7 The Pharma/Biotech Model for Drug Development: Implications for Pediatric Cancer Therapeutics

Peter T. C. Ho

Contents

7.1 The Old: Large Pharma

7.1.1 Background and History

We are all familiar with big drug companies and what they do. The drug and biological products developed and marketed by biopharmaceutical companies have contributed to improved quality of life and longer life expectancy that in the United States has increased from an average of 47 years in 1850 to 79 years in 2020. During the COVID-19 pandemic of 2020 that continues into 2022, large, multinational pharmaceutical companies such as Pfizer, Johnson & Johnson, and AstraZeneca have leveraged their considerable scientific, manufacturing, and logistical might to develop vaccines quickly and efficiently for an anxiously awaiting global public. Most large pharma companies have a long history, but the biopharmaceutical industry as a whole along with the large and small players, e.g., biotechs, that comprise it live within a very fluid environment with a plethora of foreseeable and unpredicted challenges such that the business credo "change or die" is very apt.

Today's pharma industry is rooted in small European apothecaries from the 1800s that

P. T. C. Ho (✉)
Phase One Advisors LLC, Newton Centre, MA, USA
e-mail: peter@oncologytx.com

J. DiMartino et al. (eds.), *Pediatric Cancer Therapeutics Development*, Pediatric Oncology,
https://doi.org/10.1007/978-3-031-06357-2_7

evolved to produce large quantities of drugs such as morphine and quinine and in the dye and chemical companies that discovered medicinal uses for their products (Daemmrich and Bowden 2005). For example, Merck began as an apothecary shop in Darmstadt, Germany, in 1668 that transformed into a wholesale manufacturer of drugs by the 1840s. Similarly, Schering in Germany, Hoffmann-La Roche in Switzerland, and Burroughs Wellcome in England all derived from apothecaries and drug producers from that era. The ensuing decades saw the discovery of new drugs accelerate as companies forged research collaborations with academic laboratories while synthetic chemistry and pharmacology matured as scientific disciplines. Researchers applied the theory of structure-activity relationships to chemicals and began generating experimental data in animals and humans to systematically discover new drugs. Despite these advances, most medicines sold in the United States by 1930 were without a prescription with almost half compounded by local pharmacists rather than produced by a central manufacturer.

With World War II came the demand for mass production of a variety of drugs needed by soldiers, including penicillin and antimalarials. This served to stimulate the growth of US pharmaceutical companies. In the post-war era, pharma companies in the United States, Europe, and Japan grew rapidly in the areas of research and development (R&D) and global marketing. Over the next several decades, large pharmas invested their rising revenues to build expansive state-of-the-art research campuses to drive innovation using a host of new technologies such as spectroscopy, high-pressure liquid chromatography, genetic engineering for protein production, and combinatorial chemistry. The advent of high-throughput screening technologies combined with massive chemical libraries collected and curated over decades by large pharma chemists expedited the testing of millions of chemical compounds against multiple molecular targets. This served to further advance the tradition of empirical drug discovery that began in the 1800s. It was only when high-throughput X-ray crystallography, nuclear magnetic spectroscopy, and computational biology were married in the 1980s that molecular modeling became the workhorse for the rational design of small molecule drugs that exists today.

7.1.2 Profile of a Large Pharma: Merck & Co.

Every large pharma is unique, but there are common threads with respect to their mission, organizational structure, and tactical operations. For those unfamiliar with the characteristics of a large pharma, Merck & Company, more commonly known as Merck, is profiled below as an illustrative example.

Merck was founded in the United States in 1891 by George Merck who at age 23 established the company to distribute fine chemicals throughout the New York City region. It currently describes itself as "a global health care company that delivers innovative health solutions through its prescription medicines, vaccines, biologic therapies, and animal health products." In 2020, Merck had approximately 71,000 employees worldwide of whom 26,000 were in the United States (Merck 2019). Its corporate headquarters are in Kenilworth, NJ; however, its geographic reach extends throughout the world. Merck's main pharmaceutical R&D campuses are in Rahway, NJ; West Point and Upper Gwynedd, PA; South San Francisco, CA; Boston, MA; and London, UK. Its headquarters for manufacturing is in Whitehouse Station, NJ, but Merck maintains production facilities at numerous locations all over the world including the United States, Puerto Rico, Japan, Singapore, South Africa, and countries in Western Europe, Central and South America, and Asia.

Its pharmaceutical division encompasses pharmaceutical and vaccine products that are generally sold by prescription. Merck sells their pharmaceutical products primarily to drug wholesalers and retailers, physicians, hospitals, government agencies and managed healthcare providers such as health maintenance organizations, pharmacy benefit managers, and other institutions. Its Animal Health division discovers, develops, manufactures, and markets a wide

range of veterinary pharmaceutical products, vaccines, and services for the prevention, treatment, and control of disease in all major livestock and companion animal species. These products are marketed to veterinarians, distributors, and animal producers.

As reported in its 2019 Annual Report, Merck's R&D groups employed approximately 15,600 people worldwide and spent $9.9 billion ($9.9B) in 2019. Merck's R&D programs are described as prioritizing drug candidates that represent breakthrough science for patients and payers. Its clinical pipeline includes candidate molecules for a variety of disease areas including cancer, cardiovascular diseases, diabetes, and other metabolic diseases, infectious diseases, neurosciences, pain, respiratory diseases, and vaccines. As of November 2020, Merck disclosed publicly that it had 31 programs in phase 2 development, 25 programs in phase 3, and 3 programs under regulatory review for approval. Of note, pharmas and biotechs typically define a program as a single drug candidate under clinical testing for a single disease indication. Thus, a company that is testing a single drug candidate for three different types of cancers would count that as three programs. Given the scientific and commercial success of Merck's Keytruda® (pembrolizumab), an immune checkpoint monoclonal antibody that binds to and acts through the PD-1 receptor on T lymphocytes, it is not surprising that the overwhelming majority of Merck's programs were for oncologic indications. As such, 23 of its 31 phase 2 programs, 22 of 25 phase 3, and 1 of 3 programs under regulatory review were directed at various cancers. However, of these 46 programs for oncology diseases, only one program was specifically directed at a childhood tumor indication. Koselugo® (selumetinib), an inhibitor of MEK1 and MEK2 kinases originally discovered by and developed in collaboration with AstraZeneca, was approved in 2020 by the US Food and Drug Administration (FDA) for pediatric neurofibromatosis and under review for the same indication in Europe. Like many large pharmas, Merck does not publicly disclose the number of programs in the discovery phase or phase 1 trials, but it would be reasonable to expect that programs in each of these categories would far exceed the total number of phase 2 programs.

Table 7.1 Merck's 2019 sales by top pharma products and sales of animal health products (Merck 2019)

Category	Product or subcategory	2019 Sales (in millions)
Total		$46,840
Pharmaceutical		$41,751
	Keytruda®	$11,084
	Januvia®/Janumet®	$5524
	Gardasil®/Gardasil 9®	$3737
	ProQuad/M-M-R II/ Varivax®	$2275
	Bridion®	$1131
	Isentress®/Isentress HD®	$975
	Pneumovax 23®	$926
	NuvaRing®	$879
	Zetia®/Vytorin®	$874
	Simponi®	$830
Animal health		$4393
	Livestock	$2784
	Companion animals	$1609
Other revenues		$696

All large pharmas tout their scientific prowess and commitment to patients, but as corporate entities, they are all ultimately judged on their financial performance and indeed define their own success based on their yearly top line and bottom line. In 2019, Merck generated sales of $46.8B which represented an 11% increase over that of 2018. Sales within the United States accounted for 43% ($20.3B) of this total, while the remaining 57% of sales came from outside the United States. At $11.1B Keytruda® accounted for nearly 24% of Merck's total sales (Table 7.1), and this represented a 55% increase over its sales in 2018. Januvia®/Janumet® (sitagliptin), a drug for type 2 diabetes, recorded $5.5B in sales, but this represented a 7% decline compared with that of 2018. Finally, vaccines led by Gardasil®, a vaccine against human papillomavirus ($3.7B in sales), accounted for a total of $6.8B or 14.5% of Merck's total sales.

