragmented and the total number of pharmaceutical companies has more than doubled.

Analyzing the characteristics of M&As over the years, the number of deals targeting on small molecules and biologics has remained relatively unchanged, but their percentage of overall deals has declined from about 40 % in 2007 to some 22 % in 2011. Besides, as depicted in Fig. 6.10, companies of the vaccines sector and generic manufacturers gained importance and increasingly became the target of latest M&A activity. In the same period where veterinary deals declined, big pharma further diversified into sectors like consumer health/OTC and diagnostics looking for synergies with their existing product portfolio (Ignjatovic 2012). With the beginning of 2012 the industry has seen several M&As of Big Pharma heading for biotech companies with promising research focused on oncology (Mullin 2012).

The increasing importance of the fast-growing emerging markets for pharma is depicted in Fig. 6.11. From 2007 to 2011, M&A deals in developed countries have predominately been focused on small molecule and biological branded drugs (36 %). Furthermore, almost 87 % of all deals that targeted on diagnostic or medical device companies comprised manufacturers located in developed countries. In contrast, emerging market deals mainly focused on generic manufacturers (50 %), consumer health (23.3 %), and vaccines (13.3 %) providing evidence for big pharma's continuing global expansion and the recognition of the advantages of involving local partners in emerging market operations (Ignjatovic 2012).

As Big Pharma has not yet recovered from the recent patent cliff and some more blockbusters will come off patent soon (see Fig. 6.4), companies still seek to fill up their pipelines and benefit from latest advances in areas like immunology or oncology (Staton 2013).

However, the question arises, where pharma will go next? The pharmaceutical industry is a relatively young industry compared to e.g. automotive. Considering the number of big automotive OEMs it is a significantly smaller number than Big Pharma currently comprises. Nevertheless, even in automotive some argue there are

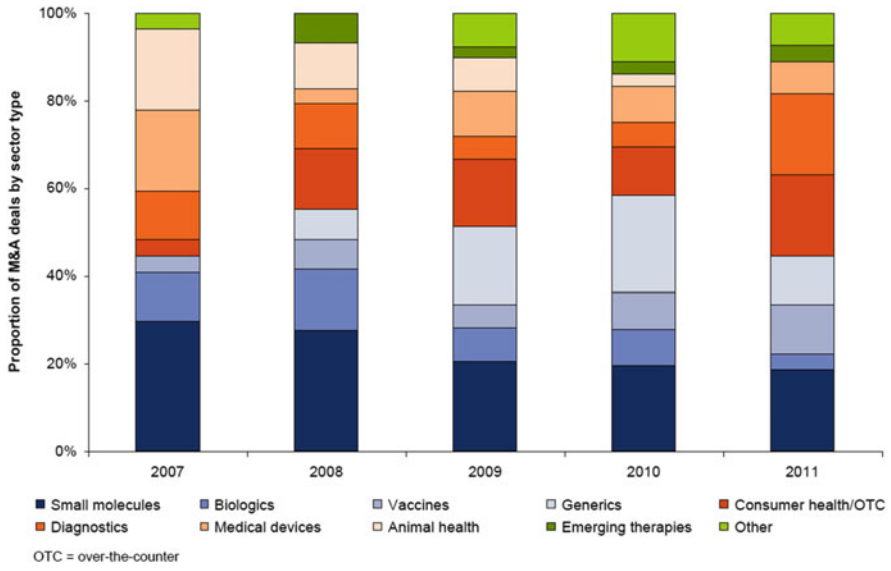

Fig. 6.10 Top 10 pharma companies' M&A deals from 2007 to 2011 by sector (Source: Ignjatovic 2012) (Ignjatovic (2012) considers the top 10 pharma companies as Pfizer, Novartis, Sanofi, Merck & Co., Roche, AstraZeneca, GlaxoSmithKline, Eli Lilly, Johnson & Johnson, and Abbott laboratories)

