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Discovery of Innovative Therapeutics: Today's Realities and Tomorrow's Vision. 2. Pharma's Challenges and Their Commitment to Innovation

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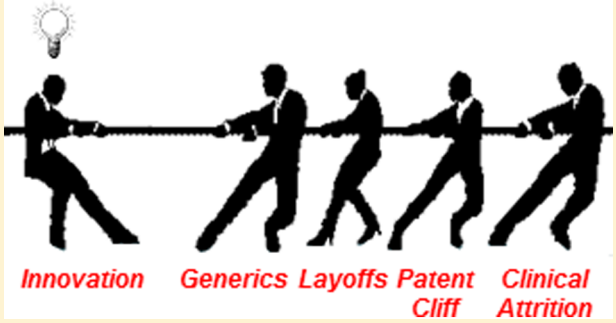
ABSTRACT: The pharmaceutical industry is facing enormous challenges, including reduced efficiency, stagnant success rate, patent expirations for key drugs, fierce price competition from generics, high regulatory hurdles, and the industry's perceived tarnished image. Pharma has responded by embarking on a range of initiatives. Other sectors, including NIH, have also responded. Academic drug discovery groups have appeared to support the transition of innovative academic discoveries and ideas into attractive drug discovery opportunities. Part 1 of this two-part series discussed the criticisms that have been leveled at the pharmaceutical industry over the past 3 decades and summarized the supporting data for and against these criticisms. This second installment will focus on the current challenges facing the pharmaceutical industry and Pharma's responses, focusing on the industry's changing perspective and new business models for coping with the loss of talent and declining clinical pipelines as well as presenting some examples of recent drug discovery successes.



INTRODUCTION

"It was the best of times, it was the worst of times..."

This famous line opens Charles Dickens' classic novel *A Tale of Two Cities* and speaks to the paradox of life and the fact that there are often both good and bad sides to things. The apropos statement was also used in a 2012 PricewaterhouseCoopers report to describe the situation that the pharmaceutical industry finds itself facing.[1] Dramatic changes to the scientific and business environments have made it impossible for pharmaceutical and biotech companies to continue operating as they have over the past 30 years. A perceived decline in innovation, fierce market competition from generics, increased regulatory hurdles, and key patent expirations on a number of blockbuster drugs (the so-called patent cliff) have all put significant pressure on branded pharmaceutical companies and threatened the future of the industry as a whole. Yet, it is this adversity and the absolute need for change that may be the industry's salvation. Things cannot go on as they have; there must be change. The industry has finally admitted this truth and has embarked upon a journey to find its path forward. Initial responses to the changing environment, beginning in the late 1990s, were harsh. Many companies have downsized, cut the number of research projects, outsourced many functions, and underwent mergers and acquisitions in an effort to survive as they seek to identify and establish business models that will guide them through the economic uncertainty. A number of initiatives have been instituted to ensure survival so that the industry can maintain its quest to identify and develop innovative new drugs to treat unmet medical needs. This second installment of our two-part series[2] presents and discusses some of the major challenges facing the pharmaceutical industry and Pharma's responses to these challenges. However, before that subject is breached, we present a short aside on the widespread impact that drug discovery has on the biomedical field as a whole and a brief review of the general drug discovery process that has been the standard over the past 30 years as background for the following discussion on challenges and changes.

BROAD IMPACT OF DRUG DISCOVERY ON BIOMEDICAL RESEARCH

In its simplest definition, drug discovery is the process by which new medications are identified. Drug discovery draws upon an integrated set of disciplines that work together to support the myriad activities needed to identify and validate drug targets relevant to a disease, to design or discover probes that elicit a desired pharmacological response from that target, and to optimize those probes to provide druglike candidates that safely and effectively treat the disease in question.[3] Those goals are important in their own right; however, many other areas of biomedical research have also benefited from drug discovery. Molecules and biological agents that may not possess the druglike properties needed to advance in the discovery process often provide tool agents that can be used by basic researchers to ask fundamental questions, to characterize biological systems and pathways, and to discover new drug targets or to

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understand existing ones better. The medical devices industry has also benefited from drug discovery. A classic example of this synergy is the advent of drug-eluting stents.[4] Percutaneous coronary intervention (PCI) has spared countless patients the need for coronary bypass surgery, but the technique was originally plagued by restenosis, the renarrowing of dilated artery segments. The introduction of drug-eluting stents (also known as coated stents, stents that slowly release drugs that inhibit restenosis) has significantly reduced the number of patients requiring follow-up revascularization (clinical trial results have recently been summarized by Li et al.[5]). Drug discovery activities also provide support to clinical research and drug development. For example, advances in formulation science have made it possible to evaluate clinically and launch drug candidates with poor physicochemical properties.[6] The antimitotic taxane analogue paclitaxel and the antifungal agent itraconazole are good examples of drugs whose development was originally threatened by poor solubility. Discovery medicinal chemists are routinely called upon to synthesize standard samples of major metabolites to support and facilitate clinical development of drug candidates. Enzymatic methods are now routinely used to obtain or scale up metabolites that are difficult to obtain through traditional organic synthesis. Chemistry platforms such as electrochemistry are now being applied to study metabolism.[7] Furthermore, the emerging field of metabolomics can assist in biomarker identification and can guide the selection of subjects for clinical trials by identifying patients more likely to respond or less likely to experience adverse effects.[8] In translational medicine, PET and SPECT imaging agents now play an integral role as biomarkers, measuring drug target engagement, guiding dose selection, diagnosing and characterizing disease states, and monitoring treatment effectiveness and progress.[9−11] Imaging agents must be endowed with a specific and specialized collection of biological, physicochemical, and ADME properties, which is the inherent specialty practiced by the discovery medicinal chemist. As can be seen from just these few examples, the quest to discover new drugs has had a widespread impact on a number of biomedical research sectors.

DRUG DISCOVERY PROCESS

Business models vary between large pharmaceutical corporations, smaller biotech companies, government research groups, and academic drug discovery laboratories, but the general drug discovery process that they all follow is essentially the same (Figure 1).[12,13] The first step is to identify a biological target whose pharmacological manipulation is expected to impact beneficially on a disease state. The target must be relevant to the disease and druggable. According to a 2006 summary by Overington et al.,[13] there are approximately 1500 drugs that have been approved for use in humans (1204 small-molecule drugs and 166 biological agents). These drugs work through their actions on 324 unique biological targets. A seminal paper by Hopkins and Groom in 2002[14] introduced the concept of the druggable genome and suggested that 600−1500 of the approximately 30 000 human genes could be relevant, druggable targets. These results did not take into account the possibility of multiple targets from a single gene through complex formation, splice variation, post-translational modification, and the existence of multiple receptor states for receptors, ion channels, and others.[15] Thus, although the number of predicted druggable genes is significantly smaller than the total genome, the chances are good that novel, viable drug targets still await discovery and exploitation. Many tools and techniques have been used to identify potential drug targets.[16] Bioinformatics, database mining, genetic association, and phenotypic screening have all been applied successfully. Precedence from known drugs and probe molecules can also assist in new drug target identification. Nearly 25% of known drugs have no known primary target or, at best, lack a well-defined mechanism of action.[17] Drug repositioning has become a popular subject for the drug discovery sector and is one of the missions of the recently formed National Center for Advancing Translational Sciences.[18] Examples of successfully repurposed drugs include gabapentin, ropinirole, buprenorphine, thalidomide, minoxidil, and aspirin.

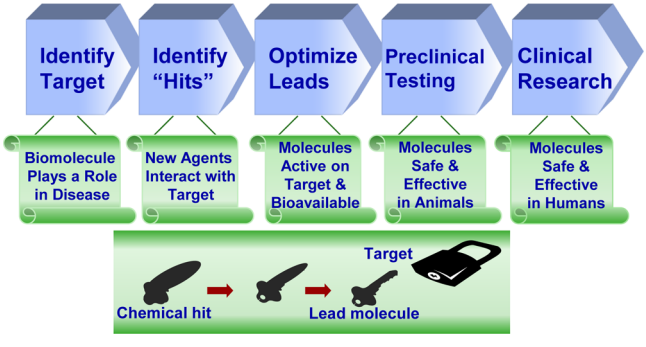

Figure 1. Drug discovery process.

Once a potential new drug target is identified, it must be validated and shown to be relevant to the disease state.[19,20] It is of the utmost importance to gain a high degree of confidence that the target is a good one before launching into a costly drug discovery campaign. The sequencing of the human genome has had a significant impact in this area.[21] Not only have potential new drug targets been identified but also the complex interaction between biochemical systems is now better understood, allowing researchers to predict potential synergy or redundancy between various systems. Today, medicinal chemists speak of families of drug targets such as the kinome, transporterome, and proteasome. There are also genetic considerations in target validation such as whether or not the target is expressed in tissues that are involved in the disease and at an appropriate age for the patient. However, a target must also pass other criteria to be considered validated. It is important to show that manipulation of the target (either enhancement or inhibition of its action) produces a biological change that will impact positively on the disease with a minimum of deleterious side effects. This question can be answered in a number of ways. The target should be characterized at as many levels as possible, including biochemical, cellular, isolated tissue, and in vivo. Transgenic animal models where the target has been either knocked out or knocked in are widely used to associate the target with a disease-related phenotype. One recent development in the field of transgenics is the use of cost- and time-efficient zebrafish in place of murine transgenics, most notably in the areas of cardiovascular safety and regenerative medicine. When small-molecule or biological tool compounds are not available to study the pharmacology of the target, antibodies, antisense technology, and RNA interference (siRNAs) can often be used to inhibit the activity or expression of the target, although these approaches are not without disadvantages such as high cost, the need for careful controls to ensure proper interpretation of

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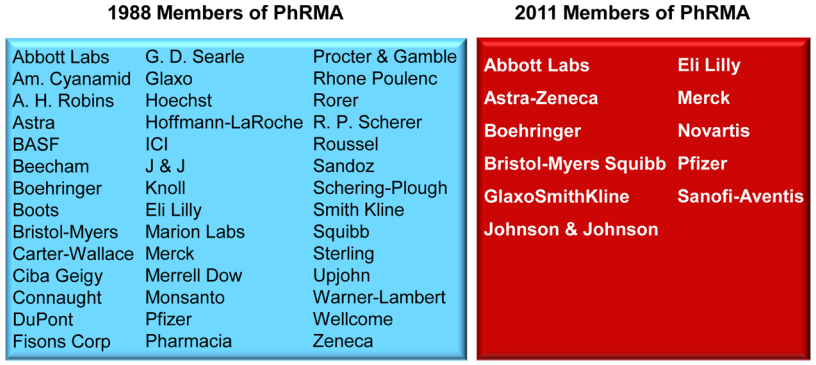

Figure 2. Comparison of PhRMA Members in 1998 and 2011.

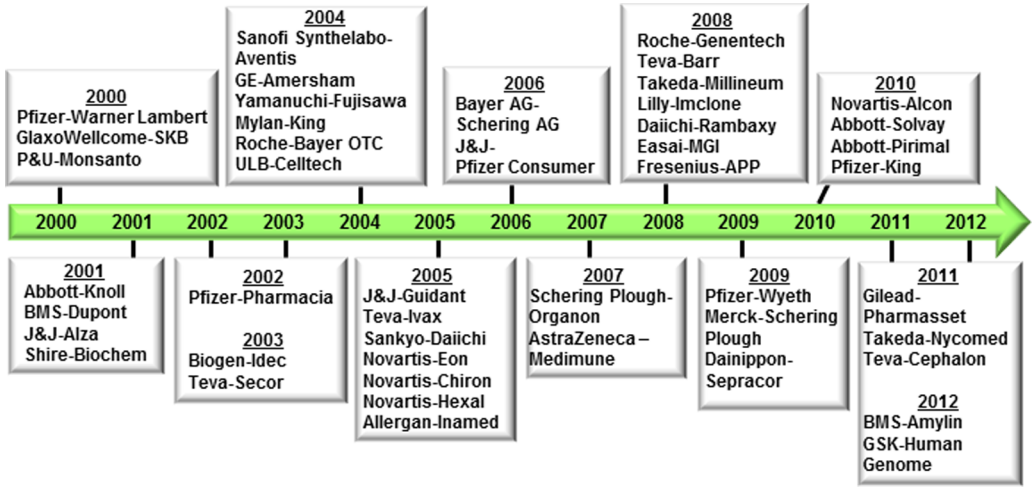

Figure 3. Timeline of mergers and acquisitions with values ≥$2 billion that occurred from 2000 to 2012.

data, and the inherent difficulties of getting such large molecules to their intracellular targets, especially in an in vivo setting. Questions of specificity and uniqueness must be addressed. Are there alternate pathways that the disease can employ if a drug is given for a candidate target? Will manipulating the target primarily affect the disease or will there be deleterious side effect that may limit dose or use of drugs affecting the target? Another issue that goes hand-in-hand with reliability is druggability. Not all potential drug targets will suitably interact with small molecules or biological agents. When the 3D structure of a target is known but that of its potential binding sites is not, computational methods can be employed to suggest likely locations.[22,23] Virtual screening of focused small-molecule or fragment-based libraries can provide additional confidence in a target before a costly high-throughput screen is attempted. Detailed thought processes for validating potential drug targets have been proposed in the literature. Wisely, the value of the human insight of experienced structural biologists and medicinal chemists is still apparent in many of these druggability rubrics.[24]

A plethora of papers and reviews discuss the hit identification, hit-to-lead, and lead optimization activities associated with drug discovery. Some have represented that process as crafting a key to fit into a 3D lock (Figure 1). An important aspect that enhances the chances for success is the identification of druggable scaffolds,[25] whether those scaffolds come from virtual screening, fragment-based design, high-throughput screening, or rational design based on known drugs or probes. To that end, Lipinski's rule of five and its variations still play an important role in triaging and prioritizing potential chemical scaffolds for initiation of structure–activity relationship (SAR) campaigns.[26] High-throughput chemistry and in vitro biology have made it possible for drug discovery teams to gather and analyze a tremendous amount of SAR information in their quest for potent, selective, and efficacious drug candidates.[27] The establishment of high-throughput in vitro physicochemical and ADME screens and in silico ADME have allowed medicinal chemists to prioritize chemical scaffolds and optimize druglike properties simultaneously with pharmacological activity, thereby identifying structure–property relationships (SPRs) in addition to SARs.[28,29] This multidimensional optimization strategy has led to a decrease in the number of compounds terminated from clinical trials for unsatisfactory pharmacokinetics.[30]

■ PHARMA CHALLENGES

It became apparent by the early 2000s that the general business model followed by most of big Pharma needed adjustment.[31,32] Dramatic changes in the economic and regulatory environments, the increased complexity of the diseases in need of treatment, a stagnation in the number of new drugs receiving approval despite increased R&D spending (relative to the 1990s), and fierce competition from generics began taking a toll on the pharmaceutical industry so that it could no longer ignore or deal with using a business as usual approach. A number of challenges needed to be addressed if the industry was to survive. Ironically, some of the initial responses by big Pharma

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have led to additional challenges rather than solutions. Those challenges and the strategies that the pharmaceutical industry has pursued to address those challenges are discussed below.

MERGERS AND ACQUISITIONS

To the outside observer, mergers and acquisitions (M&As) in the pharmaceutical industry seem like a routine occurrence these days. However, the truth is that they are anything but routine. According to a recent story by Kathlyn Stone[33] and on the basis of data from Irving Levin Associates, Inc.,[34] during the period 2000−2009, 1345 M&A deals took place, with a total value exceeding $690 billion. These M&A's have played a significant role in the loss of over 300 000 pharmaceutical jobs since 2000. Although they may have looked beneficial to both upper management and stock holders in the short term, the long-term consequences may have been detrimental to big pharmaceutical companies' R&D efforts, as succinctly described in articles written by Pharma insiders such as John LaMattina,[35] Raymond Firestone,[36] and Bernard Munos[37] as well as outside business observers such as Comanor and Scherer.[38]

As a result of M&A activity, the number of biopharmaceutical companies has decreased dramatically. In 1988, big Pharma members of the Pharmaceutical Research and Manufacturing Association (PhRMA) totaled 42 (Figure 2). By the year 2011, that number was down to 11, although one of the 1988 members, Roche, left PhRMA out of choice rather than loss of identity from an acquisition. For the most part, that period saw small-to-midsized companies swallowed up by the big Pharma giants. However, big Pharma was not immune, with a number of large companies being acquired by their competitors. Figure 3 and Table 1 provide a summary of pharmaceutical company M&A's from 2000−2012 in which the value of the deal exceeded $2 billion. In particular, Pfizer was one of the most active M&A protagonists for deals in this price range, although Abbott and Novartis also executed several multibillion dollar deals as well. A number of mega-deals received ample publicity during this time, including GlaxoWellcome's acquisition of SmithKlineBeecham to form GlaxoSmithKline in 2000, Pharmacia/Upjohn's merger with Monsanto to form Pharmacia in 2000, Pfizer's acquisitions of Warner Lambert in 2000, Pharmacia in 2002, and Wyeth in 2009, Sanofi-Synthalabo's acquisition of Aventis in 2004, Roche's complete acquisition of Genentech in 2008, Merck's acquisition of Schering-Plough in 2009, and Novartis' acquisition of Alcon in 2010. The value of each of these deals exceeded $40 billion. Since 2010, no further mega-mergers have occurred. However, many analysts believe that more multibillion dollar M&A's may be on the horizon, spurred by the completion of ongoing restructuring activities, a need to boost revenues, continued low research productivity, and the availability of large cash reserves. Big Pharma may not be the only player in the M&A game now that many biotech companies like Amgen, Celgene, and Gilead are valued at greater than $10 billion. In fact, Amgen recently announced that it will acquire Onyx for $10 billion.[39] Furthermore, M&A activity has now become common in many international markets (such as the Indian pharmaceutical market) as well as the generic market. Thus, it appears likely that the trend will continue.

Analysts agree that mergers, and especially acquisitions, occur in response to financial and business pressures, not for the sake of enhancing research capacity.[40] Grabowski and Kyle have recently categorized the motives for M&As into five major catagories (Table 2).[41] For example, the primary motivations

Table 1. List of Mergers and Acquisitions with Values ≥$2 Billion That Occurred from 2000 to 2012

date	companies[a]	approx. value (billions of dollars)
2000	Pfizer−Warner Lambert	90
	GlaxoWellcome−SKB	74
	P&U−Monsanto	50
2001	J&J−Alza	12.3
	BMS−Dupont Pharma	7.8
	Abbott−Knoll	6.7
	Shire−Biochem Pharma	4
2002	Pfizer−Pharmacia	57
2003	Biogen−Idec	6.7
	Teva−Secor	3.4
2004	Sanofi Synthelabo−Aventis	62
	GE−Amersham	10.2
	Yamanuchi−Fujisawa	8
	Mylan−King	4
	Roche−Bayer OTC	2.9
	UCB−Celltech	2.7
2005	J&J−Guidant	21
	Teva−Ivax	7.9
	Sankyo−Daiichi	7.7
	Novartis−Eon	6.8
	Novartis−Chiron	5.8
	Novartis−Hexal	5.3
	Allergan−Inamed	3.1
2006	Bayer AG−Schering AG	21
	J&J−Pfizer Consumer	16.6
2007	Schering-Plough−Organon	11
	AstraZeneca−Medimune	15.2
2008	Roche−Genentech	44
	Teva−Barr	8.9
	Takeda−Millenium	8.8
	Lilly−Imclone	6.5
	Daiiche−Rambaxy	4.6
	Easai−MGI	3.9
	Fresenius−APP	3.7
2009	Pfizer−Wyeth	68
	Merck−Schering-Plough	41
	Dainippon−Sepracor	2.6
2010	Novartis−Alcon	51
	Abbott−Solvay	4.5
	Abbott−Piramal	3.7
	Pfizer−King	3.6
2011	Gilead−Pharmasset	11
	Takeda−Nycomed	9.6
	Teva−Cephalon	6.8
2012	BMS−Amylin	5.6
	GSK−Human Genome	3

[a]Abbreviations: GE, General Electric; J&J, Johnson & Johnson; OTC, Over the Counter; P&U, Pharmacia and Upjohn; SKB, SmithKline-Beecham; BMS, Bristol-Myers Squibb; and GSK, GlaxoSmithKline.