Merck's major outlays in 2019 came from the costs of sales and general and administrative expenses which totaled $24.7B. As noted above Merck spent $9.9B in R&D that same year or

21% of their total sales. Across the industry, most large pharmas have R&D spends that equate to 15–22% of their annual sales. This range has been invariant over time, and it is extremely rare for a pharma to have R&D spending above 25% of annual sales. It is a common refrain from large pharma that high R&D costs are the primary reason for the high cost of drugs. However, as is seen for Merck, and every other major large pharma, R&D expenses typically account for only one-fifth of total sales revenues every year. Merck reported an income of $11.5B in 2019 for which it paid taxes of $1.7B for an effective corporate tax rate of 14.7%. For reference, a married couple in the United States filing jointly in 2019 would need to have an annual income of $113,466 to qualify for an effective federal tax rate as low as 14.7%. Any income above this amount for this couple would result in a higher effective tax rate than what Merck paid for earning nearly $47B. This seems rather inequitable for the average American taxpayer.

7.2 The New: Biotech

The 1980s and 1990s saw dramatic advances in molecular biology, genomics, and genetic engineering. These innovations sparked the advent of synthetic protein-based therapeutics, exemplified by insulin, interferons, interleukins, and hematopoietic growth factors, that ushered in the era of biotechnology to complement small molecule (chemical) drugs in the therapeutic armamentarium. Moreover, these "large molecule drugs" which were developed by small biotechs, such as Genentech and Amgen, served as a bellwether that large pharma's monopoly on the creation of medicines was over. Indeed, the early scientific and financial successes of California-based Genentech and Amgen paved the way for the eventual formation of thousands of biotech start-ups funded by venture capital (VC) hungry to replicate this success. The early history of these two shining stars is illustrative of the growth of the biotech sector as a whole.

In the early 1970s, Herbert Boyer at the University of California San Francisco successfully spliced genes in his laboratory using newly discovered restriction endonucleases. Confident that genetic recombination had significant commercial potential, Robert Swanson from the VC firm Kleiner Perkins convinced Boyer in 1976 to start a company that Boyer named Genentech, an amalgam of the words "genetic engineering technology." Boyer and Swanson each invested $500 to start Genentech. Within a year, they produced the human peptide, somatostatin. By 1978, Genentech successfully synthesized human insulin using the same laboratory techniques and entered into a critical R&D collaboration with Eli Lilly to develop human insulin as a replacement for porcine insulin which was extracted from pigs (Pisano 2006). This resulted in the FDA approval of Humulin®, the first genetically engineered therapeutic, in 1982. Over the next nearly 30 years, Genentech successfully developed and commercialized a host of protein therapeutics including human growth hormone (Protropin®), recombinant DNase (Pulmozyme®) for cystic fibrosis, anti-CD20 monoclonal antibody (Rituxan®) for lymphoma, anti-Her2 monoclonal antibody (Herceptin®) for breast cancer, anti-IgE monoclonal antibody (Xolair®) for asthma, and the anti-VEGF monoclonal antibody (Avastin®) for several cancers.

Genentech also broke ground by being the first biotech to transition into a public company. It raised $35 million ($35M), equivalent to $110M in 2020, in its initial public offering (IPO) in 1980 that was underwritten by the investment bank Hambrecht & Quist. Moreover, Genentech's stock price jumped from $35 to $88 in only its first hour of public trading. Genentech's subsequent track record of R&D, regulatory approvals, and commercial success along with its culture of scientific excellence made it an attractive target for pharmaceutical companies. Hoffmann-La Roche which had been collaborating with Genentech on several projects bought a controlling interest (56%) of Genentech for $2.1B in 1990. In 2009, Roche completed its acquisition, some would say "ingestion," of Genentech by buying its remaining outstanding shares for approximately $46.8B, a far cry from the initial $1000 start-up investment by Boyer and Swanson in 1976.

Amgen is another archetype of a successful biotech. It was founded a few years after Genentech in 1980 with several million dollars of VC funding and originally called Applied Molecular Genetics. Its name was shortened to Amgen in 1983 when it raised $40M (equivalent to $104M in 2020) in its IPO that year. In its early days, Amgen, like Genentech, focused on exploiting recombinant DNA technology which it applied to cloning the human erythropoietin gene. By doing so, they created their first drug Epogen® which was approved by FDA in 1989 to treat anemia associated with chronic renal failure. Amgen received its second FDA approval in 1991 for Neupogen® (filgrastim) to prevent chemotherapy-related infections.

By 2019 Amgen recorded sales of $23.4B with eight products generating the bulk of this revenue. Enbrel® (etanercept), an anti-TNF fusion protein approved to treat arthritis and other inflammatory diseases, was Amgen's biggest seller with sales of $5.2B or 30% of Amgen's annual revenue. Neulasta®, the successor to Neupogen®, was second in sales with $3.2B or 19% of total revenue. Unlike Genentech, Amgen today remains an independent corporate entity. Reflective of its financial success, $1000 invested in Amgen at the time of its IPO would have grown to be $780,692 as of April 2020 even without having reinvested dividends. This represents a consistent annual return on investment of nearly 20% over 37 years.

The founding and early success of Genentech and Amgen stimulated the creation of many other biotech start-ups. San Francisco, San Diego, and Boston served as their most common birthplaces as opposed to Philadelphia, New York, New Jersey, and the Midwest which served as the headquarters for most pharmas in the United States. The growth of biotech was made possible only through the financial investment from VC firms and investment banks which saw the opportunity for massive returns resulting from the successful development of promising new medicines. Although there were bumps in the road, e.g., the financial crisis of 2008, the marriage of VC with biotech entrepreneurs ultimately proved to be extremely financially rewarding to both and to biotech investors as a whole. From the beginning of 2009 to the end of 2020, the NASDAQ Biotechnology Index rose 6.67-fold which is nearly 60% higher than the benchmark S&P 500 Index which increased by 4.22-fold over the same period.

Fueled by investment banks that underwrote IPOs and public market investors who did not want to miss out, biotechs claiming to be the "next Genentech" positioned themselves to leverage science and their "secret sauce" to create the next big medicines. Those that eventually succeeded such as Biogen, Chiron, Genetics Institute, Genzyme, and Gilead experienced meteoric growth to become vertically integrated companies with sales and marketing capabilities just like Genentech. For some their scientific and financial success made them attractive takeover targets, e.g., Novartis's acquisition of Chiron, Sanofi's purchase of Genzyme, and Wyeth's acquisition of Genetics Institute. Others, like Biogen and Gilead, remain independent companies even today. But the high likelihood of failure inherent to drug discovery and development more commonly translates into the collapse of most biotech start-ups usually within their first few years.

However, it is precisely this high-risk, high-reward feature of biotech investment that makes it so attractive to VC firms like Kleiner Perkins, New Enterprise Associates, OrbiMed Advisors, Third Rock Ventures, and many others that excel at playing the investment game for the benefit of themselves and their investors. VC firms offset the high risk of failure for biotech start-ups with the expectation that the small fraction (10–15%) of companies that ultimately succeed will provide a 10–50-fold return on their initial investment. For example, to offset the cost of the many failures that it funds, a VC that invests $50M in a start-up biotech through several rounds of private financing before the biotech's IPO 3–5 years later will look to recoup $500M or more through the IPO and future growth in the company's market valuation when its stock becomes traded on the public markets.

The growth of the biopharmaceutical industry is fueled by interdependencies and interac-

tions between large pharma, biotech, VC, investment bankers, and Wall Street analysts. There is no greater evidence of this than at the annual JP Morgan Healthcare Conference held every January in San Francisco. For those in the industry, this convocation's invitation-only participation makes a pilgrimage to "JPM," as it is commonly called, the essential place to go, be seen, and make business deals. Absence from JPM is viewed as a negative sign that you and your organization are irrelevant players in biopharma. JPM had humble beginnings when in the early 1980s Hambrecht & Quist along with a few other investment banks saw great profitability in raising capital for biotechnology. In 1983, to highlight new technologies, showcase companies, and stimulate further investment in biotechs such as Genentech, Hambrecht & Quist (later acquired by Chase Manhattan Bank, a predecessor of JP Morgan) held its first conference which lasted just half a day in San Francisco. JPM has since grown into a 20,000 attendee behemoth that spans nearly an entire week. The conference consumes virtually all hotels in downtown San Francisco and results in even substandard hotel room rates rising to over $1000 per night. Even companies that are not invited to present at JPM feel the need to be in town to have an endless series of 30-minute "speed-dating" meetings with a seemingly endless list of investors and analysts that stretch from early morning to late evening every day.