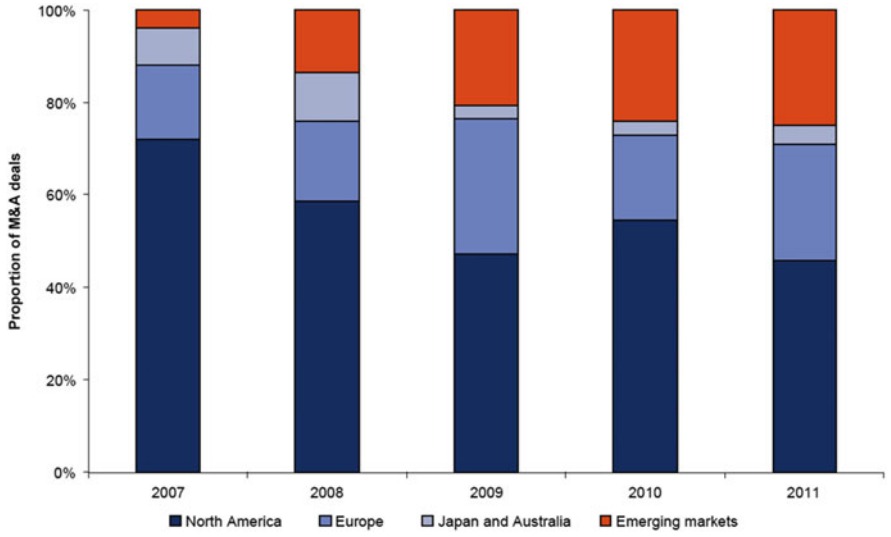

Fig. 6.11 Top 10 pharma companies' M&A deals from 2007 to 2011 by geography (Source: Ignjatovic 2012) (Ignjatovic (2012) considers the top 10 pharma companies as Pfizer, Novartis, Sanofi, Merck & Co., Roche, AstraZeneca, GlaxoSmithKline, Eli Lilly, Johnson & Johnson, and Abbott laboratories)

still too many OEMs in the market and that further consolidation will continue (Roland Berger 2009).

Overcapacities

For some time the pharmaceutical industry suffers sever overcapacity. Several factors that have been discussed in detail above e.g. R&D pipelines running dry, the patent cliff or continuous organizational restructuring to improve operational profits by cutting costs and maximizing productivity contribute to or even worsen pharma's problem. Recent M&A's like Pfizer-Wyeth, Merck-Schering Plough, Roche-Genentech, and the marriage of Sanofi-Aventis and Genzyme have led to a consolidation of the pharmaceutical sector. In addition, larger companies have bought out several mid-sized and small companies or incorporated them into their operations. These activities have resulted in numerous redundant manufacturing facilities and thus led to the industry's overcapacity and exceeding global demand by approximately 40 % (Frost and Sullivan 2009).

Facilities of leading pharmaceutical companies that lack manufacturing flexibility and which are primarily designed for the production of high-volume, high-margin, patent-protected small molecule APIs become obsolete when their original purpose loses patent exclusivity and is subjected to competition from generics overnight (Tse and Jakobs w/o date).

In their desperate search of a margin improvement many leading pharmaceutical companies enter into the CMO business offering their idle manufacturing capacity for other players (Tse and Jakobs w/o date). In order to avoid negative publicity or huge severance costs in case of a facility shut down, multinational pharma companies in the past preferred to transfer their spare facilities to private-equity firms or to management teams that continue to run the sites as CMOs. Although this approach brings relief to brand name manufacturers, it merely shifts the problem. Moreover, it provokes an unsustainable situation for the global CMO industry (Miller 2011) and on a longer term perspective such approach creates an imbalance within the entire pharmaceutical industry (Frost and Sullivan 2009).