Table 2. Motives for M&As in the Pharmaceutical Industry[a]

response to industry-wide or company-wide shocks
economics of sales and scope
access to new technology
expansion to foreign markets and other stages of the drug distribution chain
increased market power and size

[a]Source: ref 41.

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believed to be behind Pfizer's acquisition of Wyeth in 2009 were Pfizer's desire to acquire capacity in biological therapeutics and vaccines (a strength for Wyeth) and their desire to obtain Wyeth's clinical and late-phase pipeline, which was felt by many to be one of the best in the industry at the time.[42] On the surface, M&A's appear attractive. For a pharmaceutical company with a weak pipeline, M&A's are a relatively quick way to acquire products and late-stage development candidates that enhance the company's value for shareholders, at least in the short term. However, data suggest that the long-term impact of M&A's on R&D, especially in large pharmaceutical companies, is not as beneficial. A certain amount of streamlining can occur, with synergies identified, duplications eliminated, and costs cut. These measures appeal to stockholders because they immediately affect the bottom line of the company but do not necessarily translate into a more efficient, productive R&D operation. For example, one measure of long-term value, the identification of new molecular entities (NME's) approved by the Food and Drug Administration was analyzed by Munos in 2009.[37] This analysis of six large pharmaceutical companies involved in mergers, 10 large companies involved in acquisitions, and 14 small (biotech) companies involved in acquisitions showed that, for large companies, mergers did little to increase the average output of NME's and acquisitions resulted in a significant 70% decrease in NME output. Small companies fared better, with a 118% increase in average NME output following 80% of the acquisitions analyzed. Thus, on average, acquisitions may boost small-company output but, at least for the companies analyzed, do little to enhance large-company productivity. This observation is corroborated by LaMattina,[35] who noted that advancement of Pfizer's internal (i.e., nonacquired) clinical pipeline compounds slowed following their acquisition of Wyeth in 2008.

The negative impact of M&A's on R&D productivity can be felt at all stages of the drug discovery and development process. In the interest of cutting costs and eliminating duplications, projects are routinely terminated, divisions are dismantled, whole research sites are eliminated, and, of course, R&D scientists are laid off. Although in theory such endeavors offer the opportunity to retain and concentrate the best and brightest scientists, the painful truth is that often, in the name of cost cutting, the more experienced and higher-paid scientists (especially at the bench levels) are among the first to go. Since 2000, over 300 000 pharmaceutical employees have lost their jobs, many to M&A's and company downsizing. Some have found new jobs with other pharmaceutical or biotech companies, but there are no accurate reports detailing how many displaced Pharma scientists remained in the biopharmaceutical industry versus the number that had to venture outside of the private sector or change their careers to find employment. One must wonder how much of the creativity that led to many of the blockbuster drugs of the 1990s was retained when the companies that discovered those blockbusters were acquired during the 2000s. With fewer scientists to execute projects, it follows that the average number of research projects must be smaller. This reduction in human resources plays a role in how many compounds advance to development. Research budget is another factor. One would think that a merger of two large companies would lead a larger annual research budget for the combined entity. A number of studies, including a 2006 U.S. Congressional Budget Office study (summarized by Tjandrawinata and Simanjuntak[43]) suggest that higher R&D investment correlates with profitability and competitiveness of a company. However, until recently, increased spending has not correlated with an increase in the number of NCE approvals by the FDA. A number of merged entities have reportedly cut back on their research budgets to numbers significantly lower than the combined research budget of the two separate companies. For example, the combined research budget for Pfizer and Wyeth in 2008 was over $11 billion, whereas the 2012 research budget for the merged entity was around $7 billion.[44] Even merged companies that originally sought to retain a significant portion of their combined research budget, like Merck/Schering-Plough,[45] have come under criticism from Wall Street critics and have recently executed major downsizing activities and R&D budget cuts.

Fewer drug discovery scientists in the pharmaceutical industry means fewer internal projects, leading to a decreased number of home-grown compounds advancing to development. Later, we will discuss how today's big Pharma companies are trying to deal with the lost productivity and innovation that comes from reduced numbers of drug discovery scientists. However, the discovery phase of a clinical candidate represents a relatively small portion of the budget compared to the cost of developing that clinical candidate once it is identified. Companies must possess the financial resources to support costly clinical trials to get a new drug to market and into the hands of patients. Although the number of midsized biotech companies with the resources to support a limited number of clinical trials has increased since the 1990s, the number of big Pharma companies with the ability to support multiple clinical trials on multiple candidates has decreased significantly. Some data suggest that when a merger or acquisition occurs between two large companies the number of pipeline candidates advancing into clinical trials can increase, at least in the short term.[46] However, it has been argued by others[47] that clinical advancement does not necessarily represent a true measure of productivity, and, as stated earlier, there is testimony from one Pharma insider that acquisition of one large company by another can lead to a slowing of clinical advancement for the pipeline candidates that originated with the acquirer. Regardless of the source of clinical candidates, logic dictates that fewer companies with the financial ability to support multiple clinical trials means less compounds undergoing clinical trials, which has to result in fewer new drugs being developed and brought to market.[38] To this point, LaMattina makes a valid observation.[35] When critics of the pharmaceutical industry discuss the reductions in numbers of drugs approved each year by the FDA, they often compare the mid- to late-2000s with the 1990s. The truth is that there were fewer large pharmaceutical companies during the mid-to-late 2000s compared to the 1990s, which surely contributed to the reduction in number of new drug approvals.

M&A's obviously take a toll on the employees who lose their jobs in the process. However, negative impacts can also be felt by employees who are retained, and these negative "vibes" can have detrimental effects on the innovation and productivity of the emerging new corporate entity. During the merger or acquisition, preclinical research, especially for the partner undergoing acquisition, slows or stops completely as the fate of the acquired people and projects is determined. The review process takes several months and has an immeasurable but significant effect on morale and productivity. Both the acquired and the acquiring staff are affected as they worry about their futures. Many begin to seek new employment even before their

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role in the new company (or lack thereof) is determined. The onus continues for employees who are kept on after the initial acquisition activities are completed because the staff-reduction process often occurs in sequential waves that take upward of a year to complete. Retained scientists may be tempted to shift their research efforts away from risky endeavors that might lead to real breakthroughs to activities intended to enhance the job security so that they will be kept on in the event of future M&A's or staff reductions. In the current drug discovery environment, safe research that leads to incremental improvements of known therapies may not be enough to ensure the success of companies as they struggle to overcome the patent cliff, the changing world market, and the greater regulatory requirements. Unfortunately, it is these little victories that are perceived as building researcher reputations and ensuring job security in the environment of a merger or acquisition. Going forward, companies must encourage, retain, and reward those scientists who take chances with the goal of discovering breakthrough drugs.

PATENT CLIFF

The concept of the patent cliff is well-known to anyone with interest in drug development and the pharmaceutical industry. Starting in 2010, a number of blockbuster drugs (originally defined as drugs selling more than $1 billion per year, although $4 to 4.5 billion in annual sales is now considered blockbuster by most big Pharma companies) began losing patent protection (Table 3). Over $68 billion in worldwide sales of branded prescription drugs was lost because of patent expirations and resulting generic competition during the period of 2010–2012,[48] and some estimates suggest that over $290 billion in sales may be at risk for the period of 2012–2018.[49] The impact on the branded industry, as a whole, is obvious. However, the damage of losing the majority of sales from a blockbuster drug on an individual company can be devastating. Following the expiration of patent coverage on Lipitor (atorvastatin) in November of 2011, Pfizer lost 59% of its worldwide sales (81% of U.S. sales) in 2012 despite major efforts to maintain those sales and soften the blow from the loss (Figure 4).[50] Other classic examples of loss in branded sales following patent expiration can be seen with Merck's Fosamax (alendronate) and Eli Lilly's Prozac (fluoxetine). Following a successful Paragraph IV challenge in 2008 by Teva (four years before the Fosamax patents were scheduled to expire), Fosamax sales dropped by 50% in 2009.[51] A similar successful patent challenge by Barr in 2001 eroded market share of branded Prozac, which fell to generic fluoxetine by 65% in the first two months. By the end of 6 months, branded Prozac accounted for only 16% of the prescriptions written for the popular antidepressant drug.[52]

Table 3. Blockbuster Drug Patent Expirations between 2011 and 2016[a]

year	brand name	2010 sales (billions of dollars)[b]	company
2011	Actos®	4.6	Takeda
2011	Zyprexa®	5.0	Eli Lilly
2011	Lipitor®	12	Pfizer
2012	Levaquin®	1.4	Janssen
2012	Lexapro®	3.5	Forest
2012	Seroquel®	5.6	AstraZeneca
2012	Plavix®	9.1	BMS[c]/ Sanofi
2012	Singulair®	5.4	Merck
2012	Diovan®	6.1	Novartis
2013	Cymbalta®	3.5	Eli Lilly
2013	OxyContin®	2.4	Purdue
2013	Zometa®	1.5	Novartis
2014	Nexium®	5.0	AstraZeneca
2014	Celebrex®	2.7	Prizer
2014	Sandostatin®	1.3	Novartis
2015	Abilify®	4.6	BMS[c]
2015	Gleevec®	4.3	Novartis
2016	Crestor®	6.1	AstraZeneca

[a]Source: ref 49. [b]World-wide sales. [c]BMS, Bristol-Myers Squibb.

Pharma has responded to the patent cliff and impending loss of revenue in a number of ways. We have already discussed the dramatic increase in mergers and acquisitions (including a number of mega-acquisitions) that occurred in the period of 2000–2012 as large companies anticipated the unprecedented number of patent expirations and strove to replace their shrinking pipelines with those of other companies. Different companies have embraced the acquisition arena with varying degrees of enthusiasm. Some companies, with Pfizer being the notable example, have chosen inorganic growth through mergers and acquisitions as a major part of their solution to declining revenues. Other companies, such as Eli Lilly, have avoided major M&As. As discussed earlier, M&As offer a short-term solution to the patent cliff issue but may actually hurt long-term growth through their detrimental effects on internal research and development. Growing internal R&D capacity is, in theory, a more favorable solution for long-term growth provided that internal growth successfully leads to the identification and development of innovative new drugs. Only time will tell which strategy, if either, is better.

Apart from M&As and increasing internal R&D capacity, other avenues for weathering the patent cliff are being pursued by today's pharmaceutical companies as they look for the new business models that will help them survive and thrive in today's changing economic environment. A recent analysis of drug company portfolios from 2008 revealed that, with a few exceptions, most companies were not in a position to replace effectively the revenues soon to be lost to blockbuster patent expirations in the short term.[53] To overcome this weakness, companies have considered a number of approaches. We will now discuss some of those approaches.

Abandoning the Blockbuster Mentality. Some companies have shifted focus away from a preference for identifying and developing potential blockbuster drugs (the so-called blockbuster mentality) to pursuing a greater number of more focused drugs whose separate sales may not reach blockbuster levels but whose combined sales may compensate for the loss of those blockbusters. The cardiovascular drug area is a good example of this strategy. Despite the financial success of a number of cardiovascular drugs (e.g., Actos, Plavix, and Lovenox), investors and companies alike have hungered for a new drug with the level of success seen with the statins, most notably, atorvastatin, whose annual sales exceeded $12 billion for several years. Some companies have now reconsidered that approach. For example, SanofiAventis recently discussed its plans to replace Plavix and Lovenox with a range of drugs with more focused roles such as Multaq, Zaltrap, and Kynamro.[54] However, although the past 2 years has seen an increase in the number of FDA approvals of drugs with limited applications in smaller numbers of patients such as targeted cancer drugs, this approach is not without risk. Such specialty drugs rarely move

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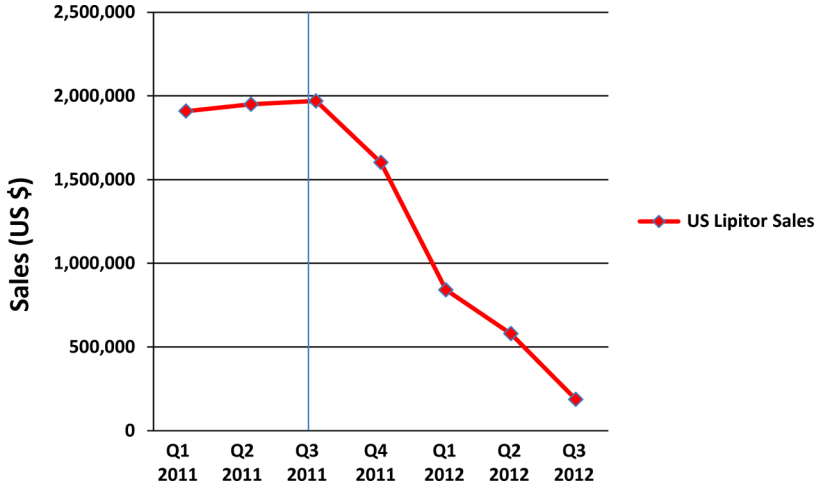

Figure 4. Effect of introduction of generic Atorvastatin on U.S. Lipitor sales (source: ref 50).

through the approval process any faster than drugs with broader application, and the cost of developing such drugs still approaches $1 billion or more. The result is that the price of such targeted drugs once they reach the market, especially in the U.S., is high because of the limited exclusivity time available to recoup the investment in the drug. For example, Vertex's Kalydeco, a drug targeting the underlying cause of cystic fibrosis (30 000 cases in the U.S., with 1000 new cases diagnosed annually), costs around $294 000 per year. The high price of such drugs, particularly for politically charged disease areas such as HIV infection and cancer, continues to face criticism and challenge from government officials, lawmakers, insurers, patients, and advocate groups. Thus, this avenue for recouping lost blockbuster revenues may see limited success.

Therapeutic Focus. In addition to a move away from the blockbuster mentality, pharmaceutical companies have been actively seeking new business models that will enhance the chances for survival in the changing environment. Two adaptations that have received significant attention are therapeutic area focus and diversification. For example, in the late 2000s, Pfizer announced their intent to focus on six invest-to-win therapeutic areas (Table 4). These areas were identified on the basis of market, unmet medical need, and the relative difficulty of getting new drugs approved in light of heightened regulatory requirements that new drugs not only be efficacious but also be better than currently available drugs for the same indication. Several other big Pharma companies have developed similar strategies based on the relative rates of success within the various therapeutic areas, and it is evident from Table 4 that there is a tremendous degree of overlap between big Pharma companies as to which areas they feel offer the best opportunities for growth. It is also evident that some therapeutic areas, like antibiotics (the term anti-infectives in Table 4 refers primarily to virology), have been abandoned by many big companies because of the increased difficulty in getting new drugs approved.

Product Diversification. Although most of the large companies are focusing their pharmaceutical R&D efforts in areas which they hope will foster success, there seems to be a difference in opinion concerning diversification. The 1960s and 1970s saw a wave of diversification by pharmaceutical companies as they sought to maintain revenue flow. This trend was reversed in the 1980s as a result of the success of a number of blockbuster drugs and a move toward the

Table 4. Therapeutic Areas of Focus for Representative Big Pharmaceutical Companies[a]

company	therapeutic areas of focus
Pfizer	oncology, pain, diabetes, AD, inflammation, psychoses
Merck	cardiovascular, diabetes/endocrinology, neuroscience/ophthalmology, oncology, respiratory/immunology, infectious disease
Novartis	hypertension, metabolism, virology/anti-infectives, neuroscience, oncology, ophthalmology, respiratory, transplantation
GlaxoSmithKline	cardiovascular/metabolic, inflammation, infectious disease, neuroscience, oncology, ophthalmology, respiratory
Eli Lilly	neuroscience, urology, cardiovascular, autoimmunity, musculoskeletal, diabetes, oncology
Abbott	chronic kidney disease, multiple sclerosis, antivirals, oncology, women's health, immunology, neuroscience/pain
BMS	cardiovascular, immunology, metabolics, oncology, virology, neuroscience
AstraZeneca	cardiovascular, anti-infectives, oncology, gastrointestinal, neuroscience, respiratory/inflammation
Takeda	cardiovascular, metabolic, neuroscience, respiratory/immunology, oncology
Johnson and Johnson	cardiovascular/metabolic, immunology, anti-infectives, neuroscience/pain, oncology

[a] Source: company websites.

blockbuster mentality paradigm. Today, many pharmaceutical companies own business units that are not based directly on branded pharmaceuticals such as animal health, consumer health, medical devices, and so forth. With the mission of focusing efforts in mind, some companies have begun spinning off some of their satellite business units. Notable examples include Pfizer, who recently spun off their animal health care unit Zoetis, and Abbott, who recently announced that they would separate their medical products and pharmaceutical units into two separate companies. Both of these moves were well-received by investors as indicated by an increase in stock price. However, other companies have taken the opposite path and have embraced diversification as a means of boosting profits and remaining solvent as they work to reinvent their ethical pharmaceuticals business model. Johnson and Johnson, a broadly diversified company, cites that diversified portfolio as one of the elements of its continued success. Companies such as Merck and SanofiAventis have recently cited diversification

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as an important part of surviving the patent cliff. For example, Bayer (an already diverse company) recently expanded into the vitamins arena with a $1.2 billion purchase of Schiff, and Novartis acquired the ophthalmology company Alcon in 2011 (a $51 billion mega-merger). However, the two major areas of diversification that several big pharmaceutical companies have embraced are biologicals and branded generics (discussed in the section on generic competition).

Patent Extensions. A common method of avoiding patent expiration is to extend the patent life for drugs. We have already covered this topic in Part 1 of this series,[2] and readers are referred to that manuscript for a detailed discussion of the subject. The Hatch–Waxman Act of 1984 provides for patent extensions in recognition of the long development times required for bringing a new drug to market. Up to 50% of the time spent in initial clinical trials and 100% of the time spent in regulatory evaluation can be added to the life of a patent, provided the applicant did not cause undue delay in either of these two processes. However, other patent strategies are routinely used by pharmaceutical companies to extend the exclusivity period of their products, a process referred to by critics of the practice as evergreening.[55] These include patenting optimal physicochemical forms of the drug, additional indications, new formulations, active enantiomers of racemates, and branded fixed-dose combinations of the drug (for example, the multiple drug combinations used in HAART treatment of HIV infection). Patent extensions are not always successful. Paragraph IV patent challenges are becoming more common, and a number of noncomposition of matter patents have fallen under litigation, such as the patent covering Norvasc, the besylate salt of the calcium channel blocker amlodipine. Generic companies are beginning to achieve a level of success with their abbreviated new drug applications (ANDAs) by carving out patented uses of drugs from their generic labels. Given the ability of physicians to prescribe a drug for a nonlabeled use in the U.S. (off-label prescribing), companies relying on use patents to protect their branded drug may be forced to police generic company's public marketing strategies to minimize off-label prescribing of generics for proprietary uses.

Emerging Markets. Another avenue that pharmaceutical companies have pursued in response to declining sales and lost revenue due to the patent cliff is expansion into emerging markets. The topic has recently been discussed in detail in a briefing from the global management firm Booz & Co.[56] Defined as countries with social or business activity in the process of rapid growth and industrialization, the pharmaceutical concept of emerging markets divides them into three tiers: the BRICMT group (Brazil, Russia, India, China, Mexico, and Turkey), the second-tier group (a diverse group of more mature economies from Eastern Europe, former Soviet bloc nations, and Southeast Asia), and Africa. As opposed to that in the U.S. and EU5 countries, the emerging markets are expected to grow significantly over the next 5 years (Figure 5). Pharmaceutical companies have already pursued these markets in the past as a source of additional income and continue to do so with renewed vigor in the wake of the patent cliff. The BRICMT nations will likely continue to draw most of the attention because of their stable economic systems and their relatively higher standard of living, although second-tier nations are now being viewed as tempting emerging markets.