7.2.1 Biotech Financing: From Birth to Adulthood

From a financial perspective, a typical start-up biotech comes into being when a VC buys into its concept and leads a "consortium" of other VCs to assemble an initial investment of $20–$50M, termed a Series A financing. This allows the biotech to hire people, buy equipment, rent labs and/or offices, and begin R&D work. Over the next several years, this invested sum is spent by the biotech necessitating subsequent rounds (Series B, C, etc.) of private financing that not only involves the original consortium but also includes an expanded set of newer investors who see opportunity in the interim R&D progress demonstrated. Since transforming a scientific concept into an investigational therapeutic becomes more expensive with every progressive step, these subsequent financing rounds generally raise progressively larger sums of money such that the aggregate amount invested in the biotech can easily reach well over $200M.

At a certain point, if the biotech makes sufficient R&D progress and the external stock market conditions are favorable, the company can "go public," as Genentech did in 1980, in an IPO. The timing of an IPO varies according to the company. For biotechs developing therapeutics, an IPO is frequently timed to coincide with its lead molecule entering a first-in-human clinical trial or demonstrating a clear path to enter the clinic in the near future. Going public achieves several financial objectives for all parties involved. It allows the VCs to cash in on their investment(s) and make an "exit." Despite the public pronouncements from VC that their biotech investments are made to drive innovation for the greater healthcare good of society, the overriding objective of VC firms is to generate a large return on investment for their investors and themselves so they can repeat the cycle with the next set of start-ups. This has proven to be a very lucrative positive feedback loop for VC firms. A successful IPO also delivers large fees, ranging from $10–$20M per IPO, for investment banks, like JP Morgan and Cowen, who underwrite the public offering. Going public provides the biotech access to capital from the public markets which can provide much larger sums of invested capital to fund clinical trials that are much more expensive to conduct than laboratory-based research. Finally, for investors in the public markets that can include mutual funds and institutional and individual investors, an IPO opens up the opportunity to invest in the biotech.

However, transitioning from a private to a public company comes at a significant cost, both literally and metaphorically, to every biotech. The company now spends a smaller fraction of its precious funds on R&D as it must hire more

finance and administrative staff to handle the legal and financial reporting obligations, e.g., Security and Exchange Commission requirements, that come with being traded on a stock exchange. Being public also imposes a veil of confidentiality over the company and its employees. Experimental data and results, especially those involving clinical trials, that previously were discussed freely among staff are now restricted to those on a need-to-know basis because it is considered "material information." If inadvertently leaked to public investors which can now include anyone outside the company, it could affect the stock price. Perhaps, the greatest cost for a biotech's going public is that it brings daily scrutiny from the external world over the goings-on within the company. Public perception can be immediately reflected in the rise and fall of the biotech's stock price. Experimental setbacks that were once simply accepted and dealt with as an R&D obstacle to be overcome now become potentially material information that must be reviewed by lawyers, described in a carefully massaged press release as part of a "communication plan," and discussed ad nauseam with nervous investors and financial analysts who demand to understand why the stock price is dropping and what the company will do about it… today.

As a result, a public biotech is forced to focus increasingly on short-term goals and milestones that are reported in its quarterly SEC filings and "earnings calls." The former is a regulatory requirement, but the latter is not. This results in perhaps one of the more inane oddities for biotechs post-IPO. Pharma companies, like Merck and GlaxoSmithKline (GSK), use quarterly earnings calls with investors and industry analysts to actually report on their top-line sales and earnings to guide future financial expectations. However, biotechs that may be years away from having their first product on the market have no profit or even earnings to report. Rather they only generate quarter after quarter of losses through their R&D expenditures. Nevertheless, it remains commonplace for biotechs to host these "quarterly earnings calls" that in the absence of any earnings to speak of usually devolve into shadow puppetry theater of analysts and investors asking about the company's R&D progress and the biotech's management dodging these questions that they cannot or will not answer.

One consequence of this focus on near-term milestones and financials is the prioritization of clinical trials over laboratory research when the two activities compete for a limited R&D budget. Biotechs generally are 100% focused on laboratory research in their early years while they aim to bring forth a molecule into clinical trials. The initiation of phase 1 studies and the transition of the biotech into a clinical-stage company are defining milestones that bring pride and joy to the biotech's employees and financial returns to its investors. However, this landmark event is frequently the beginning of the end for the laboratory research that carried the company to this same milestone.

The conduct of clinical trials is exceptionally expensive, and their costs increase every year. A single phase 1 trial in cancer typically costs $5–$15M, and a phase 2 trial can total up to $50M. These R&D expenditures easily overshadow, figuratively and fiscally, that of the laboratory research that will bring forth the next molecule from the preclinical pipeline. The biotech's investors and analysts tend to be singularly focused on the progress of the molecule(s) in clinical trials rather than on earlier discovery programs since the former will generate data necessary for an eventual FDA submission. Thus, the clinical programs of a biotech become the greatest near-term value drivers of its stock price. As such, it is common for biotechs to make resourcing and budgetary trade-offs by constricting laboratory research when their first molecule(s) enters clinical trials. In more extreme cases, a biotech may completely cease further discovery work on new or next-generation molecules in order to focus entirely on advancing their clinical portfolio. This is particularly unfortunate when the clinical-stage molecules have clear liabilities that could be solved with follow-on compounds that are a few years behind in the laboratory. This reduction or termination of discovery research means that the laboratory scientists whose hard work created the molecules behind the biotech's

success in its early years are less valued or no longer needed.

Thus, the start-up biotech that began with the promise of a portfolio of molecules that leverage its technological "secret sauce" frequently transforms itself into a one or two molecule clinical development company that bets its future on one molecule achieving FDA approval and hitting the market. Sometimes, that bet pays off handsomely for the biotech and its investors. More often than not, a highly anticipated pivotal trial fails, and there are either no other molecules left in the cupboard or not enough money in the bank, or both, to rescue the biotech facing its first major clinical failure. As a result, the landscape is dotted with shuttered biotechs that faced withering punishment to their stock price from disappointed and skeptical investors.

Recognizing that the expense of clinical trials to bring a molecule to the market is substantial, the time required is long, and the probability of failure remains high, some biotechs are content to advance their portfolio to a certain point, usually in phase 2 or phase 3 clinical trials, at which time they become an attractive acquisition target for large pharma. Earlier selling of a biotech to a pharma will generate a lower return on investment to the biotech's investors compared with when a biotech attempts to go all the way to an FDA-approved New Drug Application (NDA) or Biologics License Application (BLA). However, the risk of seeing the biotech's market value fall to near zero after a late-stage clinical trial failure and walking away with no return on investment is eliminated. The acquiring pharma assumes the risk of future failure but gains ownership of the candidate drug, portfolio, or technology platform at a much lower cost than what it might otherwise have to pay if it waits for clarity from a positive pivotal trial result. A recent example of this is Gilead's $4.9B acquisition in 2020 of Forty Seven, Inc. for the latter's magrolimab, an anti-CD47 monoclonal antibody in clinical development for myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and diffuse large B-cell lymphoma. Gilead's purchase came after Forty Seven reported interim results from a phase 1B trial of magrolimab and azacitidine wherein overall response rates of 92% and 64% were observed in 24 patients with high-risk MDS and 22 patients with untreated AML, respectively (Sallman et al. 2019).

7.3 The Drive for Pharmaceutical Innovation

It is often cited by the pharmaceutical industry that the cost of discovering a new drug in the laboratory, taking it through clinical trials, and ultimately gaining FDA approval is exorbitant and can run up to several billion dollars. Part of this calculus is based on the high failure rates in both laboratory and clinical trial phases of a new drug's gestation resulting in no financial return for most programs within a company's R&D portfolio. Even for a molecule that survives the preclinical gauntlet to enter into a phase 1 trial, the remaining probability of success for FDA approval of a cancer drug is generally considered to be only 5–10%. Although all of these probability calculations are predicated on assumptions that may be reasonably questioned, drug discovery and clinical development are nevertheless expensive and high-risk propositions that are beyond the fiscal scope of an individual or most companies in other fields of business.