The Global Dimension

The Emerging Market Opportunity

Globalization is considered as one of the most critical challenges companies face in their daily operations (Khanna et al. 2005; Burgess and Steenkamp 2006). Even though not new to companies and their managing teams globalization gathered pace especially since the late 1980s and thus intensifying global competition. After the

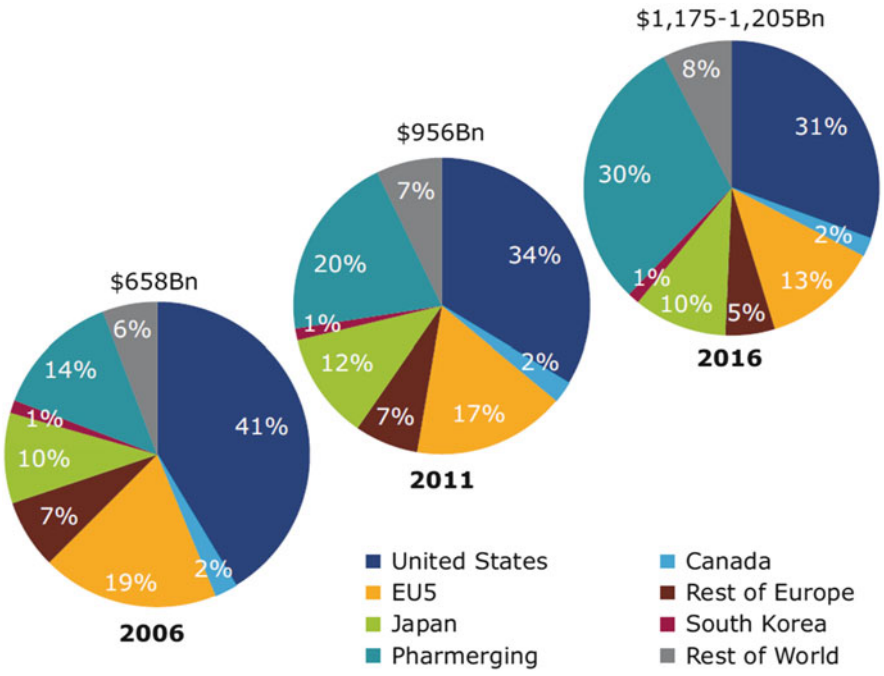

Fig. 6.12 Pharmaceutical spending by geography (Source: IMS 2012)

collapse of the Soviet Union along with other Eastern Asian countries a notable number of the world's population elided from a state-controlled and central planning to a global market economy. The revolution of information technology and the companies' willingness to outsource their operations led to global partnerships and supply chains (Hayes et al. 2005; Yip 2002). Moreover, the establishment of international trade agreements like GATT (1941); WTO (1995) as well as economic pacts like EFTA (1960); ASEAN (1967); Mercosur (1991) and NAFTA (1994) continue to drive the trend of transnational manufacturing (Ferdows 1997; Dangayach and Deshmukh 2001; Mora-Monge et al. 2008) facilitating global sourcing and distribution (Khanna et al. 2010) and spur global competition (Sheth 2011). This is also entails a rapidly changing pharmaceutical landscape on a global scale.

Historically, advanced countries have been the largest market for multinational pharma companies and will continue to do so in the future. However, with the advent of globalization the contribution of emerging markets to pharmaceutical sales will gain significant importance in the next decades (see Figs. 6.12 and 6.13).

As competition in the developed world is considerably high and pressure on prices is expected to continue, manufacturing companies are on the lookout for new sources of low cost labor (Hayes et al. 2005) and access to new markets. By establishing their operations in low labor cost countries like China, Eastern Europe, India, and Latin America (Hayes et al. 2005) by mistake companies often adopt a mind-set of "less developed countries". As such, they expect that these countries