In 2008, infectious diseases, especially those caused by the HIV virus and chronic parasite-based neglected diseases, made

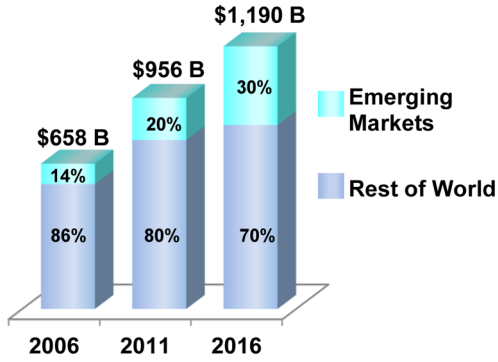

Figure 5. Pharma market development, 2006–2016.

up a significant portion of the disease patterns seen in second-tier and African nations. Pharma's response to the AIDs epidemic in developing nations has already been discussed in the previous part of this series.[2] Highly active antiretroviral therapy (HAART) involving combinations of various drugs shows promise in the ongoing battle against AIDS, but the high cost of such combination therapies, especially those whose components are still under patent protection, has become a major issue both in developing countries and in the U.S., where yearly costs for HAART can easily exceed $25 000/year. Contrary to popular criticism, pharmaceutical companies have made some efforts to combat chronic infectious diseases such as trypanosomiasis, leishmaniasis, Dengue fever, and lymphatic filariasis. This aid came in the form of donations of existing drugs and tiered pricing to facilitate drug purchase by foreign governments and involved medical groups. Concern over an inability to recoup investment dissuaded (and continues to dissuade) most companies from engaging in novel drug discovery targeting these diseases, despite their prevalence and devastating impact on victims. A shift in disease patterns in emerging markets is predicted to occur over the next 5 years (Figure 6). The prevalence of infectious diseases, particularly HIV/AIDS, is expected to decline and to be replaced by diseases that are already an issue in the U.S. and Europe. In fact, examination of the predicted future disease patterns for the emerging market countries show that their growth coincides with the therapeutic area focus strategies that almost all of the big pharmaceutical companies have already embraced, suggesting that the promise of emerging markets has been incorporated into the new R&D models. However, one issue that remains uncertain is how problematic treatment-resistant bacterial infection will become in the next 20 years. As the FDA comes under renewed pressure to relax approval criteria for new antibiotic candidates, big Pharma continues to withdraw from antibiotic drug discovery, viewing it as too risky. It remains to be seen if the current level of antibiotic research can keep up with the proliferation of multi-drug-resistant strains of bacteria.

However, despite the promise of untapped revenue, efforts to exploit those emerging markets by companies have realized limited success and have not reaped the profits originally expected. It became apparent that to be successful in emerging market countries, companies needed to establish themselves locally, either by building internal capacity in the country in question or by partnering with existing resources. A major hindrance to that goal was the inability to identify and recruit qualified local talent. Even today, in countries like China and India where the quality and quantity of local expertise have

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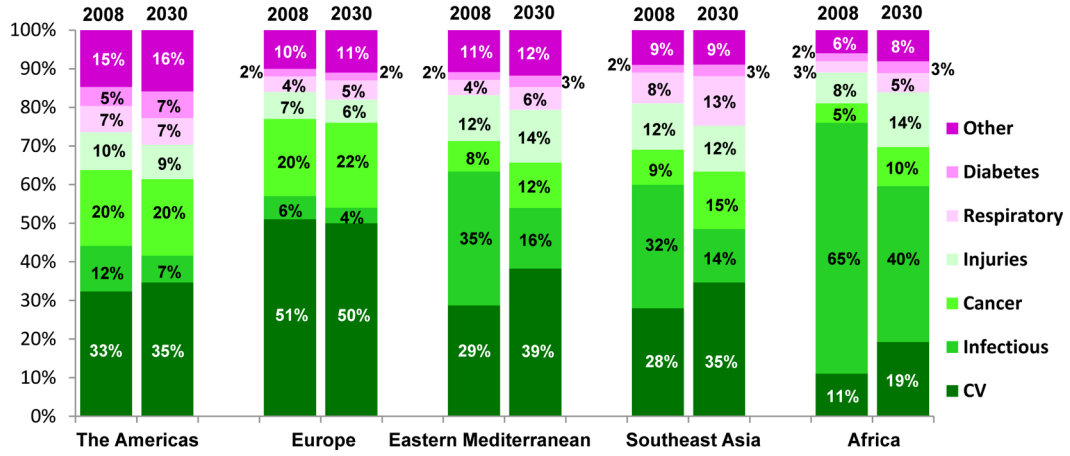

Figure 6. Disease patterns in 2008 compared to predicted patterns in 2030 (source: WHO, Booz & Company).

grown significantly, continuing competition makes it difficult to retain that talent as personnel regularly change positions to move up the corporate ladder. Other challenges also continue to hinder growth into emerging markets. Lack of a good health-care infrastructure in many countries makes it difficult to reach much of the population. Companies will need to work with governments to identify or build systems that identify patients in need of treatment, match those patients with the right drugs, and get those drugs into the hands of the patients. Despite growing economies, cost is still a major issue in emerging markets, especially for new drugs. Many developing countries do not have a prescription cost reimbursement system. Governments and internal health associations are already cognizant of the power of negotiated mass purchasing and many are already moving toward a value-driven drug-pricing system. Costs will have to be kept within the range that the emerging markets can afford to pay and, at the same time, ensure an adequate return on the investment for the companies. Cost-containment measures like local manufacturing may become necessary. Intellectual property considerations are also hindering expansion into emerging markets. This topic will be discussed further when we address competition from generics, but the same patent cliff that is driving companies to look toward emerging markets has become a challenge to tapping into those markets. Increased competition from generics as drugs lose patent protection will be a problem in developing countries just as it is in the U.S. and Western Europe, compounded by a trend toward disregarding patent protection altogether in many developing countries. All of the above-mentioned issues will have to be successfully navigated if the promise of emerging markets is to be turned into reality.

Cost Cutting. In response to declining revenues as drugs lose patent protection, companies have implemented cost-cutting initiatives to maintain value for investors as they adapt to replace those lost revenues. We have already discussed the short- and long-term impacts of M&As on companies. Consolidation, elimination of redundancy, closure of sites, and reduction in scientific work force all appear to benefit the bottom line in the short term and are usually viewed positively by stockholders. However, there is concern over the negative long-term effects that such activities may have on R&D and the ability to put new drugs on the market going forward. The plain truth is that, with few exceptions, big Pharma is significantly cutting back on internal research and is looking to fill that gap in a number of ways.

Arguably, one of the most debated cost-cutting measures that big Pharma has embraced is outsourcing, especially to developing countries like China and India. What started as a strategy to supplement internal resources occasionally has become a means of replacing much of those internal resources and cutting expenses because of the lower cost of doing business. The global pharmaceutical and chemical outsourcing business has grown into an impressive market. Commonly cited figures place the current market value at around $25 billion, with continued growth of 15% expected for several years.[57] However, one study by the Tufts University Center for the Study of Drug Development suggests that the contract R&D market could exceed $200 billion.[58] The term virtual drug discovery has become prevalent. In the early years of pharmaceutical outsourcing, contract research organizations (CROs) would be engaged to synthesize compounds assigned to them by Pharma scientists or to test compounds sent to them in an effort to supplement man power. That model has now grown to one where, oftentimes, a small number of scientists within a pharmaceutical company manage whole drug discovery projects that are now fully executed by the CRO. Additionally, medicinal chemistry and pharmacology are not the only fields to feel the effect of outsourcing. Manufacturing, formulation, ADME, safety, toxicology, and many other functions historically maintained in-house by big pharmaceutical companies are now routinely outsourced.

The lure, of course, has always been the reduced cost of supporting these activities in economic climates where the cost of living is relatively low. However, that promise of reduced expenditures has come with some challenges. Selecting a contract service provider and establishing a productive outsourcing collaboration requires significant due diligence and the establishment of a strong interorganization relationship. In the past, issues with cost overruns, quality, failure to deliver services or products, and concerns over confidentiality and intellectual property have arisen. Communication across 10−12 time zones can be difficult and inefficient. To facilitate effective contact and management, some companies have funded or built dedicated facilities for partnered CROs and have embedded company personnel at those facilities, especially in China and India (captive market outsourcing). However, recent court decisions in India to overturn or circumvent patent protection on certain expensive drugs have caused some to question the wisdom of future investment by big Pharma in foreign R&D infrastructure.

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Recent changes in the economics of outsourcing has also caused big pharmaceutical companies to rethink their outsourcing strategy. The cost of outsourcing has increased significantly in the past few years as the economies of the developing countries have grown. The gap between the cost of an outsourced full-time equivalent (FTE) in Asia and one maintained internally by a pharmaceutical company has narrowed, and some companies are considering a shift away from an FTE-based outsourcing model to ones where payment is provided for whole projects (project-based outsourcing) or deliverables (value-based outsourcing). It is up to the CRO to provide adequate resources to accomplish the job or project successfully. This model is appealing on the surface because it rewards success. However, significant governance, trust, and effective management is still required, and the potential advantage of having dedicated personnel and facilities is lost as CROs must now manage their own budgets and projects competing for their internal resources. Other outsourcing models that are starting to gain popularity involve paying bonuses above and beyond the basic funding agreement for projects that exceed expectations (incentive-based outsourcing) and sharing the cost of the project with the CRO, who reaps additional rewards if the project become successful (shared risk/shared reward outsourcing). Some companies have elected to insource some R&D rather than outsource it. Downsizing of internal work forces leaves vacant infrastructure, which is filled on a temporary basis by CRO-managed personnel who work on the company's R&D projects. The concept of insourcing was publicized within the scientific community when Lilly and Albany Molecular Research, Inc. (AMRI) announced a 6 year deal to insource 40 medicinal chemists in 2011. However, other companies had already been employing insourcing, such as J&J and Pfizer, at their research site in Sandwich, U.K. One advantage cited for the Lilly/AMRI collaboration was maximizing real-time exchange of scientific information. The significant growth of U.S.-based scientific CROs in the past 2 years suggests that insourcing may grow in popularity, assuming that adequate numbers of qualified local scientists can still be identified and recruited in the wake of the devastating numbers of jobs lost and careers reinvented over the past 13 years.

Partnerships. As the cost and risk of drug development has skyrocketed, the business models for how big Pharma companies interact with smaller biotech tech companies and with each other have also changed. The reductions in research capacity caused by the patent cliff have made companies rethink their ability to stand alone and bear the escalating costs of bringing a drug to market. Now more than ever, companies are looking outside of their own shops to feed their pipelines and for ways to mitigate risk and cost. Although acquisitions of whole companies or subdivisions and licensing of interesting drug candidates still continues to be a viable business model in some cases, the establishment of shared risk/shared reward strategic partnerships has increased dramatically.[59] In many cases, upfront payments are giving way to smaller initial compensation coupled with milestone payments and the guarantee of royalties if the subject of the partnership advances to market. Of course, there are a number of motivations for the formation of strategic alliances, but cost reduction and risk mitigation figure prominently among these motivations.[60]

The partnership model is not limited to big Pharma's interaction with smaller biotech companies. The past 15 years has seen the establishment of a number of development, marketing, and research alliances between major pharmaceutical corporations. Some examples of co-marketed drugs are given in Table 5. Research alliances are also on the rise. Perhaps

Table 5. Examples of Co-Marketed Drugs

companies	drug	indications
Bristol-Myers Squibb, Sanofi	Plavix®	anticoagulant
Bristol-Myers Squibb, Gilead, Merck	Atripla®	HIV therapy
Bristol-Myers Squibb, Pfizer	Eliquis®	anticoagulant
Bristol-Myers Squibb, Novartis	Zelmac®	irritable bowel syndrome
Briston-Myers Squibb, Otsuka	Abilify®	antipsychotic
Bristol-Myers Squibb, AstraZeneca	Onglyza®	diabetes
Bristol-Myers Squibb, Sanofi	Plavix®	anticoagulant
Merck, Schering Plough	Vytorin®	high cholesterol
Merck, Roche	Victrelis®	hepatitis C
Abbott, Takeda	Lurpon® Prevacid®	GnRH agonist ulcers, GERD
Abbott, Solvay	Simcor®	high cholesterol
Pfizer, Boeringher Ingelheim	Spireva®	COPD
Pfizer, Easai	Aricept®	Alzheimer's disease
Johnson & Johnson, Easai	AcipHex®	ulcer, GERD
Bayer, Onyx	Stivarga®	colon cancer

the best known research alliance among big Pharma companies is the Roche/Genentech alliance, touted by many to be one of the most successful alliances to date, although Roche ultimately acquired Genetech in 2009. Today, even companies like Merck, who historically took a position of independence and self-reliance, are now embracing alliances and partnerships. Merck recently won Deloitte Recap's 2013 ALLICENSE Breakthrough Alliance Award for their partnership with AiCuris, a German biotech company developing drugs to treat human cytomegalovirus.

The flexibility of the alliance model is being tested in other ways as well. In 2008, Critical Path Institute established the Coalition Against Major Diseases (CAMD), a consortium of industry, government, and academic partners dedicated to the treatment of Alzheimer's and Parkinson's diseases. In 2010, CAMD partnered with Johnson & Johnson, Sanofi-Aventis, GlaxoSmithKline, AstraZeneca, and Abbott Laboratories to accumulate and make available the data from Alzheimer's disease clinical trials in the hopes of better understanding and overcoming the failure of drugs examined to date. TransCelerate Biopharma, a consortium composed of Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, GlaxoSmithKline, Johnson & Johnson, Pfizer, Genentech, and Sanofi, was launched in 2012. The initial focus of this collaboration was the enhancement and improvement of clinical study execution. Plans are in place to share encouraging results with other alliances such as CAMD. Another recent publicized partnership is Enlight Biosciences. This consortium, backed by Abbott, Merck, J&J, Lilly, Novartis, and Pfizer, seeks out early innovation from academia and biotech, which is shared between the partners. In some cases, companies are even beginning to share screening libraries as part of alliances to enhance the chances of identifying viable hits for new targets. An example of this unprecedented action is the sharing of HTS libraries by Sanofi, AstraZeneca, and Easai as part of the Tuburculosis Drug Accellerator Partnership. The establishment of strategic alliances in their various forms seems to be on the rise, and it is hoped that this new business model of cooperation and collaboration will help the industry to survive,

evolve, and continue to pursue its essential mission of delivering innovative new medicines to treat unmet medical needs.

FIERCE GENERIC COMPETITION

Anyone associated with pharmaceutical research is aware of the impact that generic competition has had on the branded drug industry. In 2011, the generic drug market reached a new high, with 80% of prescriptions being filled with a generic.[61] We have already mentioned the loss in worldwide branded drug sales for the period of 2010−2012 because of the introduction of generics ($68 billion) and the sales that may be at risk for the period of 2012−2018 ($290 billion). Market analysis estimates that the global generic market value in 2011 was $225 billion, and future predictions suggest that the global generic market could be as high as $385 billion by 2016. Today's generic companies are focused, savvy, and organized, and the generic industry has matured to the point where mergers and acquisitions are now occurring as larger generic firms maneuver for dominance in the market.

The rise of generics, touted by governments, insurers, and special interest groups as a key factor for keeping the cost of drugs down, have not only been encouraged but also have been facilitated. The Paragraph IV certification of the 1984 Hatch−Waxman Act allows generic drug companies to attempt to invalidate patents and file Abbreviated New Drug Applications (ANDAs) as soon as 4 years after a new drug is approved and provides protection and limited risk of liability from infringement. Paragraph IV challenges have become a core business strategy for many generic companies. From the data shown in Figure 7, it is evident that the number of ANDA-related

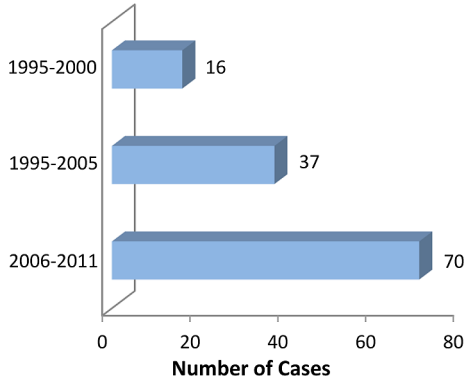

Figure 7. Court decisions from ANDA trials (source: ref 62).

litigations has trended upward since 1995.[62] On average, roughly 55% of these cases are decided favorably for the ANDA sponsor in recent years, and the issue is not limited only to U.S. drug sales. India, one of the largest producers of generic drugs, began issuing pharmaceutical patents only in 2005. However, three recent court decisions have implications on branded drug sales, not only in India but also in the rest of the world. In 2006, the Indian patent appeal board revoked an awarded patent on Roche's antiviral drug Pegasys, the first pharmaceutical patent awarded in India. In 2012, the Indian government issued a compulsory license to Natco Pharma to manufacture and sell a generic version of Nexavar, an anticancer drug comarketed by Bayer and Onyx. The high price and the need for access to the drug by Indian patients was cited as the justification for the license. Most recently, the Indian Supreme Court ruled against patent protection for Novartis' anticancer drug Gleevec. These decisions have paved the way for manufacture and distribution of these drugs, not only in India but also throughout much of the world where patent enforcement is not acknowledged or vigorously pursued. Issues such as these raise concern over how impactful the emerging markets will actually be if generic versions are immediately available to compete with new branded drugs, especially in markets where the economies already dictate the need for reduced prices.

Because of the dramatic impact that increased generic competition has had on revenues, branded pharmaceutical companies have instituted a number of strategies for mitigating the damage that this challenge has caused. We have already discussed patent life extension strategies such as patenting new indications, active enantiomers, new formulations, and fixed dose combinations. These approaches have met with mixed success in litigation proceedings, and generic companies have learned to carve out[63] newly patented indications from their ANDA applications and rely on off-label prescribing to support sales of the generic. In Part 1 of this series, we also discussed the pay for delay strategy whereby owners of branded drug owners pay generic companies to delay their ANDA applications. In fiscal year 2012, the Federal Trade Commission (FTC) received notice of 140 final settlements between branded drug companies and generic challengers. Forty of these settlements involved payments or promises not to market authorized generics in exchange for delayed generic entry into the market.[64] The FTC contends that this practice is unethical but has realized limited success in litigating against such pay for delay settlements. On June 17, 2013, the U.S. Supreme Court reversed a decision by the Eleventh Circuit Court of Appeals that a pay for delay agreement struck between Solvay and Watson (now known as Actavis) over Androgel (a testosterone supplement) was lawful but rejected the FTC's suggestion that such reverse payments be considered unlawful. In essence, the court opened the way for future litigation on the subject but did not render a definitive opinion on the lawfulness of the practice. Apart from patenting strategies and business arrangements, big Pharma has embraced two major R&D initiatives to address the challenge of increased generic competition. Those two initiatives, biopharmaceuticals and authorized generics, will be discussed in more detail in the following sections.