The drive for ever-increasing revenues in the setting of the high cost and low success rates of pharmaceutical R&D has resulted in three phenomena that are diametrically opposed to enhancing R&D investment of new therapeutics for pediatric cancers. First, to offset financial expense and risk, large pharmas and arguably many, if not most, biotechs have evolved to focus their attention on "blockbuster drugs" that are generally defined as those that generate annual sales revenues of $1B or more. This strategy drives pharmas to work on drugs for diseases of higher prevalence in the population and for which treatment is chronic or at least longer term. Childhood cancers are thankfully quite uncommon such that even the predominant pediatric solid tumors and leukemias have annual incidences in the United States of a few hundred to two thousand. Besides, treatment for these diseases ranges from several

months to 2 years rather than a lifetime. Thus, childhood cancers do not and will never meet the blockbuster criteria that large pharma seeks. It should be emphasized that a commercial sales forecast is just as important for project progression as a scientific assessment when pharmas evaluate early-stage R&D projects and decide where to place their bets. One might argue that higher drug pricing may offset lower patient numbers to generate the desired financial return. Indeed, Cerezyme®, an enzyme replacement therapy for patients with Gaucher's disease, is frequently cited as an example whereby high pricing compensates for an extremely low disease incidence. However, it must be remembered that drugs like Cerezyme® are administered for the lifetime of a patient in contradistinction to that of the treatments given to children with cancer. Even so, one may reasonably question whether pricing that amounts to $200,000 or more per year represents a sustainable solution to rising societal healthcare costs in the United States and developed world, to say nothing of the developing world.

The second consequence of the drive for pharmas to lower R&D costs and risk is to merge with or acquire other pharmas. Since 1999, over 45 mergers or acquisitions (M&A) with a value of over $10B have been consummated by large pharma resulting in companies of ever-increasing size. Take GSK as an example. Like Merck, GSK had its origins as an apothecary shop in London in 1715. This pharmacy was eventually acquired by Glaxo Labs which was established in 1935 in England. Burroughs Wellcome was started in 1880 in London. Glaxo merged with Wellcome in 1995 to form GlaxoWellcome. Across the Atlantic, Smith, Kline & French (SKF) Company, itself a product of an acquisition, was formed in 1871 in Philadelphia. SKF merged with Beecham Group to form SmithKline Beecham in 1989. GlaxoWellcome merged with SmithKline Beecham in 2000 to form GSK, a global giant of over 100,000 employees. Likewise, the Pfizer of today was founded in New York in 1849 but over its life has acquired either directly or indirectly Wyeth, Ayerst, Warner-Lambert, Parke-Davis, Pharmacia, and Upjohn pharmaceutical companies.

The rationale for M&A in the pharmaceutical industry is the same as that for corporate mergers in other industries. The annual sales of the combined entity will be much greater than either of the pre-M&A companies. Indeed, the annual revenues in 2019 for the top ten pharmas ranged from $23B to $52B (Table 7.2). Conversely, the number of employees, whether they be in R&D, sales/marketing, or administrative functions, needed to sustain the combined organization is expected to be fewer than the sum total of both at least according to the bean counters and MBAs who drive these corporate shotgun marriages. These "efficiencies" or "synergies" touted when a pharma M&A occurs typically mean early retirements or layoffs for at least some of the employees when the dust settles from the corporate fusion.

The third reaction to the challenge of bringing innovative medicines to the market in light of large pharma's desire to control R&D costs is the increasingly frequent practice of in-licensing or acquiring molecules discovered in biotech companies. Frequently, large pharma focuses on buying molecules that have met criteria demonstrating clinical proof of concept (PoC) usually comprised of positive phase 2A clinical data. The rationale for this is that it is preferable from a financial and risk management perspective to buy someone else's "de-risked" molecule than to invest money and people resources in one's own laboratory discovery efforts with no guarantees that expected innovative molecules will emanate years in the future. Pharmas are quite willing to

Table 7.2 Largest pharmaceutical companies (by revenue as of December 2020) (Anderson 2020)

Rank	Company	Annual revenue (in billions)
1	Pfizer	$51.9
2	Roche	$50.0
3	Novartis	$47.5
4	Merck & Co.	$46.8
5	GlaxoSmithKline	$43.5
6	Johnson & Johnson	$42.1
7	AbbVie	$33.3
8	Sanofi	$27.8
9	Bristol Myers Squibb	$26.2
10	AstraZeneca	$23.6

pay even a premium price for these clinical-stage molecules because they have presumptively already met the considerable hurdles of laboratory and animal studies and that of initial clinical safety, pharmacokinetic, and early efficacy data from phase 1 trials that can cause termination of numerous other molecules along the way. In essence, pharmas are willing to pay more for these molecules because the risk of failure to this point has been borne by the biotech and the attrition of other unsuccessful molecules has already occurred.

Large pharmas' acquisitions of promising molecules from biotech through a variety of means have differing financial and corporate implications on biotech. The least intrusive is when a pharma in-licenses the molecule or, in other words, buys the molecule with all of its patent rights and assumes all further responsibilities to develop and market the molecule. This maneuver leaves the biotech independent and intact with the other molecules in its portfolio. The biotech generally receives (1) an upfront licensing fee upon transfer of rights to the pharma; (2) future milestone payments when the molecule reaches certain prespecified events, such as the start of a phase 3 trial or the filing of an NDA or BLA with the FDA; and (3) royalties as a percentage of future sales achieved by the pharma.

As an example of this theme, Novartis in early 2021 licensed BeiGene's tislelizumab, an anti-PD-1 monoclonal antibody approved in China in 2019, after the clinical failure of Novartis's own immune checkpoint inhibitor spartalizumab in a phase 3 trial in melanoma. Novartis obtained the commercial rights to tislelizumab in major markets outside China, including the United States, Europe, and Japan, in return for an upfront payment of $650M and up to $1.55B in future milestones to BeiGene. While the upfront licensing payment was sizable for most industries other than biopharma, it was relatively modest for an approved biological drug for cancer. Likely this resulted because the landscape of FDA-approved immunomodulatory agents was already dotted with established monoclonal antibodies such as ipilimumab (2011), nivolumab (2014), pembrolizumab (2014), atezolizumab (2016), avelumab (2017), durvalumab (2017), and cemiplimab (2018). Thus, the commercial potential of tislelizumab in Novartis's hands was limited.

A second mechanism is a collaboration in which the pharma and biotech agree to work together to develop the molecule through late-stage trials and registration. Upon regulatory approval, the sales and marketing of the new drug will be shared between the two partners. A common way to divide the future revenues is to split the geographic rights for sales and marketing. For example, the biotech retains commercial responsibilities and revenues in the United States while the global pharma gains that for Europe and the rest of the world. This type of business arrangement is preferred by biotechs that wish to transform themselves from a pure R&D organization to a vertically integrated mini-pharma with both R&D and sales and marketing capabilities. The advantage of this strategy, and one taken by Amgen and Genentech, is that the biotech maintains control over its future sales revenues which can be much larger than a percentage royalty of the pharma's sales in the first example. Another advantage to the biotech is that it retains its corporate independence while receiving an infusion of cash or resource investment and assistance from the pharma to complete late phase clinical trials that can be large, lengthy, and expensive.

A recent example of this type of R&D arrangement is AstraZeneca's 2020 collaboration with Accent Therapeutics on the latter's discovery-stage molecules targeting RNA-modifying proteins for the treatment of cancer. Under the terms of their agreement, Accent is responsible for R&D activities for a predetermined preclinical program through to the end of phase 1 clinical trials. AstraZeneca will then lead development and commercialization activities from phase 2 onward with Accent retaining an option to jointly develop and commercialize the molecule with AstraZeneca in the United States. AstraZeneca will also have the exclusive option to license worldwide rights to two additional programs that will be prosecuted by Accent through the preclinical stage. In return Accent received an upfront payment of $55M and can receive up to $1.1B in

additional success-based payments across all three programs in the form of option fees and milestone payments, as well as royalties on future sales.