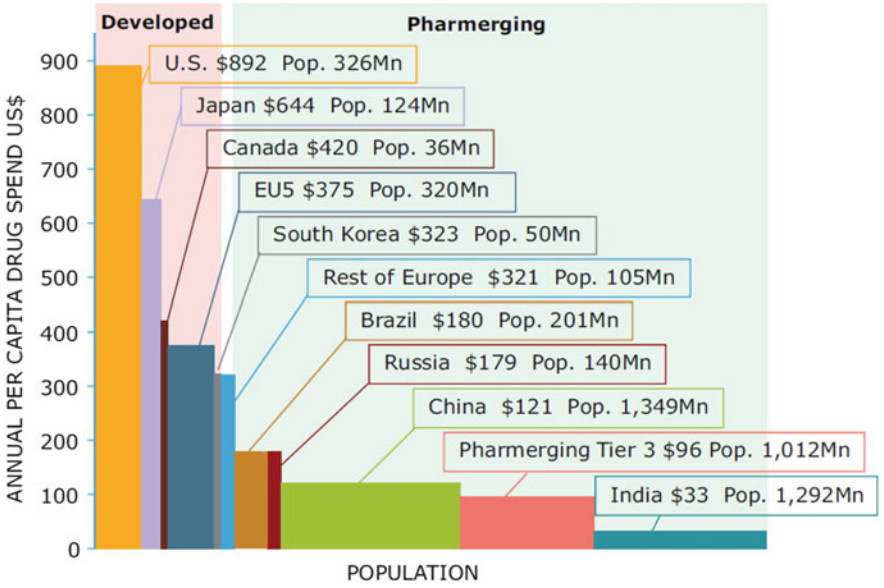

Fig. 6.13 2016 pharmaceutical spend per capita 2005$ and population (Source: IMS 2012)

follow an equal development path as followed by industrialized countries yet at an earlier stage, erroneously assuming "that the game is therefore one of catch-up, and that market evolution patterns seen previously in developed economies will be replicated in the (emerging markets) EMs" (Arnold and Quelch 1998, p. 9). The statement is supported by Khanna et al. (2010), arguing in their recent investigation that there seems to be a common sense of emerging markets to converge with already industrialized countries. However, they emphasize not only to distinguish operations in emerging markets from developed markets but also to distinguish emerging markets individually from each other (Khanna et al. 2010).

That said, it is quite obvious that these markets have to be treated differently. Familiar approaches and often highly standardized programs that work well in advanced countries for years will need country-specific adaptions to reveal their full potential in a new environment. This also comprises OPEX programs of especially Western pharmaceutical companies that have evolved from and are tailored to the culture and behavior of their country of origin.

Outsourcing for Cost Savings

In their struggle to contain fixed costs, most pharmaceutical companies are currently searching for opportunities to reduce their internal capacities in manufacturing, R&D, and even marketing. As such, pharmaceutical companies of

all sizes increase outsourcing of their operations in order to gain productivity and efficiency, and to convey solving their problems to one of the numerous service providers. Moreover, the global competitive environment, forces many organizations to especially streamline their pharmaceutical manufacturing – most affecting the manufacture of small molecule generic drugs. This trend has even been strengthened by the latest financial crisis (Zhang 2012).

In order to realize significant cost savings, many drug companies have already started or stand in a late stage consideration of outsourcing their manufacturing to e.g. Eastern Europe, China, and India (DeRuiter and Holston 2012). Pursuing their model of "more achievements for less cost" Western pharma companies enter these emerging markets utilizing both low cost manufacturing and access to these markets. Thus, many multinational drug companies looking for partnerships with domestic companies in these markets that already possess the required technical capabilities (Zhang 2012).

However, top-level executives are often blindsided by the numerous benefits of offshoring operations and may too easily refuse the downsides, taking operational risks serious. Offshore manufacturing locations pose additional quality risks, especially when partnered organizations possess employees with different culture, i.e. language and values. Thus, it is the challenge for companies outsourcing in those regions to transfer and maintain their knowledge that is required to operate and manufacture their products correctly to mitigate the quality risk (Gray et al. 2011).

It is expected that the outsourcing trend will continue for the next years and that the pharmaceutical supply chain will disaggregate compared to the automotive industry (McKinsey 2011). Moreover, the demand for outsourcing services will also be carried on by pharma companies that pursue personalized medicines and will thus increasingly rely on the outsourcing opportunity in order to handle their product portfolios becoming more diverse (Zhang 2012).