Authorized Generics. When a generic pharmaceutical company successfully prosecutes a Paragraph IV challenge, the first to file the ANDA receives a 180 day exclusivity period during which no other generic companies can market their own generic version of the drug in question. The price of the generic drug during this exclusivity period is usually higher (on average, 82−86% of the pre-entry branded price) than when additional generic competition begins after the 180 day period, which is an incentive for being the first to file an ANDA. However, this proviso in the Hatch−Waxman Act does not apply to the original owner of the branded drug, who can market their own authorized generic version of the drug during the exclusivity period. The authorized generic version contains both active and inactive ingredients that are identical to those of the branded form. This differs from other generic versions, which only contain the identical active agent. The branded company usually commissions a generic company to market the authorized generic drug under their name, although some companies such as Abbott, Novartis, Sanofi, and AstraZeneca have chosen to establish or purchase their own generic subsidiaries to support the regional or worldwide marketing

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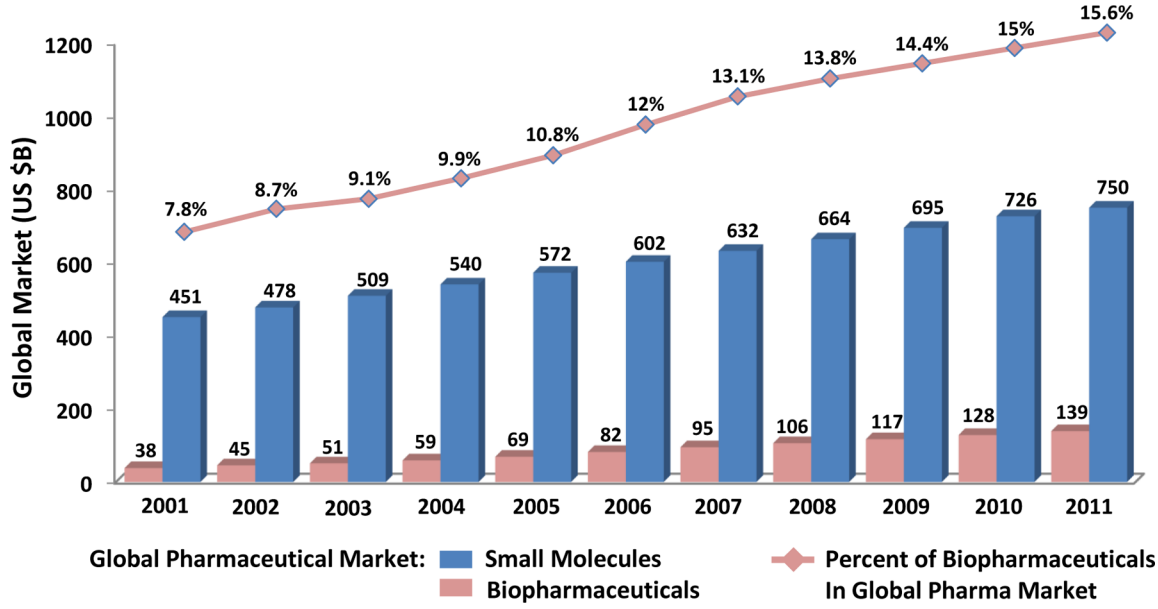

Figure 8. Percentage of biopharmaceuticals in the pharmaceutical market, 2001−2011 (source: ref 69).

of branded generics. A current list of authorized generic drugs can be found on the U.S. FDA's web site.[65]

Branded pharmaceutical companies contend that the driving force for authorized generics is the maintenance of revenues following patent expiration or Paragraph IV challenge. Generic companies and critics of the pharmaceutical industry contend that the major reason for the practice is to discourage generic competition by eliminating the profit for the generic company, a position also held by the FTC. However, although the practice of marketing authorized generics may be perceived as unethical by the FTC, the patient population apparently does not agree with that assessment. According to a 2005 public survey carried out by Roper Public Affairs & Media for Prasco Laboratories, an authorized generic drug company, over 80% of Americans want the option of choosing authorized generics.[66] Interestingly, what could be perceived as bad for generic competition may actually contribute to lower generic costs during the 180 day first to file exclusivity period, according to the 2011 report from the FTC.[67] On average, the retail cost of generic drugs during the first 180 days was 4−8% lower in the face of authorized generic competition.

Internal records from generic companies do not specifically discuss how the threat of authorized generics affects their Paragraph IV strategies, and the steady increase in Paragraph IV challenges suggests that the threat is not a significant deterrent. However, the FTC's analysis does suggest that authorized generics do have a significant impact on the revenues of competing generic firms during the 180 day exclusivity period. Depending on how the data are analyzed, the presence of authorized generic competition reduced the revenues of the ANDA first filer by 40−52% on average. Additional evidence for the impact of authorized generics can be found in a 2012 follow-up analysis to the 2011 FTC report.[64] Of the 40 pay for delay settlements reported to the FTC in 2012, 19 of them involved compensation in the form of a no-authorized-generic commitment (up from the 11 no-authorized-generic settlements reported in 2011). Regardless of the driving force, authorized generics seem to be one of the more successful strategies for addressing the challenge of increased generic competition.

Biopharmaceuticals. Another strategy that the branded pharmaceutical industry has undertaken to counter the challenge of increased generic competition is expansion into the area of biopharmaceuticals.[68] This general class of drug comprises proteins derived from recombinant DNA technology. Examples of marketed biopharmaceuticals include cytokines, clotting factors, hormones, enzymes, antibodies, vaccines, and cell- and tissue-based therapies. The first biopharmaceutical approved for human use was Humulin (recombinant human insulin), developed by Genentech and marketed by Lilly in 1982. Since that time, the biopharmaceutical market has grown significantly. In 2011, biopharmaceuticals accounted for nearly 16% of the global pharmaceutical market (Figure 8), and some estimates suggest that the biopharmaceutical market could grow to over $320 billion by 2020.[69]

The biopharmaceutical industry has come a long way since the introduction of Humulin. For example, the therapeutic antibody field has realized success, particularly in the areas of cancer and immunological disorders. In the cardiovascular field, recent clinical results show that REGN727/SAR236553, a monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9), reduces low-density lipoprotein cholesterol in heterozygous familial hypercholesterolemia patients, including those on stable statin therapy and those intolerant to statin therapy.[70,71] Today, thousands of companies worldwide are associated with or focus specifically on biopharmaceutical R&D, manufacture, and development. A list of the top 10 biopharmaceutical companies based on 2012 revenues from sales of biopharmaceuticals is given in Table 6. Many of these companies started life as small biotech firms but have grown significantly. In addition, a number of big Pharma companies with a history of focus in small molecules has expanded into biopharmaceuticals, partly as a way of countering the onslaught of generic competition. For example, Roche initially partnered with and ultimately acquired Genentech and now considers itself to be essentially a biopharmaceutical company. One of the primary motivations for Pfizer's purchase of Wyeth was to acquire its biopharmaceutical R&D resources and pipeline. Analysts predict that the scramble to establish or

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Table 6. Top 10 Biopharmaceutical Companies in 2012[a]

	company	2012 biopharma revenues (billions of dollars)
1	Roche/Genentech	37.6
2	Amgen	17.3
3	Novo Nordisk	13.5
4	Merck Serono	8.2
5	Baxter	6.2
6	Biogen Idec	5.0
7	CSL Behring	4.6
8	Allergan	1.8
9	Alexion	1.1
10	Regeneron	0.9

[a]Source: company annual reports.

acquire biopharmaceutical capacity will continue over the next several years, with smaller low-valuation companies being the target of M&As throughout the world.[72]

Because of their complex structures, biopharmaceuticals are produced by living organisms. Specialized techniques and facilities are required to generate the quantities of GMP-quality biopharmaceuticals needed to market one of these agents as a drug. It is their structural complexity that also gives biopharmaceuticals their appeal as a means of staving off generic competition. That structural complexity makes them difficult to reproduce exactly, and that aspect is what has attracted the branded pharmaceutical companies. The process for producing any given biopharmaceutical is specific, and the conditions, cell lines, and reagents used can affect the outcome. Often, the process for preparing a marketed biopharmaceutical is patented along with the actual drug. Although a version of the biological agent in question produced via different conditions may have the same primary-structural sequence, secondary-structural features such as glycosylation pattern can vary, and those subtle variations can affect safety and clinical efficacy. For these reasons, there are no biogenerics, which, by definition, contain the identical active agent. Rather, the biological generic industry has been left with the pursuit of similar agents with similar clinical profiles. These agents have come to be known as follow-on biologicals or biosimilars.[73]

Apart from the difficulty in production and the expense, a significant competitive advantage for biopharmaceuticals comes from the regulatory requirements imposed on biosimilars. Generic approvals require only that bioequivalence is achieved and that safety and tolerance is demonstratred. This can usually be accomplished with phase I clinical trials at an average development cost of $1−5 million. Development times are relatively short, and postmarketing pharmacovigilance is not required. Biosimilars do not contain the exact active agent as the branded biopharmaceutical that they are trying to replace and are treated more like new chemical entities (NCEs). Both safety/tolerance and efficacy must be demonstrated in clinical trials, with development times often running 6−10 years and development costs exceeding $100 million. Like NCEs, postlaunch safety updates and pharmacovigilance are required for biosimilars. Another added incentive is that, unlike traditional generics, biosimilars cannot be automatically substituted for the branded biopharmaceutical that they intend to replace by the pharmacy or insurance provider. They must be specifically prescribed. This gives the branded pharmaceutical company the opportunity to maintain market share by cultivating prescriber and patient loyalty.

However, it is not clear how long the biopharmaceutical sector will continue to be a safe haven for branded pharmaceutical exclusivity. With the realization that biopharmaceuticals can be effective drugs that sometimes treat conditions and diseases that small molecules do not has come pressure to facilitate the availability of lower-priced biosimilars. Regulatory agencies throughout the world are beginning to issue guidelines for accelerated approval of biosimilar agents,[74] and some biosimilars have already reached the market such as Sandoz's Omnitrope (marketed in the European Union in 2006). In the U.S., President Obama signed the Patient Protection and Affordable Care Act on March 23, 2010.[75] This Act contained the Biological Price Competition and Innovation Act, which established an abbreviated approval pathway for biosimilars in the U.S. This pathway requires that biosimilar agents meet two basic criteria: (1) the biosimilar must be highly similar to the reference product not withstanding minor differences in minor inactive components and (2) no clinically meaningful differences can exist between the biosimilar and the reference product in terms of safety, purity, and potency. Also, it must be shown that the biosimilar has the

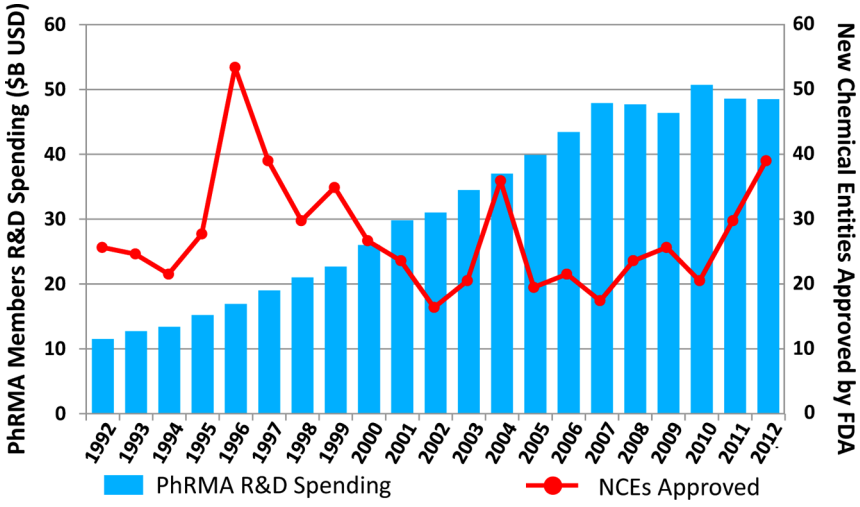

Figure 9. Correlation of R&D spending by PhRMA members and number of new chemical entities approved by the FDA from 1995 to 2012 (source: PhRMA web site).

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Table 7. Small Molecule New Chemical Entities Approved by the FDA in 2011 and 2012[a]

drug	2011 company	indication	drug	2012 company	indication
Adcetris™,[b]	Seattle Genetics	Hodgkin lymphoma	Amyvid™	Avid	PET imaging
Arcapta™	Novartis	COPD	Aubagio®	Sanofi	multiple sclerosis
Benzysta®	GSK/Human Genome	lupus	Belviq®	Arena	obesity
Brilinta™	AstraZeneca	acute coronary syndrome	Bosulif®[b]	Pfizer	CML
Caprelsa®[b]	AstraZeneca	thyroid cancer	Choline C11 Injection	Mayo Clinic	PET imaging
Daliresp®	Forest	COPD	Cometriq™,[b]	Exelixis	thyroid cancer
DaTscan™	GE	SPECT imaging	Elelyso™,[b]	Prizer/Protalix	Gaucher disease
Dificid®	Optimer	Clostridium-associated diarrhea	Eliquis®	Pfizer/BMS	anticoagulant
Edarbi™	Takeda	hypertension	Erivedge®	Genentech	basal cell carcinoma
Edurant®	Jannsen	HIV	Fulyazq™	Salix	HIV-associated diarrhea
Erwinaze™,[b]	EUSA	ALL	Fycompa®	Eisai	epilepsy
Eylea®	Regeneron	macular degeneration	Gattex®[b]	NPS	short bowel syndrome
Ferriprox®[b]	ApoPharma	thalassemia	Iclusig™,[b]	Ariad	CML
Firazyr®[b]	Shire	angioedema	Inlyta®	Pfizer	kidney cancer
Gadavist™	Bayer	CNS imaging	Jetrea®	ThromboGenics	symptomatic vitreomacular adhesion
Horizant™	GSK/Xenoport	restless legs syndrome	Juxtapid™,[b]	Aegerion	familial hypercholesterolmia
Incivek™	Vertex	hepatitis C	Kalydico™,[b]	Vertex	cystic fibrosis
Jakafi™	Incyte	myelofibrosis	Kyprolis®[b]	Onyx	myeloma
Natroba™	ParaPRO	head lice	Linzess™	Ironwood	IBS
Nulojix®[b]	BMS	transplant rejection	Myrbetriq®	Astellas	overactive bladder
Onfi™,[b]	Lundbeck	Lennox-Gastaut syndrome	Neutroval™	Sicor/Teva	neutropenia from kidney disease
Protiga™	GSK/Valient	seizures	Omontys®	Affymax	anemia from kidney disease
Tradjenta™	Boehringer	type-2 diabetes	Perjeta®	Genentech	breast cancer
Victrelis™	Merck	hepatitis C	Picato®	LEO	actinic keratosis
Viibryd®	Forest	depression	Prepopik™	Ferring	colonoscopy preparation
Xalkori®[b]	Pfizer	lung cancer	Abthrax™	Human Genome/GSK	anthrax
Xarelto®	Jannsen	anticoagulant	Signifor®[b]	Novartis	Cushing's disease
Yervoy™,[b]	BMS	melanoma	Sirturo™,[b]	Johnson & Johnson	tuburculosis
Zelboraf®	Genentech	melanoma	Stendra™	Vivus	erectile dysfunction
Zytiga®	Janssen	prostate cancer	Stivarga®[b]	Bayer	colorectal cancer
			Stribild®	Gilead	HIV
			Surfaxin®	Discovery Laboratories	respiratory distress
			Synribo®	Teva	CML
			Tudorza™ Pressair™	Forest	COPD
			Voraxaze®[b]	BTG	methotrexate toxicity
			Xeljanz®	Pfizer	arthritis
			Xtandi®	Astellas	prostate cancer
			Zaltrap®	Gilead	HIV
			Zioptan™	Merck	glaucoma

[a]Abbreviations: ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; COPD, chronic obstructive pulmonary disorder; HIV, human immunodeficiency syndrome; IBS, irritable bowel syndrome; PET, positron emission topography; and SPECT, single photon emission computed tomography. Source: FDA website (fda.gov). [b]Signifies orphan drug status.

same indication, route of administration, dosage form, and strength as the reference product.

The Patient Protection and Affordable Care Act was designed to facilitate the approval of biosimilars. However, it does provide the owner of the original branded biopharmaceutical considerable protection, which is an added incentive for using biopharmaceuticals to counter generic competition. An abbreviated Biological License Application (BLA) cannot be filed by the biosimilar drug's applicant less than 4 years following approval of the reference product, and the FDA must wait at least 12 years following original licensing of the reference product before a BLA on a biosimilar can be approved. As with ANDAs, the first to file a BLA on a biosimilar is awarded an exclusivity period during which no other biosimilars can be introduced. The FDA has established the Biosimilar Implementation Committee, but the committee has not issues guidelines on what specific clinical data will be required for approval of biosimilars. Thus, at present, investment in biopharmaceuticals remains an effective business strategy, especially in the U.S. However, the generic industry in the rest of the world has already expanded into the biosimilars arena, especially in Europe, India, and other emerging market countries. There is growing pressure on the FDA to clear the way for biosimilar approvals. Thus, it is unclear how long biopharmaceutical investment will remain an effective tool in the branded pharmaceutical company's arsenal of tools to counter generic competition.

STAGNANT SUCCESS RATE

The data shown in Figure 9 have been presented many times. Some argue that new drug approvals may not be the best way to judge productivity, but the data in Figure 9 speak clearly to one of the issues facing the pharmaceutical industry: a stagnant return on increased R&D spending and new drugs whose earnings will not be able to replace the lost revenue of blockbusters going off-patent. This discrepancy has been dubbed the innovation gap. The recent increase in FDA approvals in 2011 and 2012 has been cited as an encouraging trend that could signify that the new drug drought may be coming to an end. However, an examination of those 2011 to 2012 approvals (Table 7) suggests that the vast majority of new small-molecule drugs approved during that time period are intended for limited use in smaller numbers of patients. Similar trends can be seen for compounds in phase III clinical trials in 2012.[76] Many of these new drugs and drug candidates have orphan drug status. Thus, despite the higher cost of many of these agents,[77] they will not likely recoup revenues to match those of blockbuster drugs like atorvastatin. So, apart from fewer major players in the field, why are no more drugs crossing the finish line despite a 4-fold increase in spending? Several factors are believed to contribute to the lack of correlation between R&D spending and the number of new drug approvals. Some of these factors are discussed in the following sections.

Increased Cost. First and most obviously, salaries and the cost of developing drugs have gone up significantly since the early 1990s. The U.S. Bureau of Labor Statistics estimates that the cost of living has increased by over 65% since 1992. The fees for a U.S. NDA in 1995 were in the range of $200 000. In 2012, those fees exceeded $1.8 million.[78] Second, as discussed earlier, the number of large pharmaceutical companies capable of supporting several multiple-site clinical trials has declined. Examination of Table 7 shows that 64% of the NMEs approved by the FDA in 2012 were developed by smaller companies. This is in contrast to 1996 (the year when a record-setting 53 NMEs were approved), where big Pharma companies accounted for over 50% of NME approvals and several companies had multiple approvals in that year. In fact, the data in Figure 9 suggest that the 53 NMEs approved in 1996 and the 36 NMEs approved in 2004 are, in fact, aberrations and that 20−25 NME approvals per year is a more realistic average. Still, despite a 3- to 4-fold increase in R&D spending since the early 1990s, the number of NMEs approved each year has remained roughly the same, and it is this apparent stagnation in productivity that has many interests within the biomedical arena concerned.