The final mechanism is acquisition or the outright purchase of the biotech by the pharma which by definition transfers the rights for the biotech's entire portfolio of molecules to the pharma. This swallowing whole of the biotech also results in the transfer of all the biotech's physical assets (labs, equipment, buildings), people, and remaining cash to the pharma. Although there are instances when the biotech's staff are retained by the pharma, more often than not many if not most of the biotech's employees move onto other companies, whether by their own choice or their new employer's. The driver for most biotech acquisitions is its assets (molecules and intellectual property) rather than its people. A relevant example to the contrary is Eli Lilly's $8.0B acquisition of Loxo Oncology in 2019 for the latter's Vitrakvi® (larotrectinib), a TRK inhibitor that had recently received FDA approval for adults and children with solid tumors having a neurotrophic receptor tyrosine kinase gene fusion, along with LOXO-292, a RET kinase inhibitor, and LOXO-305, a BTK inhibitor. In this case, many of Loxo's employees were retained at Lilly including Loxo's CEO, Josh Bilenker, who later assumed leadership of Lilly's oncology R&D franchise.

There are countless variations of pharma/biotech in-licenses, collaborations, and acquisitions that are beyond the scope of this high-level overview. The aforementioned examples are representative but not meant to be comprehensive for all of the different business arrangements that can be made when pharma and biotech work together to create and develop innovative new medicines.

An acquisition of a company or in-license of several investigational molecules from a biotech's portfolio may yield unexpected value from molecules that were not perceived originally as the value driver. In 2009, Bristol Myers Squibb (BMS) acquired Medarex for $2.1B. In its press release announcing the purchase, BMS touted that it was gaining full ownership and rights to ipilimumab, an anti-CTLA-4 monoclonal antibody in phase 3 trials at the time, rights to ten additional clinical-stage antibodies, and Medarex's fully human antibody technology platform. At the time, the most prized asset of this transaction was ipilimumab which became the first immune checkpoint inhibitor approved for cancer treatment. However, by 2019, Yervoy® (ipilimumab) generated sales of $1.5B for BMS, while Opdivo® (nivolumab), an anti-PD-1 monoclonal that turned out to be one of the hidden gems in the ten other Medarex antibodies that BMS acquired in 2009, generated sales of $8.1B. The Medarex acquisition proved to be highly valuable for BMS not only financially but by paving the way for its becoming a leading pharma in the area of immuno-oncology with nivolumab ultimately becoming the unanticipated jewel of this acquisition.

One consequence of pharma's strategy of sourcing candidate molecules from biotech is that the size and scope of large pharma R&D groups have been steadily reduced over the past two decades as large pharmas have increasingly turned to biotech to discover the molecules in their pipelines. The initial layoffs or "reductions in force" in R&D generally involved the biologists, chemists, and pharmacologists within large pharma laboratory discovery groups charged with identifying and characterizing molecules that would be brought to a first-in-human clinical trial. Then large pharma clinical pharmacology groups that conducted phase 1 studies in healthy volunteers were downsized or eliminated along with the hospital-based clinical pharmacology units that many pharmas owned and operated in the past. For example, GSK in 2002 had three clinical pharmacology units (Philadelphia, PA; Cambridge, UK; Sydney, Australia) that performed healthy volunteer phase 1 studies on the company's portfolio. By 2020, only the Addenbrooke's Hospital site in Cambridge remained operative as the others were closed or sold to contract research organizations (CROs). Finally, clinical scientists, in particular those responsible for the planning and conduct of early phase clinical trials in patients, were made redundant as pharmas increasingly relied on biotechs to generate early clinical trials data for them.

7.4 Current Trends in Pharmaceutical R&D

Although successful R&D has powered scientific innovation and financial success in the pharmaceutical industry for decades, there has been increasing concern about declining R&D productivity since the late 1990s. This is so despite consistent rising annual investment. For example, R&D spending by the pharmaceutical industry totaled $186B globally in 2019 compared with $136B in 2012 (Mikulic 2020). As evidenced above with Merck, it is common for a large pharma to spend several billion dollars each year on R&D. Moreover, R&D productivity as reflected by the simple (but simplistically flawed) ratio of total R&D annual expenses of a pharma divided by its number of new molecular entities (NMEs) approved has resulted in a steady increase of this already shockingly high benchmark. For example, in the 1990s this calculated metric was generally accepted as $1B per NME, but more recent analyses have determined this to be as much as $5B per NME for large pharmas (Harper 2013). Beyond expenditures, R&D productivity loss can also be reflected in employees and time. A typical large pharma company may employ tens of thousands of scientists and support staff at multiple research campuses around the world. The road to getting a new drug approved from the time of its first discovery in the lab is inordinately long, averaging 14 years (Paul et al. 2010) compared to product development cycles as short as a few months in other industries such as high tech and software.

Finally, "attrition" or the sequential reduction in the size of a pharma's R&D portfolio resulting from project failures due to insufficient efficacy, unacceptable toxicity, technical challenges of manufacture, or changes in the competitive landscape is an inescapable consequence of the high-risk nature of pharmaceutical R&D. In an analysis of 4451 drugs from 835 companies in clinical development from 2003 to 2011, the aggregate probability of successfully turning a phase 1 molecule into an approved drug is only 10.4% (Hay et al. 2014). All of these factors have contributed to the leadership and investors of large pharmas questioning the traditional model of pharmaceutical R&D in which a large pharma is staffed with a stable of the best scientists, performs cutting-edge R&D inside the company, generates its own intellectual property (IP), and successfully drives regulatory approval of innovative first-to-market or best-in-class medicines.

In response, large pharmas have faced the challenge of declining R&D productivity by reducing their internal R&D budgets and staffing while seeking creative methods of conducting R&D. These may be categorized into three primary strategies: "open innovation"; restructuring to create smaller entrepreneurial R&D units; and virtualization/outsourcing.

7.4.1 Open Innovation

Led by Chief Scientific Officer Paul Stoffels (Mullard 2013), Janssen, the pharmaceutical arm of Johnson & Johnson, has pushed the concept of "open innovation" since the mid-2000s with a variety of R&D initiatives designed to grow Janssen's commercial product lines (Wang 2009). Janssen studiously avoids the "not-invented-here" syndrome that resides in many pharma R&D organizations. Its historically poor productivity from its internal drug discovery apparatus (excepting for its Centocor unit) may be one reason for Janssen's embrace of open innovation. Over the past two decades, Janssen's oncology unit has been arguably more successful than its peers at in-licensing or partnering molecules discovered by much smaller biotechs. For example, its 2020 commercial product line for oncology includes treatments for myeloma (Darzalex® [daratumumab], Velcade® [bortezomib]), prostate cancer (Zytiga® [abiraterone], Erleada® [apalutamide]), lymphoma/leukemia (Imbruvica® [ibrutinib]), ovarian cancer (Doxil® [liposomal doxorubicin]), sarcoma (Yondelis® [trabectedin]), Castleman's disease (Sylvant® [siltuximab]), and bladder cancer (Balversa® [erdafitinib]). Of note, all of these except for Sylvant® and Balversa® are molecules discovered by biotech companies who partnered with or were bought outright by Janssen. Nevertheless, Janssen maintains large research campuses replete with scientists and labs in the United

States, the United Kingdom, Belgium, the Netherlands, France, Spain, and Switzerland.

Janssen has also aggressively advanced the concept of "innovation centers" as globally located life science hubs situated to capture externally derived ideas and technology that can eventually become Janssen products of the future (Robaczewska et al. 2019). Located in San Francisco, Boston, London, and Shanghai, these centers provide laboratory and office space to entrepreneurial scientists to nurture collaborations between them and co-located Janssen scientific and business staff who can follow their technology as it develops and be ready to execute licensing or partnership deals to advance these programs for the benefit of both parties.

7.4.2 Small Entrepreneurial Units

GlaxoSmithKline took the approach of restructuring its R&D organization into smaller units to emulate the entrepreneurial risk-taking, autonomy, and ownership spirit characteristic of smaller biotechs, but absent from large pharma. In 2001, then Chairman of R&D Tachi Yamada decentralized GSK's R&D organization to create six "Centres of Excellence for Drug Discovery" (CEDDs) (Huckman and Strick 2005). These CEDDs were charged with discovering new drug candidates within targeted therapeutic areas and taking their molecules through phase 2 "proof-of-concept" (PoC) clinical trials. CEDDs, comprised of medicinal chemists, biologists, pharmacologists, toxicologists, and physicians, could number no more than 350 to operate nimbly and autonomously from that of the rest of GSK R&D. Their limited size and multidisciplinary integration were designed to remove the bureaucratic layers and processes that frequently strangle scientific innovation in the traditional centralized "command and control" R&D units typical of large pharmas (Naik 2003).