Summary and Conclusions

The Pharmaceutical Industry has undergone tremendous change over the last years, having seen the deterioration of its former blockbuster business model. An increased global competition combined with the described productivity crisis in pharmaceutical R&D and record high losses of patent protection for major drugs have led to a huge cost pressure on every single activity within a pharmaceutical value chain. The regulatory environment on the one hand makes needed changes more difficult, having a history of avoiding or at least complicating them. On the other hand, the latest regulatory requirements are based on a process-oriented understanding and continuous verifications fostering a more science-based approach to pharmaceutical production. But still a legacy of no-change culture has to be overcome on the way to true excellence. The third dominant factor is the globalization of the business and the globalization of value chains increasing again

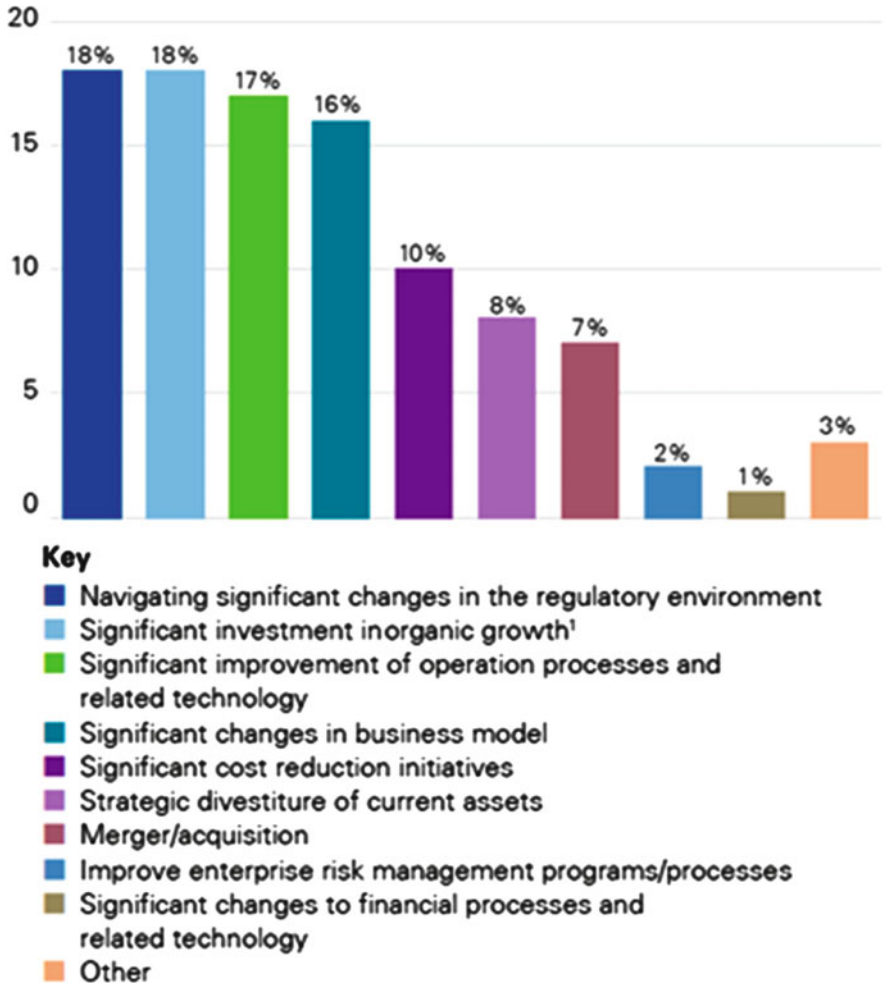

Fig. 6.14 Top initiatives on the mind of management (Source: KPMG 2012)

the complexity of the business. The global production network has to be managed from a true network perspective in the future to ensure competitiveness. We will come back to this at the end of the book in our part 4.

As illustrated in Fig. 6.14, the highest ranked priorities of top management in the pharma industry are all related to operations. Therefore to be successful in the future the pressure of changing to a continuous improvement culture ensuring a steady increase of productivity while keeping the quality level will become a mandatory prerequisite for pharmaceutical companies. Additionally, OPEX will more and more have to work as well in the emerging countries as production capacities are currently shifting. A new generation of OPEX will have to deal with the global logic of today's healthcare business.

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