Higher Safety Hurdles. Another reason for a stagnant success rate is the difference in the requirements for a NME to be approved today compared to 15 years ago. Safety hurdles for new drugs are much higher than they were back in the 1990s. That is not to say that unsafe drugs were approved back then. Rather, following a pair of high-profile drug recalls in the 2000s (Wyeth's fenfluramine, part of the Fen-Phen anti-obesity drug combination and Merck's anti-inflammatory drug Vioxx) and elevated safety concerns over Wyeth's conjugated estrogens drug Premarin, the FDA began postponing or rejecting significantly more NDAs based on safety concerns. There was a dramatic increase in the number of approvable letters issued by FDA review committees, requiring additional costly clinical trials for NDA applications that might otherwise have been approved 5 years earlier. This increase in safety requirements resulted in a number of companies dropping late-stage development of drugs after having invested hundreds of millions of dollars.[79] The obvious question that follows is, if safety requirements are much more stringent now, then how was it possible to get 30 NMEs approved in 2011 and 39 in 2012? The first answer to this question lies in a policy change by the FDA. In 2008, the FDA announced that it would replace the approvable letter with a clear response delineating what was needed to approve an NDA.[80] The frustration and lack of a path forward experienced by NDA applicants was now replaced by guidance that helped companies continue to move late-stage programs forward. The second answer lies in the indications for those 69 recent NME approvals. From Table 7, it can be seen that the majority of the NMEs approved in 2011 and 2012 were for life-threatening diseases or for orphan diseases where no other drugs exist. In those cases, some risk can be tolerated. In contrast, many of the NDAs filed just after the post-recall debacle in 2002−2004 were for drugs intended to treat big-market diseases. There were drugs already approved for many of these indications. The presence of existing safe, effective treatments for these diseases made it easier for the FDA to delay or deny second-generation or me-too drugs that did not display exceedingly good safety profiles.

Need for Differentiation. Another reason for the apparent decrease in NME approvals is the increased demand not only for efficacy but also for differentiation from existing treatment options. A 2012 commentary by Light and Lexchin, while quite critical of the pharmaceutical industry, did present some interesting figures on the percent of drugs approved since the mig-1970s that were considered as important therapeutic gains.[81] In the 1990s, approval was contingent on the drug being safe and showing efficacy. In fact, physicians expressed approval for having several options in treating their patients because of idiosyncratic differences in how patients responded to a particular drug class, structural scaffold, or individual drug. Times have changed. Although the FDA says that no regulations have changed for drug approvals, they are now using comparative data to make some decisions and are scrutinizing noninferiority data in NDAs, according to a 2010 report by the U.S. Government Accountability Office.[82] The scrutiny does not stop at the regulatory level. In today's economy, payers, health care providers, and even patients are reluctant to pay for new drugs that do not provide significant benefits to patients, especially those with high price tags. International health care assessment agencies such as the U.K.'s National Institute for Health and Clinical Excellence and Germany's Institute for Quality and Efficiency in Health Care are having considerable influence on a drug's commercial potential as well as the FDA's decision on whether or not to approve it. Drug approvals are increasingly becoming dependent on value.

In response to these heightened regulatory and economic hurdles, the industry has modified a number of its development strategies. Portfolio management within companies has begun embracing the concept of value-driven drug development, focusing efforts on drugs that demonstrate value to the many stakeholders that now influence the commercial potential and regulatory approval process, including payers, insurers, health care providers, and even patients.[83] Efficient project management with clear goals, go/no-go points, and advancement criteria are critical for this approach to have a meaningful impact. Some companies use a clinical utility index or medical

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differentiation index,[84] a mathematical algorithm that weighs a number of characteristics and compares them to those of competing drugs that are already on the market. The concept of differentiation is being introduced earlier in the drug discovery process. Marketing and regulatory team members are becoming involved earlier in projects as well. Drug candidates that are less likely to meet safety or differentiation criteria are being dropped from development earlier, before costly phase III clinical trials begin. Consulting agencies have sprung up that provide guidance and insight on how to differentiate new drug candidates from currently existing products.[85,86] Phrases like "streamlined clinical trials" and "if you must fail, then fail early" have become commonplace and reinforce the fact that the industry has finally begun to accept the need for increased efficiency and a change in its development strategy.

Decrease in Preclinical R&D Innovation. The wave of consolidation and downsizing that the industry has experienced in the past 10 years has led to one undeniable conclusion: there are less preclinical drug discovery scientists, which means less internal capacity for discovering new drugs. Although internal basic research into new drug targets was a part of some companies' business models in the 1980s, that trend declined throughout the 1990s. Companies came to rely on government, academic, and biotech research as the source of their targets. In fact, many companies have begun downsizing or spinning off their preclinical discovery R&D groups in an effort to focus on the development phase. With the loss of over 300 000 pharmaceutical jobs since 2001, it is reasonably accurate to assert that little basic research is now performed internally in major pharmaceutical company laboratories. This is relevant in light of the fact that the regulatory agencies and stakeholders who impact the pharmaceutical industry are beginning to demand an increase in the true therapeutic value of the new drugs coming to market. The untreated or poorly treated diseases of today seem to be more complicated. For example, it has become increasingly obvious that there will probably be no one universal drug to treat cancer because each cancer type has its own individual characteristics. Despite decades of drug discovery and development for Alzheimer's disease, no drug exists that can halt the progression of this devastating disease. Finding effective drugs for these and other treatment-defying diseases will require innovation and breakthroughs in our basic understanding of the disease processes. That innovation has to come from somewhere if the industry is to survive.

One source of the much needed innovation is the highly focused biotech industry, where companies tend to specialize in one disease area or drug target. The synergy between big Pharma and the biotech industry has been discussed in many venues and is well-known. The one change in that relationship that merits comment here is the approach that big Pharma has adapted in their deals with biotech companies. Because of the cost of development and the increased risk, many big Pharma companies have moved away from the traditional licensing arrangements of the 1980−1990s in favor of codevelopment agreements where both the cost of development and the rewards of success are shared. From Table 7, it can be seen that five of such codeveloped drugs received FDA approval in the past 2 years.

Another source of innovation and basic research that big Pharma has embraced is academic laboratories. Pharmaceutical companies have made investments in academic research and continue to do so, although at a significantly diminished level because of cost constraints. Historically, academic laboratories have focused on basic research because they were primarily funded by public money in the form of government grants. The ideas coming out of academia were innovative (they had to be to compete successfully for grant money) but still required significant work to turn them into viable drug targets. This translation from concept to target was the subject of much of the basic research that was being done internally by big Pharma in the 1980−1990s. However, as internal basic research diminished, so did their capacity for turning basic discoveries from academia into drug discovery projects.

However, a new entity has arisen that hopes to help fill the innovation gap left behind by the downsizing of Pharma preclinical research groups. That entity is the academic drug discovery group. One of the primary missions of an academic drug discovery group is to help academic scientists with innovative ideas turn those ideas into something that will appeal to an industrial partner. A few academic groups have been successful at getting whole research projects funded by pharmaceutical companies, but for the majority of academic research, the term "appealing to an industrial partner" is synonymous with "clinical candidate". Academic drug discovery groups provide the early discovery capacity to help mold innovative findings into tangible products that can be patented and licensed to development partners.

Recently, a group from the University of North Carolina at Chapel Hill (UNC) conducted a survey of 78 academic drug discovery groups and compiled some intriguing responses and statistics.[87] What started out as a modest effort (<25% of the survey responders founded before 2004) accelerated rapidly in the past 9 years. Often led and staffed by scientists with industry experience, today's academic drug discovery centers possess the skills, experience, and resources needed to execute successfully all phases of early drug discovery, including target validation, hit-to-lead, and lead optimization. Resources originally associated with an industrial setting, such as high-throughput screening and in vivo efficacy profiling, are now carried out in half of the academic facilities surveyed. Universities have recognized the potential of academic drug discovery and have significantly expanded patenting activity and their internal support of drug discovery groups. University technology transfer groups have grown in size and experience and now proactively shop around their university's intellectual property rather than wait for companies to come looking for them. To facilitate the technology transfer process, some universities have commissioned dedicated incubator space, facilities that can be offered to university groups with potentially valuable commodities so that they can form start-up companies around those commodities. Although some still debate whether a university is the appropriate setting for such endeavors, the growing number of new academic drug discovery groups suggests that many university administrations and boards of trustees see the combination of potential revenue and faculty members with practical experience as a win−win situation.

Some critics of academic drug discovery question how impactful these groups will be in the drug development arena. Academic groups will inevitably face the same risk and drop-out rate that has hindered drug discovery in the industrial setting. Certainly, most academic drug discovery groups lack the funding needed to advance a compound to clinical trials. The NIH has responded to a certain extent by establishing programs that provide IND-enabling resources to projects that align with its priorities, but the availability of these resources is limited and

cannot provide the funding needed to advance all of the deserving advanced leads coming out of academia. Additionally, relatively few government grant programs target the early stages of drug discovery such as lead identification or hit-to-lead activities. Most government grants focus either on basic research or final lead optimization, even though they are only part of the drug discovery paradigm.

Opinions also vary over what role academic drug discovery groups should play. Some feel that academic groups should limit their endeavors to the special expertise that their faculty members possess and that the industrial mind set (team- and goal-oriented) does not fit well with the academic atmosphere.[88] Some question the reliability of target validation performed in an academic setting and its translatability to the industry environment.[89] Others believe that academic drug discovery laboratories should take on more of the activities historically based in the industrial setting.[90] Many wonder whether the goal driven, project-managed environment that is important for drug discovery can meld with the environment of academic freedom that is key to a university. It has been these authors' experience that some academic colleagues are able to think and work in a team-oriented environment and some are not. This is the essence of academic freedom: in academia you do not have to collaborate with any given person or group. You can choose to do so or not to do so. For academic drug discovery groups to be successful, they must identify collaborators who can adapt to a work model that has the best chance for identifying a drug candidate. In fact, we have found that many of our academic collaborators are amazed by how much can be accomplished when team work and project management are incorporated into the research plan. In addition, the immigration of industry scientists to academia as a result of job loses has been beneficial on multiple fronts. Several universities are now reaping the rewards of employing faculty that not only can teach biomedical science and research from a practical, industrial point of view but also naturally fit in with the operating model that academic drug discovery groups employ.

As far as the impact that academic research groups have had on drug development, it is certainly true that academic groups have contributed to early-stage basic research by identifying biological tool molecules as summed up in a recent article.[91] However, the UNC survey showed that academic drug discovery laboratories are involved with many high-profile therapeutic areas as well as orphan diseases and less well validated targets that are of interest to pharmaceutical companies. Companies certainly recognize the potential of tapping into academic research. For example, Merck recently formed the California Institute for Biomedical Research (Calibr), a facility dedicated to academic partnerships. In a 2011 follow-up interview to the UNC survey,[92] a number of universities confirmed that they have seen an increase in the number of deals made with Pharma. Furthermore, projects started in academia have successfully delivered clinical candidates and even marketed drugs. Scripps Institute's agreement with Receptos in 2009 led to a clinical candidate. In 2011, Scripps' sphingosine-1-phosphate receptor-1 agonist RPC1063 entered phase I trials for multiple sclerosis. That compound advanced to phase II/III pivotal trials in 2012. Dennis Liotta's group at Emory University discovered Emtriva. Vorinostat came out of Ron Breslow's group at Columbia University, and Richard Silverman's group at Northwestern University invented Lyrica. What the future holds is uncertain, but as the pharmaceutical industry continues to downsize staff and eliminate projects (especially ones that are considered high risk), it is hoped that academic drug discovery will continue to serve as a source of new projects and products that will help big Pharma overcome the innovation gap.

CLINICAL DROP-OUT

Another challenge faced by the pharmaceutical industry is the failure rate for compounds entering clinical trials. Costs escalate dramatically as clinical candidates move from preclinical development through safety and tolerance studies (phase I) and into phase II and phase III efficacy trials. More recent figures could not be found in the public domain, but 2008 numbers suggest that the greatest percentage of clinical candidates today fail in phase II, when preliminary efficacy and differentiation data become available (Figure 10a).[93] Although the rate of attrition has remained similar over the past 20 years, some of the reasons for clinical failure have changed (Figure 10b,c).[94] For example, in 1991, poor

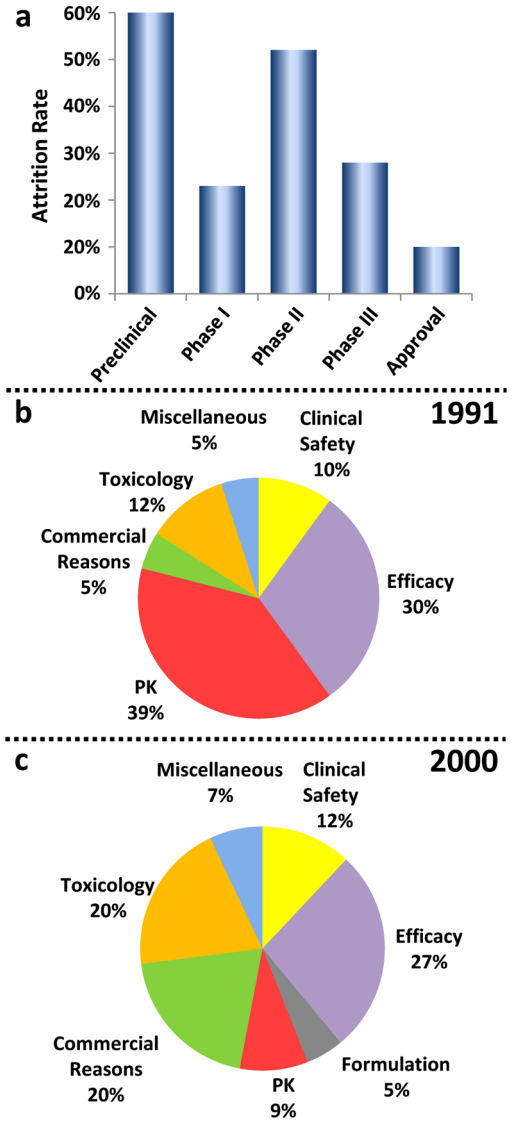

Figure 10. Clinical attrition statistics: (a) attrition rate by stage of development, (b) reasons for clinical failure in 1991, and (c) reasons for clinical failure in 2000 (source: refs 93 and 94).

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pharmacokinetics accounted for nearly 40% of clinical failures. That number had decreased to roughly 9% by 2000. Unfortunately, the encouraging results for PK-associated failures seem to have been countered by increases in failure resulting from commercial considerations (which likely included cost to the patient and differentiation concerns) and increased toxicology as crowded intellectual space forced companies to pursue more complex structural scaffolds that were still patentable.

The obvious place to start addressing clinical dropout is by designing cost-effective, more efficient clinical trials, ones that facilitate good go/no-go decisions. When possible (as in cancer), genetic typing is being employed to target new clinical candidates to trial subjects that stand the best chance of responding. Many companies are now incorporating small efficacy arms into their advanced safety/tolerance studies (the ones run in actual patients) and are analyzing those safety studies for potential signs of short-term efficacy. Of course, these results cannot match the accuracy of those obtained from larger, statistically powered phase III clinical trials, but they can be used to help in deciding whether or not to advance the drug to the next more costly stage. Clinical research has become more sophisticated in response to the changing pharmaceutical environment, but how has preclinical research responded to the challenges? Below we discuss some of the preclinical tactics that the industry has employed in its attempt to improve the success rate.

One outstanding feature in the data presented in Figure 10 is the decline in the number of clinical failures because of unacceptable PK properties from 1991 to 2000. The reason for this is straightforward: PK became important earlier in a clinical candidate's evolution. Spurred on by a pivotal paper by Prentis et al. in 1988,[95] medicinal chemists began thinking about PK and bioavailability as early as the hit identification stage, and project teams started routinely incorporating PK considerations into their decision-making process from that stage forward. In vivo PK studies, formerly prioritized to advanced leads being considered for IND-enabling studies, were now deployed during the course of hit-to-lead and lead optimization campaigns. However, during this time many companies did not have the infrastructure and personnel required to take on this increased workload and still support predevelopment and clinical projects. Outsourcing of PK studies took some of the added burden off of preclinical research resources, but the advent of a breakthrough concept provided pharmaceutical companies with a new way of tackling the issue of PK. That concept was the high-throughput in vitro screening of compounds for druglike properties.[28]

High-Throughput Screening for Druglike Properties. Since the revelation of Lipinski's rule of five,[96] several analyses have confirmed the undeniable fact that pharmacokinetics and toxicology are dependent on the physicochemical properties of compounds (for a recent review, see ref 97). It stands to reason that a clinical candidate that possesses both good pharmacological activity and druglike properties will have a better chance of making it to market than one that has suboptimal properties. To facilitate the ability of medicinal chemists to incorporate druglike properties into their drug design on a routine basis, companies have invested a great deal of time and money into developing batteries of in vitro high-throughput assays that monitor physicochemical parameters. Properties like solubility, stability, and permeability through cellular membranes (or artificial membranes) are now assessed in HTS plate format and rapidly monitored using LC/MS/MS or fluorescent-based quantitation. Similar technologies have been used to develop PK- and toxicology-specific HTS assays such as plasma stability (a predictor of hydrolysis metabolism), stability in liver microsomes (a predictor of phase I/phase II hepatic metabolism and in vivo half-life), and inhibition of human liver cytochrome P450 enzymes (a predictor of drug−drug interactions). HTS assays for monitoring p-glycoprotein (P-gp), breast cancer-related protein (BCRP), and other xenobiotic transporter activities provide input on potential issues with oral absorption, tissue penetration (especially the CNS), and liver toxicity (OATP's, OCT's, OAT's, etc.). Even specific toxicity targets like the human ether-related a-go-go ion channel can be assessed in high-throughput binding and functional assays. More importantly, the high-throughput nature of these assays (usually performed in 96- or 384-well plates) means that every target molecule synthesized by chemists on a project can be screened for multiple druglike properties and the data can be generated and returned to the chemist in a timely manner so that the resulting information can be used to address any physicochemical/ADME/toxicity issues that exist. Most of today's pharmaceutical chemists are very familiar with the typical traffic light spreadsheet shown in Figure 11, which

Compound	logP	Solubility	t1/2, HLM
MC-100,000	3.79	10 ug/mL	16 min
MC-100,001	4.88	> 1 ug/mL	5 min
MC-100,002	2.12	61 ug/mL	2 min
MC-100,003	2.55	73 ug/mL	> 30 min
MC-100,005	5.03	> 1 ug/mL	> 30 min

Figure 11. Typical traffic light spreadsheet used to report in vitro physicochemical/ADME data.

classifies a compounds' measured or calculated properties into druglike catagories (red, poor; yellow, moderate; and green, good). This concept has been dubbed multidimensional optimization or multiparameter optimization and has undoubtedly contributed to the reduction in clinical failures resulting from poor PK since 1991.

The advances in HTS-based in vitro screening of physicochemical/ADME/toxicology parameters have been paralleled by significant advances in virtual in silico methods for predicting druglike parameters, although some warn against relying solely on these ranking methods for compound triage.[98,99] Of course, algorithms for calculationg logP and topological polar surface area (TPSA) have been available for some time. However, today's drug discovery scientists have access to software platforms and algorithms capable of predicting permeability,[100] metabolism,[101] off-target liabilities,[102] potential toxicology,[103] and even aqueous solubility.[104,105] The incorporation of ligand efficiencies[106] and other discoveries into their SAR design and analogue synthesis provides a quantifiable metric that medicinal chemists can use to prioritize lead molecules that have a greater chance of surviving the multitude of development challenges. The original concept,[107] a ratio of the potency of the molecule to the size of the molecule, has been extended to include other parameters such as number of heteroatoms, number of rotatable bonds, lipophilicity,[108] and, more recently, organizational factors such as fraction of sp^3-hybridized carbons (Fsp^3) and ratio of aromatic carbons to sp^3 carbons (Ar-sp^3).[109] Support for the validity and usefulness of ligand efficiencies has been provided

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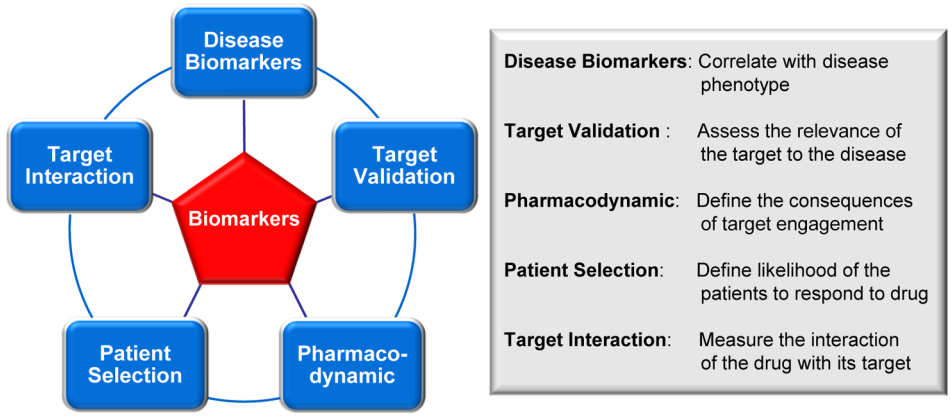

Figure 12. Utilitarian classification of biomarkers[117].