Yamada's rationale was that the critical bottleneck to pharma R&D productivity was the scarcity of molecules that successfully demonstrate clinical PoC and advance to large phase 3 registrational trials. By freeing up the scientists and physicians who conduct discovery and early clinical development (phase 1 and phase 2A trials), GSK hoped to see a dramatic increase in molecules that advance to late development. In hindsight, the CEDD experiment was a mixed success. Led initially by Allen Oliff (Whalen 2006), GSK's Oncology CEDD in just 5 years generated several molecules that achieved PoC and were eventually approved by FDA and European regulators. These included the erbB2 kinase inhibitor Tykerb® (lapatinib), VEGF receptor kinase inhibitor Votrient® (pazopanib), thrombopoietin receptor agonist Promacta® (eltrombopag), B-Raf kinase inhibitor Tafinlar® (dabrafenib), MEK inhibitor Mekinist® (trametinib), and the prolyl hydroxylase inhibitor Duvroq® (daprodustat). Together these products account for nearly $4B in sales revenues in 2020 (Novartis 2020).

However, many of GSK's other CEDDs did not come close to achieving this same degree of success as judged by the number and quality of clinical PoCs. In hindsight, there were several reasons for the variable output between different CEDDs. For example, the psychiatry and cardiovascular CEDDs were working in areas where scientific advances at that time did not reliably translate into successful drug discovery programs—not just at GSK but throughout the industry. Another differentiating factor was the degree to which the heads of each CEDD manifest the triumvirate leadership requisites of scientific insight, experimental creativity, and out-of-the-box thinking that proved to be the critical determinants of success.

In a further effort to mimic start-up biotechs, GSK R&D under Patrick Vallance extended the "smaller-is-better" approach in 2008 and replaced the CEDDs with Discovery Performance Units (DPU) (Vallance 2010). These much smaller groups of only 50–60 scientists still covered the same disciplines—biology, chemistry, and clinical research—as the CEDDs but were even more narrowly focused. For example, instead of being responsible for an entire therapeutic area, e.g., oncology, a DPU worked solely in one area of disease biology, e.g., cancer epigenetics. In retrospect, this experiment was a dismal failure, and GSK's oncology R&D productivity declined dramatically over the next several years. The inherent advantages of vast scientific and technological

resources that large pharmas can bring to bear on novel drug discovery were partitioned into too many small and ineffectual groups with each competing against the others for the same pot of resources rather than working collaboratively. Moreover, the breadth of a typical large pharma therapeutic area portfolio consisting of 10–20 programs running simultaneously allows for projects deserving to be abandoned to be terminated thus freeing people and budget to be redeployed onto other projects that are progressing more favorably. The DPUs were so small that they could run only a few projects at a time such that to give up on any single project could result in the dissolution of the DPU and unemployment for its members (Torsoli 2011). Lastly, the DPUs did not and could not incentivize GSK researchers with the same opportunity for substantial individual wealth creation through equity that scientists in real biotechs can experience through an IPO or bringing a drug to market. Thus, GSK R&D could not be transformed into a biotech simply by replicating the staffing and portfolio size of a start-up. The DPU experiment ended in 2017 when GSK disbanded the DPUs, significantly trimmed its R&D portfolio by 30 programs, and restructured itself back to a more typical R&D organization (Pagliarulo 2017).

7.4.3 Virtualization and Outsourcing

Another major evolution in how pharma and biotech conduct discovery and development to create innovative new medicines while reducing R&D expenditures is to outsource R&D activities that were previously performed within their own walls (Schuhmacher et al. 2016). This strategy results in lower fixed costs to the pharma or biotech in the form of fewer R&D employees, lower capital investment on R&D, and fewer, smaller, or even no research campuses. Pharmas began the trend of outsourcing their synthetic chemistry activities to specialty chemistry companies in the 1990s as a way to expand their capacity for discovery research without having to hire additional staff and open new laboratories. Synthetic chemistry was considered to be straightforward to do and required less scientific creativity than medicinal chemistry which remained a prized discipline within pharma and was retained as an in-house function. When that proved to be successful, pharmas began experimenting with outsourcing medicinal chemistry in the early 2000s mostly as a means of expanding their throughput but now with the added goal of reducing R&D costs. Whereas a team of 15–20 medicinal chemists might have worked on a single discovery program in the past, it was now run instead by 2 or 3 internal chemists directing a team of medicinal chemists at one or more chemistry CROs. It proved far more cost-effective to hire a contingent of medicinal chemists at a CRO, especially when that CRO was located in a lower-cost country such as China or India, to do what was previously conducted solely by a pharma's own chemists. This industry-wide practice led to a proliferation of CROs such as Charles River Laboratories, WuXi AppTec, Evotec, Covance, and countless others that can perform virtually any R&D activity needed by pharmas and biotechs. These R&D activities range from chemistry to biology to animal toxicology to biopharmaceutical processing to clinical trials support to biostatistics and data management to regulatory affairs. The list is endless.

The outsourcing of a myriad of pharma R&D functions continues to grow in large part because outsourcing expenditures do not entail long-term budgetary commitments and can be flexed from year to year unlike R&D spends for internal headcount and research campuses which are generally fixed over time. Pressured by its investors, large pharmas have been willing to reduce their R&D headcount and physical footprint to improve the bottom line while maintaining or even increasing total R&D spends through outsourcing. For example, in 2005 GSK's R&D organization consisted of 14,963 employees which represented 15% of its total global workforce (GlaxoSmithKline 2005). By 2017, GSK's R&D staffing was reduced to 11,576 or 11.6% of its total workforce (GlaxoSmithKline 2017). By contrast, GSK's R&D spending during this period was relatively stable at $5.71B (£3.13B) in 2005 compared with $5.77B (£4.47B) in 2017.

Eli Lilly took a very innovative and radical approach to outsourcing when it virtualized an entire segment of its development portfolio. In 2002, it created the Chorus unit, a small, operationally independent clinical development organization that was separate from the rest of its sizable R&D organization (Owens et al. 2015). Chorus focused strictly on advancing molecules from late preclinical stages (roughly 1 year from entry into phase 1 trials) through clinical proof of concept which was typically a phase 2A trial. Chorus's mission was to achieve proof of concept rapidly and at a low cost using a "quick-win, fail-fast" model. Successful projects from Chorus would then return to the larger Lilly clinical development organization to complete late-stage (phase 2B or 3) clinical trials. At its peak, Chorus was able to sustain a portfolio of 15–17 active projects with approximately 40 full-time staff members who were selected for being experienced drug developers. This small group utilized an extensive network of CROs and other external vendors to design and implement activities in biology, preclinical toxicology, manufacturing, and phase 1 and 2 clinical trials in a diverse range of therapeutic areas including neuroscience, endocrine, inflammatory, oncologic, and cardiovascular diseases. From 2002 through 2012, the Chorus group prosecuted 41 molecules ranging from small molecules, synthetic peptides, engineered proteins, and monoclonal antibodies that originated from Lilly's discovery research. Of 35 molecules that completed clinical development within Chorus, 8 (23%) reached a positive outcome consisting of 5 that demonstrated a positive proof of mechanism and 3 that provided evidence of PoC. Although not an apples-to-apples comparison, the progression of a molecule to a phase 2A decision point by the Chorus approach was estimated on average to be faster and cheaper (28 months, $6.3M/molecule) than a more traditional large pharma approach to arrive at phase 2B decision (48 months, $42M/molecule).

In contrast to large pharma, biotechs, especially start-up or early-stage ones, do not have an option and must outsource its R&D liberally. Absent the armies of scientists and acres of laboratories that reside within large pharma, biotechs must conduct their laboratory and clinical research mostly, if not entirely, through CROs and their drug manufacturing through contract manufacturing organizations (CMOs). The voracious appetite from both large pharmas and biotechs for CROs and CMOs to conduct pharmaceutical R&D has resulted in their global revenues reaching $39B in 2018 with expected growth to $44B in 2021. This insatiable demand for their services is reflected by growth both in the number and organizational size of CROs and CMOs. In the areas of preclinical biology and medicinal chemistry, two of the leading CROs are Charles River Laboratories ($2.6B revenues in 2019, 17,000 employees) and WuXi AppTec ($1.8B revenues in 2019, 21,000 scientists). Catalent ($2.5B revenues in 2019, 15,000 employees) and Lonza ($6.6B revenues in 2019 15,000 employees) represent the largest CMOs in the areas of small molecules and biologicals, respectively.

Due to many clinical trials having substantial logistical complexity, worldwide reach, and requisite adherence to regulatory requirements, CROs that primarily support clinical development can be multinational enterprises with broad therapeutic area capabilities like Covance ($11.5B in 2019 revenues, >75,000 employees) or IQVIA ($11.1B in 2019 revenues, >67,000 employees). Frequently these large CROs are favored by large pharma that must conduct phase 3 clinical trials involving thousands of subjects across many continents. Biotechs, however, frequently prefer to work with mid-sized clinical CROs like Medpace ($861M in 2019 revenues, 2500 employees) or small regional companies like Quotient Sciences (2019: $138M in revenues, 850 employees) that focus on therapeutic areas such as oncology or specialty disciplines like clinical pharmacology and formulation development.

7.5 Implications for Pediatric Cancer Therapeutics

Given that large pharma and biotechs have R&D infrastructures that have a track record for scientific successes, especially in oncology, over sev-

eral decades and have grown dramatically as an industry, it is reasonable to ask why the discovery and development of novel medicines to treat pediatric cancers have not paralleled that of adult malignancies. A retrospective review of FDA approvals over a prior 20-year period through 2002 revealed a striking paucity of New Drug Application submissions for pediatric cancer indications (Hirschfeld et al. 2003). In fact, of over 100 drugs approved by the FDA at that time for the treatment of cancer, only 15 had any pediatric use information in their labeling with the majority of these drugs having been approved in the 1950s and 1960s. Furthermore, from 1979 to 1997, there were only six NDA or BLA submissions to the FDA for pediatric oncology indications of which just three received regulatory approvals.

The number of new drugs and biologics approved for use in childhood cancers, usually in concert with an approval for an adult malignancy but occasionally without a parallel adult indication, has without question improved since 2005. For example, since 2015, dinutuximab beta was approved for high-risk neuroblastoma, blinatumomab and tisagenlecleucel were approved for both adult and pediatric B-cell precursor acute lymphoblastic leukemia (ALL), and larotrectinib was approved for any adult or pediatric solid tumor having an NTRK gene fusion. However, there remains a substantial disparity in R&D activities and regulatory submissions and approvals from the biopharmaceutical industry when it comes to pediatric vs. adult oncology. There are many systemic reasons for the relative inattention by industry to pediatric cancer therapeutics.

The first and foremost reason is the projected financial return on investment. Both VCs when making their decisions to invest in start-up and early-stage companies and large pharma when determining which programs within its R&D portfolios to continue funding closely evaluate and model the commercial potential for every investigational drug. At its simplest distillation, these decisions are driven by a few key variables. First is the epidemiology, in particular the incidence, of the disease in question since that provides the number of new patients with the disease who may be prescribed the drug. Second is how long a patient will take the drug since the revenue from a drug taken for a few days like an antibiotic is far less than one taken indefinitely for a chronic condition like rheumatoid arthritis. And third is the price that the payors will agree to pay for the new drug. New drug pricing frequently reduces down to "what the market will bear" based on the competitive landscape of other drugs used to treat the disease, the therapeutic advance offered by the new drug, and once again the number of patients involved. All of these factors are quantified and placed into financial models that generate a net present value calculation that represents the profitability of the R&D investment based on what needs to be spent to get the drug to market vs. the future projected revenues of the new drug.

The critical limitation for pediatric cancers is their far lower disease incidence compared to commonly occurring adult cancers. For example, the American Cancer Society estimates that the annual US incidence of osteosarcoma and pediatric AML is only 1000 and 750, respectively. Even pediatric ALL, the most common childhood cancer, has an annual US incidence of only 2400. Compared to lung cancer and breast cancer with their respective US incidences of >235,000 and >281,000, respectively, it becomes obvious why adult cancers have been and remain the focus of VCs and large pharma when it comes to R&D investment decisions. Recall that the high-risk, high-reward strategy of VCs demands a projected 10- to 50-fold return on investment. This further underscores that childhood cancers with relatively small numbers of patients are severely disadvantaged when it comes to VC funding to create a start-up biotech or for a large pharma to invest in a discovery program that is 10 years or more from arriving at the FDA as an NDA or BLA submission.

The competition for R&D investment dollars extends beyond the decision to initiate a pediatric program but persists through the program's life in R&D. For example, Epizyme was advancing tazemetostat, an EZH2 inhibitor, in clinical trials targeting both follicular lymphoma, a common adult cancer, and atypical teratoid rhabdoid tumor (ATRT), a rare pediatric brain tumor. The clinical

program reached the point of needing R&D investment to develop an approvable liquid oral formulation since infants and toddlers are diagnosed with ATRT. Upon learning the cost of creating an oral suspension for tazemetostat, Epizyme's chief operating officer not only proposed stopping the formulation work but also all pediatric trials because the return on ATRT paled in comparison to follicular lymphoma, a more lucrative adult indication. When questioned about the ethics of potentially depriving children of a new drug for this rare cancer, he offered to "just give away" the adult-sized tablets after the drug would be approved for lymphoma and leave pharmacists to crush the pills for children's use. While this extreme example is not representative of the ethics within the biopharmaceutical industry as a whole, it does highlight the significant disincentives for long-term investment needed to successfully discover and develop a drug for childhood cancers within the current industry environment that emphasizes financial performance and returns.

It has long been recognized by regulators that inducements to the biopharmaceutical industry can be important to the development of pediatric therapeutics for all therapeutic areas, not just in oncology. A variety of regulatory "carrots" and "sticks" have been put into place with varying levels of effectiveness. Pediatric exclusivity and the Rare Pediatric Disease Priority Review Voucher are two of the more successful incentives instituted through the FDA. In 1997, Congress enacted the Food and Drug Administration Modernization Act which included a provision for pediatric exclusivity intended to encourage pharma sponsors through the provision of financial incentives to conduct clinical trials in children. The law provided for 6 months of additional marketing exclusivity to be added to existing patent life for an approved drug. Thus, a pharmaceutical sponsor that performed clinical studies in children in accordance with specific FDA requests could gain a longer period of sales as the entry of generic competition following the expiry of its patent protection would be delayed by one-half year.

The Rare Pediatric Disease Priority Review Voucher was created by FDA in 2012 and is closely modeled off a predecessor voucher program that covered tropical diseases. Importantly, a pediatric voucher obtained by a pharma or biotech sponsor for its candidate drug for a rare childhood disease can then be transferred (sold) to another, usually large pharma, sponsor. The buyer of a pediatric voucher whose drug has nothing to do with pediatric therapeutics can then receive a 6-month priority review by FDA for their NDA or BLA. A priority review by FDA that results in regulatory approval facilitates the drug reaching the market faster to generate greater sales revenues during its patent life. Pharmas quickly recognized the commercial value of these vouchers. The first-ever pediatric voucher was awarded in 2014 and purchased by Sanofi and Regeneron for $67M and used for the approval of Praluent® (alirocumab), a monoclonal antibody for adults with cardiovascular disease. In August 2015, AbbVie paid $350M for a pediatric voucher that it used to accelerate the approval of Rinvoq® (upadacitinib), a Janus kinase inhibitor for adults with rheumatoid arthritis. Since that time, the purchase price for rare pediatric disease vouchers has generally averaged $100M.

Finally, alternative models from within the biopharmaceutical industry have recently emerged that may provide innovative avenues to discover and develop novel drugs for children with cancer. In particular, three start-up biotechs—Day One Biopharmaceuticals, Oncoheroes Biosciences, and M4K Pharma—are deserving of mention. In aggregate these three companies have taken a mix of approaches to building an internal pipeline of drugs aimed at pediatric oncology indications. One focuses on licensing molecules already studied by large pharma in clinical trials for one or more primarily adult tumors and "repurposing" the molecule instead for treatment against a pediatric tumor. Another takes the more traditional path conducting discovery research to identify and optimize molecules created in the laboratory specifically for pediatric cancers of interest. A third is attempting to execute both of these strategies in parallel.