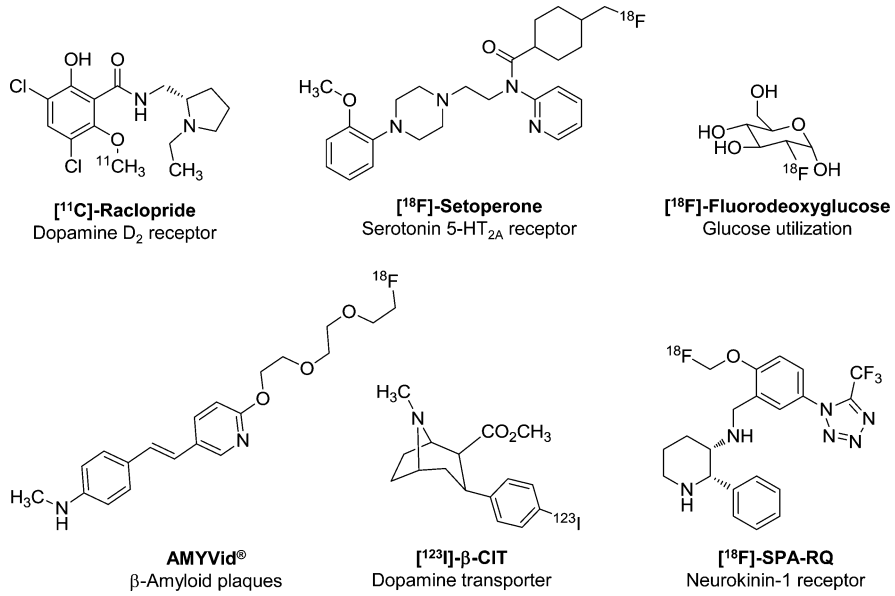

Figure 13. Representative PET and SPECT biomarker imaging agents and their biological targets.

in the form of retroanalysis studies similar to the one that led to the Lipinski rules.[110,111] Analysis of successful drugs and the lead molecules from which they evolved shows that, for the most part, the drugs possessed superior ligand efficiency indices compared to their corresponding leads. This trend held true for a number of physicochemical parameters including molecular weight and lipophilicity. Although in vitro predictors may not be a replacement for the intuition that comes from experience in medicinal chemistry, they have become invaluable tools that help medicinal chemists efficiently identify clinical candidates that have a better chance of making it across the finish line.

Translational Medicine. Another field that has emerged in the quest to reduce clinical dropout is translational medicine.[112] The term translational medicine means different things to different stakeholders in the pharmaceutical industry, but one of the important goals of this field is to increase the predictability of preclinical research in order to enhance the chances that a clinical candidate will cross the finish line and effectively treat a disease or condition. The concept has been popularized in the term bench to bedside, which has been associated with numerous research centers and projects and has even been used to designate an NIH funding program.[113] Two major components of enhancing clinical predictability that have received significant attention are (1) establishing biomarkers and (2) genetic targeting of drug candidates to patient populations more likely to respond (personalized medicine).

The development of reproducible, objective biomarkers to establish a correlation between target modulation and clinical outcome and to confirm target engagement has become a cornerstone of modern drug discovery.[114] The concept of a biomarker was formalized at the turn of the 2000s by the NIH's Biomarkers Definitions Working Group.[115] Pharmaceutical companies and clinical research groups embraced the concept, and biomarker identification and development eventually became a staple in the clinical and preclinical research paradigms. In an attempt to overcome the confusion over the roles of biomarkers in the scheme of drug development,[116] a number of groups have proposed classification systems for biomarkers based on their use such as the one shown in Figure 12.[117]

Arguably, a tool that has had one of the greatest impacts in translational medicine in the past 20 years is imaging. Imaging techniques have been used to confirm target validation, to monitor target engagement, and to assess the effectiveness of treatment. Well-known imaging techniques such as X-ray and X-ray-based computer-assisted topography (CAT) have

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become commonplace in today's clinical setting and are used to diagnose diseases and to monitor the progress of drug treatment. However, the routine use of PET (positron emission tomography) and SPECT (single-photon emission computed tomography) imaging agents have allowed preclinical and clinical scientists to establish whether advancing drug candidates reach and engage the biological target at high enough concentrations to correlate with the in vitro concentrations that are thought to be therapeutically meaningful and that target engagement is maintained for the desired period of time.[118] Using such data, researchers can correlate pharmacokinetics with the expected pharmacodynamics predicted from animal efficacy models and increase the efficiency of clinical trials through proper dose and dosing regimen selection. Alternatively, if unacceptable target engagement is identified, then development of the compound can be halted prior to incurring the cost of further clinical trials. A plethora of published examples of PET and SPECT biomarkers use to drive go/no-go decisions exists in the literature, and it is beyond the scope of this manuscript to discuss them in detail. Notable examples (Figure 13) of the use of PET imaging biomarkers include confirming the role of 5-HT_{2A} antagonism in the neuroleptic activity of atypical antipsychotics,[119] demonstrating that poor receptor occupancy was not the reason for a lack of human efficacy seen with the neurokinin-1 antagonist aprepitant,[120,121] and monitoring glucose utilization with the PET ligand ^{18}F-fluorodeoxyglucose[122] in a myriad of preclinical and clinical applications.[123,124] SPECT imaging has also found use in a number of applications. The use of technetium-99 for bone and brain scans is well-known, and its incorporation into tissue-specific chelates or attachment to antibodies has broadened its impact as a biomarker to additional fields such as cardiovascular, metabolic, and oncology medicine. One of the most recent examples is ProstaScint (capromab pendetide), an antibody for prostate specific membrane antigen labeled with indium-111 used to diagnose prostate cancer and to monitor tumor response to treatment.[125,126] Of course, radioisotope-based imaging is not the only methodology that has had significant impact in translational medicine. For example, magnetic resonance imaging (MRI) has become a critical tool in the stroke drug development field and is critical for the diagnosis of stroke in the clinical setting and determination of whether or not the patient is a candidate for the only approved intervention for stroke, thrombolytic therapy. Additionally, combining radioisotope and nonradioisotope techniques can provide greater detail and image resolution.

The authors' backgrounds in CNS drug discovery, perhaps, bias them toward an appreciation of radioisotope-based imaging; however, we would be remiss not to acknowledge the considerable contributions to drug discovery that nonimaging-based biomarkers have made. For example, focused use of distal and proximal biomarkers such as plasma glucose levels and plasma dipeptidyl-peptidase IV activity allowed Merck to move the type 2 diabetes drug sitagliptin (Januvia) from phase I to phase III in 60% of the average time for most clinical candidates.[127] Prostate specific antigen remains an invaluable plasma biomarker for prostate cancer diagnosis and monitoring tumor progression and treatment.[128] In addition, efficacy and target engagement are not the only drug properties that can be monitored through the use of biomarkers. Safety is another critical aspect of drug development that has benefited from the use of biomarkers. For example, the association of a prolongation in the QTc interval seen in electrocardiograms with an increased risk for sudden cardiac death (i.e., Torsades de pointes) led to the recognition of blockade of the human KI_R current (associated, in part with the Kv11.1 potassium channel encoded by the notorious human ether-a-go-go related gene hERG) as a potential safety concern. As a result, the U.S. Food and Drug Administration (FDA) released guidance in 2005 on what hERG-related data were expected in IND applications.[129] It cannot be denied that the concept of biomarkers and their application have had beneficial impacts on drug discovery.

However, despite significant advances, there is an unmet medical need for predictive biomarkers in many areas. Two neurodegenerative diseases that come to mind are Alzheimer's disease (AD) and Parkinson's disease (PD). The challenge for AD biomarker research has been to identify biomarkers that can help to diagnose the disease in its early stages and to monitor accurately the effect of the drug on the progression of the disease process. Significant progress has been made in AD biomarker research both in imaging (e.g., whole-brain imaging, ^{18}F-fluorodeoxyglucose, and Lilly's recently marketed amyloid plaque imaging agent AMYViD)[130] and in plasma and cerebrospinal fluid biomarkers.[131] It remains to be seen whether these biomarkers accurately correlate with disease presence and progression, especially in light of the doubt cast on the amyloid hypothesis by the recent clinical failures of the gamma secretase inhibitors semagacestat and avagacestat. Identifying a viable biomarker for PD is an ongoing priority for many groups, including the National Institute of Neurological Disorders and Stroke and the Michael J. Fox Foundation. Preliminary data with the SPECT imaging agent [^{123}I][β]-CIT (2β-carbomethoxy-3β-(4-iodophenyl)tropane) suggested that clinical outcome of recently diagnosed PD patients correlated with striatal dopamine transporter density.[132] Under appropriate assay conditions, decreased cerebrospinal fluid levels of α-synuclein and Parkinson Protein 7 (PARK7, aka, DJ-1) correlates with the existence of PD, although there was no association between biomarker levels and disease severity.[133] Although these tools may find greater use in PD, what is ultimately needed is reliable biomarkers that can help diagnose PD early in this devastating disease where much of the substantia nigra has been destroyed before the typical symptoms begin to manifest.

An extension of the use of biomarkers is the concept of targeted or personalized medicine. With the sequencing of the human genome came the ability to use genetic information to identify patients whose diseases would be particularly responsive to a given drug both in clinical trials and in the patient population once the drug is approved. At the forefront of the biomarker-driven personalized medicine arena has been the field of oncology. A key turning point for the acceptance of genetic biomarkers was Herceptin, a drug targeted through genetic profiling to breast cancer patients whose tumors overexpress the HER2/neu receptor.[134] Since that time, a number of cancer-associated genetic biomarkers have been identified that have potential clinical utility,[135] and several drugs have entered focused, biomarker-driven clinical trials.[136] The subject of genetic biomarkers recently received significant public attention. In February, 2013, American actress Angelina Jolie announced that she had elected to undergo a preventive double mastectomy after learning from a genetic screen that she possessed a mutation in her BRCA1 gene that significantly elevated her risk for developing aggressive breast cancer.

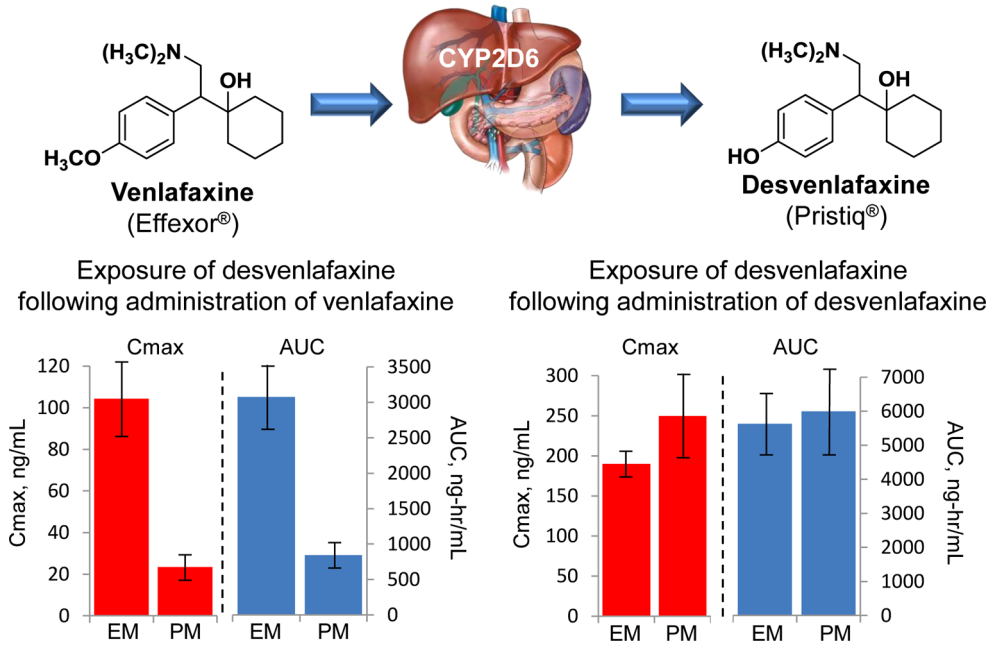

Figure 14. Structures of venlafaxine (Effexor) and desvenlafaxine (Pristiq) and pharmacokinetic data for administration of the two drugs. EM, extensive metabolizers; PM, poor metabolizers. (Data taken from ref 143.)

Although various sides continue to debate the merit of Jolie's decision and, more importantly, publicity of the event, it cannot be denied that the event has raised public awareness of genetic screening and the use of genetic biomarkers to make health decisions.

Unfortunately, other therapeutic areas have lagged behind the oncology field. For example, in CNS drug discovery, only two diseases have seen significant genetic biomarker research. In AD, it has been recognized that patients carrying the apolipoprotein E4 (ApoE4) allele, especially the E4/E4 gene pair, are at higher risk for developing the late-onset form of the disease (reviewed by Sadigh-Eteghad et al.[137]) and may respond differently to treatment. Unfortunately, this discovery has had limited impact on the identification of a drug that can halt the progression of the disease. Extensive genotyping of schizophrenic patients has been pursued in an attempt to differentiate the 20% of patients who respond well to an antipsychotic drug from the 80% who respond less well or show no response. However, the unexpectedly large number of genes underlying the disease has proven to be challenging to analyze.[138] As research into genetic biomarkers continues, an underlying concern with the concept of personalized medicine is that of cost. Despite the savings that focusing clinical trials toward smaller numbers of treatment-susceptible patients may provide, the overall cost of developing a personalized drug is still going to be substantial. Smaller numbers of target patients means that the cost of the drug will have to be high to recover the R&D investment. This concern has already become a reality, with the yearly cost of many personalized cancer drugs exceeding $10 000/year and a few, like the biological anticancer drugs Yervoy and Provenge, expected to approach $100 000/year. Provenge, in some ways, can be considered the epitome of personalized medicine because it is an antiprostate cancer vaccine that is prepared individually for each patient. Some insurers have already refused to pay for some high-cost personalized drugs targeting small patient populations, essentially denying access of these to drugs to patients who stand the best chance of benefiting from them. Without the ability to make back the money that they laid out developing such focused drugs, it stands to reason that most companies will not be able to afford developing such drugs, even if good genetic biomarkers are available to guide patient selection. The ability of the pharmaceutical industry and the market to reach a mutually beneficial compromise between patient cost and investment recovery will likely play a major role in the future of personalized medicine.

■ PHARMA'S COMMITMENT TO INNOVATION: SUCCESS STORIES FROM THE AUTHORS' PAST

Despite the challenges discussed above, the industry continues to embark on a range of initiatives and projects to address unmet medical needs or to identify superior drugs in place of ones with weaknesses, risks, or less than desirable efficacy. Attempts to identify additional indications for drugs or drug classes, superior formulations that make taking the drug more convenient (thus enhancing patient compliance), or drug combinations that treat diseases better than the separate components have all been criticized as evergreening exercises or franchise maintenance. However, in an environment where many of the most pressing unmet medical needs like neurodegenerative diseases and stroke have yet to yield to pharmaceutical intervention, even small innovations can be useful as the greater goals are being pursued, and these are often taken for granted by critics of the industry. For example, although not a disease cure, the advent of highly active antiretroviral therapy (HAART) and the use of drug combinations has brought hope to numerous HIV sufferers. It will be the small innovations that sustain the industry as the scientific community continues to search for the keys to unlock the secrets of diseases like AD.

In the following sections, we will briefly describe three success stories from our past association with Wyeth. Their inclusion in this Perspective does not mean that we believe that these successes overshadow others. The industry as a whole has

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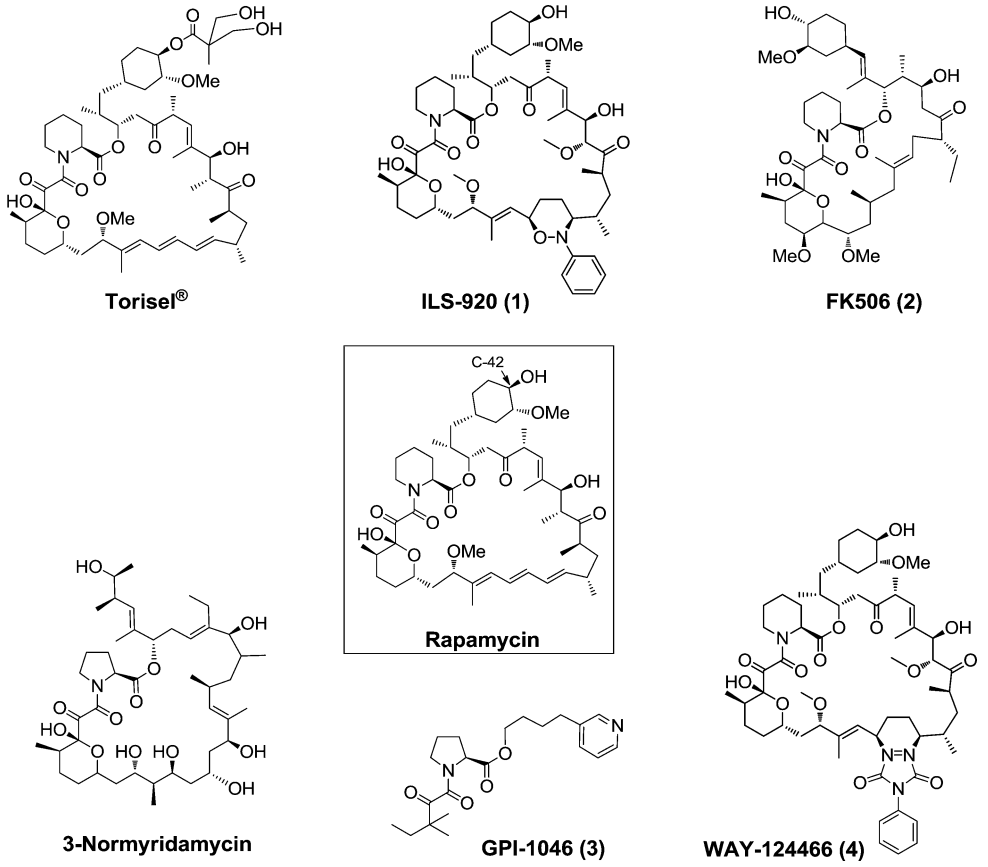

Figure 15. Structures of immunosuppresive and nonimmunosuppresive immunophilins.

realized many innovative successes throughout the past 30 years, both big and small. The ones that we present below are simply most familiar to us. The first example, the small-molecule antidepressant Pristiq, describes how attempts to overcome the weaknesses with a blockbuster drug led to a follow-on agent that is much more convenient to use. The second example, natural product-derived immunophilins, presents how the search for follow-on agents with improved physicochemical properties led to new indications and even new biological targets. The final example from the vaccines platform, Prevnar13, shows how an attempt to address a biological issue caused by a predecessor agent has provided an innovative therapy that jump-started one company's vaccines program and has demonstrated that, like small molecules, vaccines can achieve blockbuster status.