Day One Biopharmaceuticals, based in South San Francisco, launched in 2020 with a $60M

Series A investment. Its first molecule, DAY101, is a brain-penetrant pan-RAF kinase inhibitor from Sunesis Pharma, previously licensed to Takeda Pharmaceutical Company, that Day One is developing as a targeted treatment for children with low-grade gliomas harboring wild-type BRAF fusion proteins. Under Takeda, this molecule had been tested in over 200 adults with melanoma, glioma, and other solid tumors at the time of licensing. In 2021, Day One raised another $130M in a Series B round and licensed pimasertib and MSC2015103B, both allosteric inhibitors of MEK1/2, a key enzyme in the MAPK signaling pathway, from Merck KGaA. Pimasertib had been studied in over ten phase 1 and phase 2 clinical trials in approximately 900 cancer patients by Merck KGaA. Day One has disclosed that it intends to conduct combination development of DAY101 with pimasertib.

Based in Toronto, M4K Pharma is eschewing in-licensing and instead undertaking a robust medicinal chemistry approach to discover its own molecules for children with diffuse intrinsic pontine glioma, a highly lethal and devastating brain tumor of early childhood. Unlike Day One and Oncoheroes, M4K Pharma does not have any VC investment nor does it ever intend to. Instead, M4K which started in 2017 is wholly owned by a charity, the Agora Open Science Trust. M4K is predicated on using the principles of "open science" to revolutionize how affordable new treatments are discovered and developed. In this case, open science for M4K means that it is committed to not restricting access to its research by filing patents, instead freely sharing the scientific knowledge derived from its programs. In fact, M4K records its bimonthly research project team meetings and loads it onto YouTube for anyone with an interest to view in their entirety. M4K's discovery research occurs at academic and government laboratories, such as McGill University, the Institute of Cancer Research in England, Canada's Ontario Institute for Cancer Research, and many others. In addition, CROs like Charles River Laboratories perform research activities for M4K without charge as a charitable in-kind service. By taking this approach and with an initial funding of less than $3M, M4K has been able to identify five potential lead ALK2 inhibitor molecules as it advances through preclinical development.

Oncoheroes Biosciences, started in 2017 and based in Boston and Barcelona, is taking a dual approach of both repurposing existing clinical molecules that it licenses and conducting drug discovery to bring forth its own original molecules. For repurposing, Oncoheroes in 2019 licensed Boehringer Ingelheim's volasertib, a polo-like kinase 1 (PLK1) inhibitor, that had failed to demonstrate sufficient clinical efficacy in combination with low-dose cytarabine in an earlier phase 3 trial in elderly adults with AML (Döhner et al. 2016). However, based on PLK1's involvement in stabilizing PAX3/7-FOXO1, a chimeric oncoprotein implicated in rhabdomyosarcoma, Oncoheroes is pursuing the clinical development of volasertib in children with this soft tissue sarcoma. In 2020, Oncoheroes received Rare Pediatric Disease Designation from the FDA. This would qualify Oncoheroes to receive a priority review voucher should volasertib be approved thus allowing it to further monetize its R&D investment in volasertib by selling the voucher as described above. On the drug discovery front, Oncoheroes is utilizing a synthetic lethality approach in an attempt to identify a preclinical molecule or combination of molecules for high-risk pediatric medulloblastoma with MYC gene amplification.

Day One Biopharmaceuticals, Oncoheroes Biosciences, and M4K Pharma are all too early in their respective gestations as biotechs to have reached the goal that they all seek, namely, the successful clinical development and regulatory approval of a novel medicine for pediatric cancer. The strategy of repurposing molecules for indications other than the one originally intended has occasionally succeeded, e.g., Viagra was first developed for cardiac-related chest pain, but more often than not, this strategy has failed. At the same time, discovering a molecule from scratch is a long, arduous process that in most cases never yields a molecule that even enters into clinical trials. Nevertheless, given the substantial hurdles described above that make pediatric oncology the poor and neglected stepchild

of adult malignancies when it comes to attention, investment, and resources from large pharma and biotech, the paths taken by these three innovative biotechs bring hope that atypical avenues may yet be found to stimulate the development of novel and better treatments for children with cancer.

References

Anderson M (2020) Top 10 pharma companies by revenue. Becker's Hospital Review. https://www.beckershospitalreview.com/pharmacy/top-10-pharma-companies-by-revenue.html. Accessed 15 Jan 2021

Daemmrich A, Bowden ME (2005) A rising drug industry. Chem Eng News 83:28–42

Döhner H, Symeonidis A, Sanz MA et al (2016) Phase III randomized trial of volasertib plus low-dose cytarabine (LDAC) versus placebo plus LDAC in patients aged ≥65 years with previously untreated AML, ineligible for intensive therapy. Haematologica 101:abstract S501

GlaxoSmithKline (2005) Annual report

GlaxoSmithKline (2017) Annual report

Harper M (2013) The cost of creating a new drug now $5 billion, pushing big pharma to change. Forbes. https://www.forbes.com/sites/matthewherper/2013/08/11/how-the-staggering-cost-of-inventing-new-drugs-is-shaping-the-future-of-medicine/?sh=2e00f10b13c3. Accessed 16 Jan 2021

Hay M, Thomas DW, Craighead JL et al (2014) Clinical development success rates for investigational drugs. Nat Biotechnol 32:40–51

Hirschfeld S, Ho PTC, Smith M, Pazdur R (2003) Regulatory approvals of pediatric oncology drugs: previous experience and new initiatives. J Clin Oncol 21:1066–1073

Huckman RS, Strick E (2005) GlaxoSmithKline: reorganizing drug discovery (A). Harvard Business School Case 605-074

Merck (2019) Annual report

Mikulic M (2020) Total global spending on pharmaceutical research and development from 2012 to 2026. Statistica. https://www.statista.com/statistics/309466/global-r-and-d-expenditure-for-pharmaceuticals/. Accessed 15 Jan 2021

Mullard A (2013) An audience with... Paul Stoffels. Nat Rev Drug Discov 12:258

Naik G (2003) Glaxo's decentralized discovery pays off. Wall Street Journal, 24 Mar 2003

Novartis (2020) Annual report

Owens PK, Raddad E, Miller JW et al (2015) A decade of innovation in pharmaceutical R&D: the Chorus model. Nat Rev Drug Discov 14:17–28

Pagliarulo N (2017) GSK overhauls R&D, axes 30 programs to regain edge. Biopharma Dive. https://www.biopharmadive.com/news/glaxosmithkline-gsk-rd-pipeline-restructuring-cut-q2-earnings/447924/. Accessed 21 Feb 2021

Paul SM, Mytelka DS, Dunwiddie CT et al (2010) How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov 9:203–214

Pisano GP (2006) Science business: the promise, the reality, and the future of biotech. Harvard Business School Press, Boston, pp 84–87

Robaczewska J, Vanhaverbeke W, Lorenz A (2019) Applying open innovation strategies in the context of a regional innovation ecosystem: the case of Janssen Pharmaceuticals. Glob Transit 1:120–131

Sallman DA, Asch AS, Al Malki MM et al (2019) The first-in-class anti-CD47 antibody magrolimab (5F9) in combination with azacitidine is effective in MDS and AML patients: ongoing phase 1b results. Blood 134(Supplement 1):569

Schuhmacher A, Gassmann O, Hinder M (2016) Changing R&D models in research-based pharma companies. J Transl Med 14:105–115

Torsoli A (2011) Glaxo scientists 'live or die' with project in research overhaul. Bloomberg News. https://www.bloomberg.com/news/articles/2011-11-30/glaxo-scientists-live-or-die-with-project-in-biggest-research-experiment. Accessed 21 Feb 2021

Vallance P (2010) An audience with Patrick Vallance. Nat Rev Drug Discov 9:834. https://doi.org/10.1038/nrd3307. Accessed 12 Feb 2021

Wang SS (2009) J&J's Stoffels says 'Open Innovation' is the R&D answer. Wall Street Journal, 29 Jan 2009

Whalen J (2006) Bureaucracy buster? Glaxo lets scientists choose its new drugs. Wall Street Journal, 27 Mar 2006