Pristiq (Desvenlavaxine). In 1993, Wyeth marketed the first nontricyclic serotonin/norepinephrine reuptake inhibitor (SNRI) antidepressant Effexor (venlafaxine, Figure 14).[139] The clinical efficacy seen with venlafaxine has benefited over 20 milllion patients, and studies have shown that patients resistant to treatment with other antidepressants often respond to venlafaxine.[140] The success of venlafaxine encouraged the discovery of other nontricyclic SNRIs, including Cymbalta (duloxetine), Savella (milnacipran), and, most recently, the active enantiomer of milnacipran, Fetzima (levomilnacipran). Venlafaxine is metabolized in man by cytochrome P450 2D6 to give the major active O-desmethyl metabolite desvenlafaxine (Figure 14). Desvenlafaxine is also a mixed serotonin/norepinephrine reuptake inhibitor, although the compound is somewhat more selective for the serotonin transporter than venlafaxine (desvenlafaxine is 10-fold more potent at inhibiting serotonin uptake[141] than norepinephrine, whereas venlafaxine is 3-fold more selective for serotonin uptake[142]). Because of genetic polymorphisms in the 2D6 subtype, different people metabolize via 2D6 at different rates, leading to phenotypic classifications such as poor metabolizers (PM) and extensive metabolizers (EM). Clinical data (Figure 14, left) revealed that significantly higher plasma levels of desvenlavaxine (both in terms of C_{max} and AUC) were seen in EMs than in PMs following administration of Effexor.[143] As a result, the dose of venlafaxine for patients initiating treatment has to be titrated until steady-state plasma levels of both the drug and active metabolite are reached. To overcome this issue, Wyeth developed the active metabolite desvenlafaxine as a follow-on to venlafaxine. From the data shown on the right in Figure 14, it can be seen that direct administration of desvenlafaxine results in similar plasma levels in both EMs and PMs. Additionally, the lack of a role for 2D6 in desvanlafaxine's metabolism translates to a reduced risk for 2D6-associated drug−drug interactions, including those likely to occur with other antidepressant drugs that inhibit CYP 2D6 such as paroxetine. This is pertinent because depressed patients are often cotreated with multiple antidepressant drugs. Wyeth marketed the succinate salt of desvanlafaxine as Pristiq in 2008. Since Pristiq's introduction, sales have grown to approximately $500 million per year. However, beginning earlier this year, nonbranded versions of desvenlafaxine became available outside of the U.S. despite the fact that patents on the drug are not scheduled to expire until the 2022−2027 time frame. In light of this fierce generic competition (including generic venlafaxine itself), it remains to be seen if Pristiq will achieve the blockbuster status once enjoyed by its predecessor Effexor.

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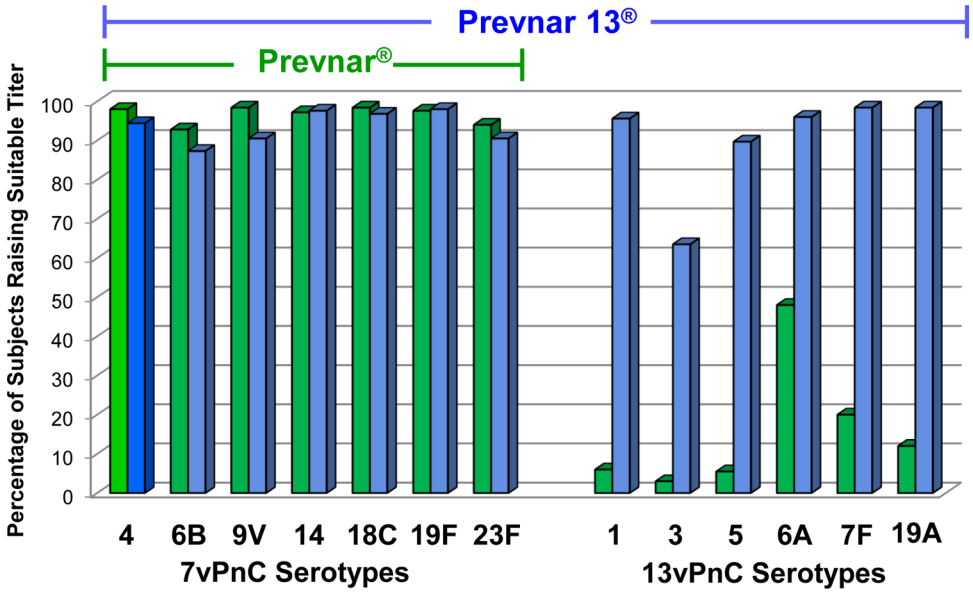

Figure 16. *S. pneumoniae* serotypes covered by Prevnar and Prevnar 13 (data taken from ref 155).

Immunophilins. The history that led from the discovery of Rapamune (rapamycin) to Torisel (temsirolimus) and then on to the innovative experimental agent ILS-920 (**1**, Figure 15) has been told by us[144,145] and others.[146] Therefore, in this Perspective, we will only summarize the details that can be found in other manuscripts. The journey from rapamycin to **1** is a good example of how a class of molecules can have multiple therapeutic applications.

Rapamycin (Figure 15) was an innovative product in its own right. It was the tool molecule that led to the discovery of mammalian target of rapamycin (mTOR), a new drug target and the center of a pair of previously unknown signaling pathways. Rapamycin's immunosuppressant activity is well-known and has been discussed elsewhere.[147] Rapamycin was the first in its class and finds utility in the treatment of organ-transplant rejection and as a restenosis-preventing agent in coronary stents. However, its development for cancer was never prioritized despite the pivotal role that one of the mTOR pathways holds in many cancers.[148] Rapamycin's relatively poor water solubility was perceived to be a weakness, and a medicinal chemistry program was initiated to identify more soluble semisynthetic analogues of rapamycin that could be targeted for the cancer indication.[149,150] An X-ray cocrystal structure of rapamycin bound to the FKBP12/mTOR complex revealed that the region of the molecule surrounding the C-42 hydroxyl was relatively solvent-exposed and could be altered without affecting the terniary complex.[151] Thus, a series of aqueous solubility-promoting substituents were appended to the C-42 hydroxyl to give compounds that retained immunosuppressant and antiproliferative activity. In 2007, Wyeth marketed temsirolemus for the treatment of advanced renal cell carcinoma, a disease that routinely possessed a poor prognosis following diagnosis. Temsirolemus was one of the first drugs to improve statistically the overall survival time for renal cell carcinioma patients and validated mTOR as a relevant therapeutic target for cancer. Its success ultimately led other companies to develop and market similar water-soluble anticancer rapamycin analogues such as everolimus and ridaforolimus.

The discovery of **1** (Figure 15) began with a few key observations. Both rapamycin and the structurally related FK506 (**2**, Figure 15) were reported to show neuroprotective effects in vitro. However, although the in vitro activity translated into efficacy in a rodent model of ischemic stroke for **2**, rapamycin was not effective in the same study. It was generally accepted that the immunosuppressive activity shown by **2** precluded it from development for stroke. Other immunophilins that bound to FKBP12 such as GPI-1046 (**3**, Figure 15) also demonstrated some neuroprotective activity in vitro but were not immunosuppressant, leading some to hypothesize that the neuroprotective activity seen with FK506 and GPI-1046 may be the result of binding to other targets. A breakthrough for Wyeth came with the isolation of a macrocyclic derivative structurally related to rapamycin, 3-normyridamycin (Figure 15). 3-Normyridamycin showed little binding to FKBP12 and no immunosuppressant activity but was potently neuroprotective and neuroregenerative in a cellular model of Parkinson's-like neurodegeneration.[152] These results encouraged Wyeth to embark on a reassessment of their immunophilin analogue library using a pair of phenotypic assays that assessed neuroprotective and neuroregenerative potential. Hits were cross-screened for immunosuppressant activity. This exercise identified the nonimmunosuppressive rapamycin analogue WAY-124466 (**4**, Figure 15), a derivative where the polyene moiety thought to interact with mTOR had been modified using Diels–Alder chemistry.

A focused medicinal chemistry campaign concentrating on Diels–Alder adducts of rapamycin led to **1**, which advanced to clinical trials for stroke in 2008. The detailed biological profile of **1** has been published elsewhere.[153] This nonimmunosuppressive macrocyclic derivative showed potent neuroprotective and neuroregenerative activity in vitro as well as reduction of infarct volume and enhanced functional recovery in animal models of ischemic stroke. Affinity purification experiments suggested that the biological targets for **1** were the β1-subunit of the L-type calcium channel and FKBP52, a target associated with neuroregenerative activity. Thus, the initial discovery of a natural product from a soil sample from Easter Island ultimately led not only to additional drugs with different indications but

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also to the discovery of new signaling pathways that remain an area of intense research and new discoveries even today.

Prevnar 13. In 2000, Wyeth introduced Prevnar, a vaccine targeting *Streptococcus pneumoniae*, the leading cause of serious infections in children, including pneumonia, meningitis, and sepsis as well as less invasive infections such otitis media and sinusitis. Prevnar targeted seven of the most common serotypes of *S. pneumoniae* (Figure 16). Prevnar was different from many vaccines in that it targeted cell surface polysaccharides rather than proteins because *S. pneumoniae* is encapsulated in a polysaccharide coat, which is its major virulence factor. To elicit a suitable response, protein-conjugation technology was employed to produce Prevnar. By 2001, the number of new cases of *S. pneumoniae* in the U.S. (mainly in the form of otitis media) had dropped by nearly 70%. However, as a result of the use of Prevnar, the incidence of serotypes of *S. pneumoniae* not covered by the vaccine increased, especially the virulent 19A serotype.[154] An agent with broader coverage was needed.

Wyeth began research soon afterward to extend the coverage of Prevnar. In 2009, they submitted the BLA for Prevnar 13, a vaccine targeting 13 *S. pneumoniae* serotypes, including A19 (Figure 16). The new vaccine was marketed in 2010,[154,155] and has been a gratifying success. As of 2012, Prevnar 13 was licensed in over 90 countries for use in children and has become part of national immunization programs in over 50 countries worldwide.[156] It is commonly held that the Prevnar franchise and Wyeth's vaccine development capabilities were one of the primary driving forces behind Pfizer's acquisition of Wyeth in 2009, and the investment has paid off. Prevnar 13 was the first vaccine to achieve blockbuster status, with sales of over $1.8 billion in 2012.[157] In essence, Prevnar 13 has done for the vaccines platform what Tagamet did for the small-molecules platform: demonstrate that good, innovative products can reap significant rewards for the companies who take the risk and invest in their development. Prevnar 13 has shown that vaccines can be blockbuster products too.

■ CONCLUDING REMARKS

So where does the pharmaceutical industry stand? We previously discussed the various criticisms levied at Pharma and concluded that although many of those criticisms are the result of misconceptions or unavoidable some are at least partly valid and deserved. A similar conclusion can be reached regarding the many challenges that the industry faces today in its quest to develop new medicines. Some of today's challenges are the result of changes that the industry could not have been predicted 20 years ago. The hurdles that must be cleared to achieve regulatory approval are higher today, thanks in part to some high-profile cases of unexpected adverse events surfacing after the drugs in question were marketed and administered to large numbers of patients. Some initiatives, such as multi-dimensional optimization and translational research, are helping to increase the success rate both at the preclinical and clinical stages, but the high price of clinical development requires that even greater efforts are made to ensure that compounds entering clinical trials cross the finishing line.

Generic competition today is fiercer than ever. Not only are generic companies encouraged to bust the patents of branded drugs in order to market cheaper generic versions earlier but also they are protected from much of the liability that would otherwise result in the event that their activities are ruled to be infringement. Additionally, the hope of expanding into international markets to compensate for stagnant revenues in the U.S. is being threatened by the apparent willingness of generic-producing countries to deny or bypass patents in those countries, opening the way for generic versions of drugs to be made available in developing markets before their patent lives have ended. To withstand the onslaught of generics, many big Pharma companies have expanded their biopharmaceutical efforts, and a significant number of new drugs approved in the last 5 years have been therapeutic proteins and antibodies. Many of these biotherapeutics represent personalized medicine approaches and hold promise for specifically targeting diseases that will be particularly susceptible. However, the high price tag of many of these biotherapeutics (partly because biotherapeutic drugs are inherently more expensive than small molecules and partly because of the small market share expected from targeted therapy) are running afoul of the current political and economic environments that are pushing back against high prices. That same environment is also turning its back on purely me-too second- and third-generation drugs that offer little advantage over currently available therapies. Going forward, new drugs will have to offer something unavailable or at least significantly superior to receive approval and a guarantee of insurer's support.

Yet, some of the challenges that the industry faces today are at least partly of their own making. A focus on the development of blockbuster drugs ultimately contributed to the patent cliff that has received so much attention and has impacted significantly on the future of Pharma. Although many analysts feel that the worst of the patent cliff is over, the industry is left trying to develop business models that will shield them from such situations in the future. Another challenge that the industry must address is how to compensate for the loss of talent and capacity in the wake of the massive layoffs that have occurred over the past 13 years. At the time that this Perspective was being revised, two companies just announced additional multithousand employee layoffs, with a number of other companies already having executed smaller layoffs in 2013. One company, rather than reduce staff, has elected to freeze employee base pay for 2014. Outsourcing has compensated, to some extent, for the loss in manpower, but innovation has stagnated, partly because of the resistance of companies to tackle high-risk targets, but also because of the loss of scientists who are the source of the innovation. To insource innovation while minimizing risk, companies are changing their approach to how they partner with biotech companies and academic research groups. To facilitate the transfer of innovative ideas from academia to Pharma, many universities have supported the establishment of academic drug discovery groups who can help academic scientists craft their innovative ideas into the products that will appeal to an industrial partner. The challenges for these groups include overcoming the same risk and drop-out rate faced by industrial research groups and identifying funding after the initial investment made by the university. Most government grants and foundation awards target early basic research or late-stage drug discovery where the identification and optimization of a preclinical candidate has already occurred. Relatively few requests for applications (RFAs) specifically address the early lead identification and hit-to-lead stages, not nearly enough to support the many innovative and promising projects that are going on in today's academic laboratories. If academic drug discovery is to play a relevant role in boosting pharmaceutical innovation, a supportive funding system will need to be

established so that good ideas have a chance to become realities.

Despite all of today's challenges, pharmaceutical companies continue to develop innovative new products, as summarized in a recent article by Chemical and Engineering News writer Rick Mullin.[158] Some of the worst may be over, but the quest to rise from the ashes of last century's Phoenix continues. Regardless of the inevitable fact that pharmaceutical companies are for-profit entities, the need for their successful navigation of today's uncertain times impacts us all. The industry must find a path forward so that we can all continue to enjoy the irreplaceable benefits that pharmaceuticals offer.

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Notes

The authors worked for several years in the pharmaceutical sector; however, they are not spokesmen for the pharmaceutical industry. The views expressed in this perspective are entirely their own. The authors declare no competing financial interest.

Biographies

Magid Abou-Gharbia received his B.Sc. in Pharmacy and his M.Sc. in Medicinal Chemistry from Cairo University in 1971 and 1974, respectively, and his Ph.D. in Organic Chemistry from the University of Pennsylvania in 1979. Following an NIH postdoctoral fellowship at Temple University, Magid joined Wyeth Pharmaceuticals in 1982, where he was ultimately promoted to Senior Vice President of Chemical and Screening Sciences. His team's efforts led to the identification of eight marketed drugs and several clinical candidates. In 2008, Magid joined Temple University School of Pharmacy as Professor of Pharmaceutical Sciences, Associate Director of Research, and Director of the Molder Center for Drug Discovery Research. Magid serves on the Scientific Advisory Board of several companies and professional societies and has adjunct professor appointments at several universities.

Wayne E. Childers received his B.A. in Chemistry from Vanderbilt University in 1975 and his Ph.D. in Organic Chemistry from the University of Georgia in 1984. While pursuing his Ph.D. studies, Wayne served as Assistant Adjunct Professor at Bucknell University from 1982−1984. Following a postdoctoral fellowship at Johns Hopkins University School of Medicine, Wayne joined Wyeth in 1987, where he led CNS-directed project teams that advanced four new chemical entities to clinical trials. In 2010, Wayne joined Temple University School of Pharmacy to serve as Associate Professor of Pharmaceutical Sciences and Associate Director of the Molder Center for Drug Discovery Research. Wayne's research interests involve applying state-of-the-art techniques to the identification and development of new chemical entities for treating unmet medical needs.

ABBREVIATIONS USED

AD, Alzheimer's disease; ADME, absorption, distribution, metabolism and elimination; AMRI, Albany Molecular Research, Inc.; ANDA, abbreviated new drug application; ApoE4, apolipoprotein E4; BCRP, breast cancer resistance protein; BLA, biological license application; BRICMT, Brazil, Russia, India, China, Mexico, Turkey; Calibr, California Institute for Biomedical Research; CAMD, Coalition Against Major Diseases; CNS, central nervous system; CRO, contract research organization; CT, computed tomography; EM, extensive metabolizers; EU, European Union; FDA, Food and Drug Administration; FKBP12, FK506 binding protein-12; FKBP52, FK506 binding protein-52; FTC, Federal Trade Commission; FTE, full-time equivalent; GMP, good manufacturing practice; HAART, highly active antiretroviral therapy; hERG, human ether-related a go-go; HIV, human immunodeficiency virus; HTS, high-throughput screen; IND, investigational new drug; J&J, Johnson and Johnson; LC/MS/MS, liquid chromatography−tandem mass spectroscopy; M&A, merger and acquisition; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; NDA, new drug application; NIH, National Institutes of Health; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; PCI, percutaneous coronary intervention; PD, Parkinson's disease; PET, positron emission tomography; P-gp, P-glycoprotein; PhRMA, Pharmaceutical Research and Manufacturing Association; PK, pharmacokinetics; PM, poor metabolizers; R&D, research and development; RFA, request for applications; RNA, ribonucleic acid; SAR, structure−activity relationship; siRNA, small interfering ribonucleic acid; SPECT, single-photon emission computed tomography; SPR, structure−property relationship; TPSA, topological polar surface area; UNC, University of North Carolina (Chapel Hill); U.K., United Kingdom; U.S., United States; WHO, World Health Organization

REFERENCES

(1) Arlington, S. *From Vision to Decision: Pharma 2020*. Technical Report from PricewaterhouseCoopers: 2012; http://www.pwc.com/jp/ja/japan-knowledge/archive/assets/pdf/pharma-2020-vision-to-decision.pdf.

(2) Abou-Gharbia, M.; Childers, W. E. Discovery of innovative therapeutics: Today's realities and tomorrow's visions. 1. Criticisms faced by the pharmaceutical industry. *J. Med. Chem.* **2013**, *56*, 5659−5672.

(3) Hughes, J.; Rees, S.; Kalindjian, S.; Philpott, K. Principals of early drug discovery. *Br. J. Pharmacol.* **2011**, *162*, 1239−1249.

(4) Grech, E. ABC of interventional cardiology. Percutaneous coronary intervention. I: History and development. *Brit. Med. J.* **2003**, *326*, 180−1082.

(5) Li, Y.; Bhindi, R.; Khachigian, L. Recent developments in drug-eluting stents. *J. Mol. Med.* **2011**, *89*, 545−553.

(6) Harikumar, R.; Aggarwal, G. Formulation tactics for the delivery of poorly soluble drugs. *Int. J. PharmTech Res.* **2012**, *4*, 914−923.

(7) Alvarez-Lueje, A.; Perez, M.; Zapata, C. Electrochemical methods for the in vitro assessment of drug metabolism. In *Topics on Drug Metabolism*; Paxton, J., Ed.; InTech, Rijeka, Croatia, 2012; Chapter 9.

(8) Nordstrom, A.; Lewensohn, R. Metabolomics: Moving to the clinic. *J. Neuroimmune Pharmacol.* **2010**, *5*, 4−17.

(9) Ametamey, S.; Honer, M.; Schubiger, P. Molecular imaging with PET. *Chem. Rev.* **2008**, *108*, 1501−1516.

(10) Bailey, D.; Willowson, K. An evidence-based review of quantitative SPECT imaging and potential clinical applications. *J. Nucl. Med.* **2013**, *54*, 83−89.

(11) Mariani, G.; Bruselli, L.; Kuwert, T.; Kim, E.; Flotats, A.; Israel, O.; Dondi, M.; Watanabe, N. A review on the clinical uses of SPECT/CT. *Eur. J. Nucl. Med. Mol. Imaging* **2010**, *37*, 1959−1985.

(12) *Drug Discovery and Development: Understanding the R&D Process*; Report from the Pharmaceutical Research and Manufacturers of America: Washington, DC, 2007; http://www.innovation.org/drug_discovery/objects/pdf/RD_Brochure.pdf.

(13) Overington, J.; Al-Lazikani, B.; Hopkins, A. How many drug targets are there? *Nat. Rev. Drug Discovery* **2006**, *5*, 993−996.

(14) Hopkins, A.; Groom, C. The druggable genome. *Nat. Rev. Drug Discovery* **2002**, *1*, 727−730.

(15) Kubiyni, H. Drug research myths: Hype and reality. *Nat. Rev. Drug Discovery* **2003**, *2*, 665−668.

(16) Hughes, J.; Rees, S.; Kalindjian, S.; Philpott, K. Principals of early drug discovery. *Br. J. Pharmacol.* **2011**, *162*, 1239−1249.
(17) Gregori-Puigjane, E.; Setola, V.; Hert, J.; Crews, B.; Irwin, J.; Lounkine, E.; Marnett, L.; Roth, B.; Schoichet, B. Identifying mechanism-of-action targets for drugs and probes. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 11178−11183.
(18) Boguski, M.; Mandl, K.; Sukhatme, V. Drug discovery, repurposing with a difference. *Science* **2009**, *324*, 1394−1395.
(19) Plenge, R. M.; Scolnick, E. M.; Altshuler, D. Validating therapeutic targets through human genetics. *Nat. Rev. Drug Discovery* **2013**, *12*, 581−594.
(20) Chen, X.-P.; Du, G.-H. Target validation: A door to drug discovery. *Drug Discovery Ther.* **2007**, *1*, 23−29.
(21) Brunschweiger, A.; Hall, J. A decade of the human genome sequence − how does the medicinal chemist benefit? *ChemMedChem* **2012**, *7*, 194−203.
(22) Halgren, T. Identifying and characterizing binding sites and assessing druggability. *J. Chem. Inf. Model.* **2009**, *49*, 377−389.
(23) Skolnick, J.; Gao, M. Interplay of physics and evolution in the likely origin of protein biochemical function. *Proc. Natl. Acad. Sci. U.S.A.* **2013**, *110*, 9344−9349.
(24) Campbell, S.; Gaulton, A.; Marshall, J.; Bichko, D.; Martin, S.; Brouwer, C.; Harland, L. Visualizing the drug target landscape. *Drug Discovery Today* **2010**, *15*, 3−15.
(25) Keller, T.; Pichota, A.; Yin, Z. A practical view of 'druggability'. *Curr. Opin. Chem. Biol.* **2006**, *10*, 357−361.
(26) Lipinski, C. Lead- and drug-like compounds: The rule-of-five revolution. *Drug Discovery Today* **2004**, *1*, 337−341.
(27) Merritt, A. High throughput chemistry in drug discovery. In *New Synthetic Technologies in Medicinal Chemistry*; Farrant, E., Ed.; RSC Publishing: Cambridge, UK, 2012; pp 6−41, Chapter 2.
(28) Kerns, E.; Di, L. *Drug-Like Properties: Concepts, Structure Design and Methods*; Academic Press: Boston, MA, 2008.
(29) Gleeson, M.; Hersey, A.; Hannongbua, S. In-silico ADME models: A general assessment of their utility in drug discovery applications. *Curr. Top. Med. Chem.* **2011**, *11*, 358−381.
(30) Kola, I.; Landis, J. Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug Discovery* **2004**, *3*, 711−715.
(31) Gilbert, J.; Henske, P.; Singh, A. Rebuilding big pharma's business model. *In Vivo Bus. Med. Rep.* **2003**, *21*.
(32) Kleemann, A. Metamorphosis of the pharmaceutical industry. *Pharm. Ind.* **2013**, *75*, 562−574.
(33) Stone, K. Big pharma's merger mania. *About.com*; http://pharma.about.com/od/BigPharma/tp/Big-Pharmas-Merger-Mania.htm.
(34) Deal Search Online Home Page, Irving Levin Associates, Inc.; http://www.levinassociates.com/dealsearch/.
(35) Lamattina, J. The impact of mergers on pharmaceutical R&D. *Nat. Rev. Drug Discovery* **2011**, *10*, 559−560.
(36) Firestone, R. Lessons from 54 years of pharmaceutical research. *Nat. Rev. Drug Discovery* **2011**, *10*, 963.
(37) Munos, B. Lessons from 60 years of pharmaceutical innovation. *Nat. Rev. Drug Discovery* **2009**, *8*, 959−968.
(38) Comanor, W.; Scherer, F. Mergers and innovation in the pharmaceutical industry. Harvard Kennedy School Faculty Research Working Paper Series, 2011;https://research.hks.harvard.edu/publications/workingpapers/citation.aspx?PubId=8053&type=FN&PersonId=219.
(39) Amgen Press Release, Aug 25, 2013; http://www.amgen.com/media/media_pr_detail.jsp?releaseID=1849611.
(40) Scannell, J.; Blankley, A.; Boldon, H.; Warrington, B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat. Rev. Drug Discovery* **2012**, *11*, 191−200.
(41) Grabowski, H.; Kyle, M. Mergers, acquisitions and alliances. In *The Oxford Handbook of The Economics of the Biopharmaceutical Industry*; Danzon, P., Nicholson, S., Eds.; Oxford University Press: New York, 2012; pp 552−577.
(42) Kumar, B. Mergers and acquisitions in the pharmaceutical industry. In *Mega Mergers and Acquisitions: Case Studies from Key Industries*; Palgrave MacMillan: Hampshire, UK, 2012' pp 1−59.
(43) Tjandrawinata, R.; Simanjuntak, D. The impact of mergers and acquisitions in research-based pharmaceutical companies on productivity. Social Science Research Network: Rochester, NY, 2012; http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1981889.
(44) LaMattina, J. A holiday gift from Merck's Ken Frazier. *Drug Truths*, Dec 20, 2011; http://johnlamattina.wordpress.com/2011/12/20/a-holiday-gift-from-mercks-ken-frazier/.
(45) Weaver, C. Merck CEO defends strategy to pursue new drugs, research. *Wall Street Journal*, Dec 13, 2011; http://online.wsj.com/article/BT-CO-20111213-711338.html.
(46) Danzon, P.; Epstein, A.; Nicholson, S. Mergers and acquisitions in the pharmaceutical and biotech industries. *Managerial and Decision Economics* **2007**, *28*, 307−328.
(47) Grabowski, H.; Kyle, M. Mergers and alliances in pharmaceuticals: effects on innovation and productivity. In *Economics of Corporate Governance and Mergers*; Gugler, K., Yurtoglu, B., Eds.; Edward Elgar: Cheltehham, UK, 2008; pp 262−287.
(48) Davis, P. J. Beyond the patent cliff − signs of recovery in biopharma's new normal. *Accenture Life Sciences*, 2012; http://www.accenture.com/SiteCollectionDocuments/PDF/Accenture-Life-Sciences-Beyond-The-Patent-Cliff-Signs-Of-Recovery-in-Biopharmas-New-Normal.pdf.
(49) World preview 2018: Embracing the patent cliff. *EvaluatePharma*, 2012; http://info.evaluatepharma.com/WP2018_ELS_LP.html.
(50) Lipitor sales data. *Drugs.com*; http://www.drugs.com/stats/lipitor.
(51) Higgins, M.; Graham, S.; Higgins, M.; Graham, S. Balancing innovation and access: Patent challenges tip the scales. *Science* **2009**, *326*, 370−371.
(52) Paragraph four explained: Why generic drug companies challenge patents. Parry Ashfold, Inc.: Exton, PA, 2012; http://paragraphfour.com/explained/why_challenge.html.
(53) Harrison, C. The patent cliff steepens. *Nat. Rev. Drug Discovery* **2011**, *10*, 12−13.
(54) Powers, M. Despite short-term revenue hit, Sanofi manages patent cliff. *BioWorld*; http://www.bioworld.com/content/despite-short-term-revenue-hit-sanofi-manages-patent-cliff-0.
(55) Hitchings, A.; Baker, E.; Khong, T. Making medicines evergreen. *Br. Med. J.* **2012**, *345*, e7941.
(56) Buente, M.; Danner, S.; Weissbacker, S.; Ramme, C. Pharma emerging markets 2.0. How emerging markets are driving the transformation of the pharmaceutical industry. *Booz & Co*, 2013; http://www.booz.com/media/file/BoozCo_Pharma-Emerging-Markets-2.0.pdf.
(57) Schumacher, C. CRAMS outsourcing in pharmaceutical and chemical research and manufacturing, part II. *StepChange Innovations GmbH*, 2012; http://blog.stepchange-innovations.com/2012/08/crams-outsourcing-in-pharmaceutical-and-chemical-research-and-manufacturing-part-ii/#_edn1.
(58) Getz, K.; Lamberti, M. J.; Mathias, A.; Stergiopoulis, S. Resizing the global R&D contract service market. *Contract Pharma* **2012**, *14*, 54.
(59) Roijakkers, N.; Hagedoorn, J. Inter-firm R&D partnering in pharmaceutical biotechnology since 1975: Trends, patterns and networks. *Res. Policy* **2006**, *35*, 431−446.
(60) McCutchen, W. W., Jr.; Swamidass, P. M. Motivations for strategic alliances in the pharmaceutical/biotech industry: Some new findings. *J. High Technol. Manage. Res.* **2004**, *15*, 197−204.
(61) The use of medicines in the United States: Review of 2011. *IMS Institute for Healthcare Informatics*, April 2012; http://www.imshealth.com/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/IHII_Medicines_in_U.S_Report_2011.pdf.
(62) Barry, C.; Arad, R.; Johnston, A.; Parent, A.; Ansell, L.; Arnold, M. 2012 patent litigation study. *PricewaterhouseCoopers*, Sept 2012;

http://www.pwc.com/us/en/forensic-services/publications/2012-patent-litigation-study.jhtml.
(63) Rai, A. Use patents, carve-outs, and incentives − a new battle in the drug-patent wars. *N. Engl. J. Med.* **2012**, *376*, 491−493.
(64) Agreements filed with the Federal Trade Commission under the Medicare Prescription Drug, Improvement and Moderinization Act of 2003: Overview of agreements filed filed in FY 2012; A report by the Bureau of Competition, Federal Trade Commission: Washington, DC, Jan 2013; http://www.ftc.gov/os/2013/01/130117mmareport.pdf.
(65) List of authorized generic drugs. U.S. Food and Drug Administration: Washington , DC; http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm126389.htm.
(66) More than eight in ten Americans want the option of choosing authorized generic prescription drugs. *Roper Public Affairs & Media*, 2005; http://www.prasco.com/wp-content/uploads/2012/03/Roper_Poll.pdf.
(67) Authorized generic drugs: Short-term effects and long-term impact. Federal Trade Commission: Washington, DC, 2011.
(68) Ryu, J. K.; Kim, H. S.; Nam, D. H. Current status and perspectives of biopharmaceutical drugs. *Biotechnol. Bioprocess Eng.* **2012**, *17*, 900−911.
(69) Global biopharmaceutical market expected to reach $320 billion by 2020. *Global Information, Inc.*, Oct 4, 2012; http://www.giiresearch.com/press/6805.shtml.
(70) Stein, E. A.; Gipe, D.; Bergeron, J.; Gaudet, D.; Weiss, R.; Dufour, R.; Wu, R.; Pordy, R. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimebe therapy: A phase 2 randomized controlled trial. *Lancet* **2012**, *380*, 7−13.
(71) Sullivan, D.; Olsson, A. G.; Scott, R.; Kim, J. B.; Xue, A.; Gebski, V.; Wasserman, S. M.; Stein, E. A. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients. *JAMA* **2012**, *308*, 2497−2506.
(72) Herd, T.; Sheehy, D. A.; Ural, A. Mergers & acquisitions: A strategy for focused growth in the biopharmaceutical industry during uncertain times. *Accenture*, 2011; http://www.accenture.com/SiteCollectionDocuments/PDF/Accenture_A_Strategy_for_Focused_Growth.pdf.
(73) Kanase, S. J.; Gavhane, Y. N.; Khandakar, A.; Gurav, A. S.; Yadav, A. V. Biosimilar: an overview. *Int. J. Pharm. Sci Res.* **2013**, *4*, 2132−2144.
(74) Kay, J. Biosimilars: A regulatory perspective from America. *Arthritis Res Ther.* **2011**, *13*, 112.
(75) Patient Protection and Affordable Care Act of 2009, Pub. L. No. 111-148, Title VII, Subtitle A Biologics Price Competition and Innovation Act of 2009, §7001-7003; http://www.gpo.gov/fdsys/pkg/BILLS-111hr3590enr/pdf/BILLS-111hr3590enr.pdf.
(76) Notte, G. T. New chemical entities entering phase III clinical trials in 2012. In *Annual Reports in Medicinal Chemistry*; Bronston, J.; Desai, M. C., Eds.; Academic Press: Waltham, MA, 2013; pp 451−469.
(77) Jarvis, L. M. A bountiful year. *Chem. Eng. News* **2013**, 15−17.
(78) LaMattina, J. When it comes to NDA approvals, is 30 the new 50? *Drug Truths*, 2012; http://johnlamattina.wordpress.com/2012/01/17/when-it-comes-to-nda-approvals-is-30-the-new-50/.
(79) Armstrong, W. FDA's approvable problem. *Pharmaceutical Executive*, Nov 1, 2007; http://www.pharmexec.com/pharmexec/PE+Features/FDAs-Approvable-Problem/ArticleStandard/Article/detail/469652.
(80) FDA revised process for responding to drug applications; Press Release by the U.S. Food and Drug Administration, July 8, 2008; http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116920.htm. Complete http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2004-N-0510-nfr.pdf.
(81) Light, D.; Lexchin, J. R. Pharmaceutical research and development − what do we get for all that money? *Br. Med. J.* **2012**, *344*, e4348. http://www.bmj.com/content/345/bmj.e4348.pdf%2Bhtml.
(82) FDA's consideration of evidence from certain clinical trials. *United States Government Accountability Office*, July 2010; http://www.gao.gov/assets/310/308301.pdf.
(83) Bode-Greuel, K.; Nickisch, K. J. Value-driven project and portfolio management in the pharmaceutical industry: Drug discovery versus drug development − commonalities and differences in portfolio management practice. *J. Commer. Biotechnol.* **2008**, *14*, 307−325.
(84) Poland, B.; Hodge, F. L.; Kahn, A.; Clemen, R. T.; Wagnar, J. A.; Dykstra, K.; Krishna, R. The clinical utility index as a practical multiattribute approach to drug development decisions. *Clin. Pharmacol. Ther.* **2009**, *86*, 105−108.
(85) Sartori, V.; Steinmann, M.; Evers, M.; Jantzer, P. Value-driven drug development − unlocking the value of your pipeline. *McKinsey Quarterly*, 2011; http://www.mckinsey.com/Search.aspx?q=sartori&l=Insights%20%26%20Publications.
(86) Dykstra, K.; Hodge, L.; Poland, B.; Carrothers, T. J. Methods for developing differentiated drug products. *Pharsight*, 2009; http://www.pharsight.com/library/Methods%20for%20Developing%20Differentiated%20Drug%20Products.pdf.
(87) Frye, S.; Crosby, M.; Edwards, T.; Juliano, E. US academic drug discovery. *Nature Rev. Drug Discovery* **2011**, *10*, 409−410.
(88) Huryn, D. H. Drug discovery in an academic setting: Playing to the strengths. *ACS Med. Chem. Lett.* **2013**, *4*, 313−315.
(89) Prinz, F.; Schlange, T.; Asadullah, K. Believe it or not: How much can we rely on published data on potential drug targets? *Nat. Rev. Drug Discovery* **2011**, *10*, 713.
(90) Silber, B. M. Driving drug discovery: The fundamental role of academic labs. *Sci. Transl. Med.* **2010**, *2*, 30cm16-1−30cm16-6.
(91) Huryn, D. H.; Resnick, L. O.; Wipf, P. Contributions of academic laboratories to the discovery and development of chemical biology tools. *J. Med. Chem.* **2013**, *56*, 7161−7176.
(92) Kotz, J. Small (molecule) thinking in academia. *SciBX* **2011**, *4*, 1−4.
(93) Donatella, V. Predictive methods as a powerful tool in drug discovery. *Biochemica Medica* **2010**, *20*, 314−318.
(94) Kola, I.; Landis, J. Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug Discovery* **2004**, *3*, 711−715.
(95) Prentis, R. A.; Lis, Y.; Walker, S. R. Pharmaceutical innovation by the seven UK-owned pharmaceutical companies. *Br. J. Clin. Pharmacol.* **1988**, *25*, 387−396.
(96) Lapinski, P. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Res.* **1997**, *23*, 3−25.
(97) Gleeson, M. P.; Hersey, A.; Montanari, D.; Overington, J. Probing the links between in vitro potency, ADMET and physicochemical parameters. *Nat. Rev. Drug Discovery* **2011**, *10*, 197−208.
(98) Shultz, M. D. Setting expectations in molecular optimizations: strengths and limitations of commonly used composit parameters. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5980−5991.
(99) Kenny, P. W.; Montanari, C. A. Inflation of correlation in the pursuit of drug-likeness. *J. Comput.-Aided Mol. Des.* **2013**, *27*, 1−13.
(100) Refsgaard, H. H. F.; Jensen, B. F.; Brockhoff, P. B.; Padkhaer, S. B.; Buldbrandt, M.; Christensen, M. S. In silico prediction of membrane permeability from calculated molecular parameters. *J. Med. Chem.* **2005**, *48*, 805−811.
(101) Peach, M. L.; Zaknarov, A. V.; Liu, R.; Pugliese, A.; Tawa, G.; Wallqlvist, A.; Nicklaus, M. C. Computational tools and resources for metabolism-related property predictions. 1. Overview of publicly available (free and commercial) databases and software. *Future Med. Chem.* **2012**, *4*, 1907−1932.
(102) AbdulHameed, M. D.; Chaudhury, S.; Sing, N.; Wallqvist, S. H.; Tawa, G. J. Exploring polypharmacology using a ROCS-based target fishing approach. *J. Chem. Inf. Model.* **2012**, *52*, 492−505.

(103) Valerio, L. G. In silico toxicology for the pharmaceutical sciences. *Toxicol. Appl. Pharmacol.* **2009**, *241*, 356−370.
(104) Hewitt, M.; Cronin, M. T. D.; Enoch, S. J.; Madden, J. C.; Roberts, D. W.; Dearden, J. C. In silico prediction of aqueous solubility: the solubility challenge. *J Chem. Inf. Model.* **2009**, *49*, 2572−2587.
(105) Davis, A. M.; Bruneau, P. In silico prediction of solubility. In: *Drug Bioavailability: Estimation of Solubility, Permeability, Absorption and Bioavailability*, 2nd ed.; van de WaterBeemd, H., Testa, B., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2009; Vol. *40* , pp 53−68.
(106) Abad-Zapatero, C.; Metz, J. T. Ligand efficiency indices as guideposts for drug discovery. *Drug Discovery Today* **2005**, *10*, 464−469.
(107) Hopkins, A. L.; Groom, C. R.; Alex, A. Ligand efficiency: a useful metric for lead selection. *Drug Discovery Today* **2004**, *9*, 430−431.
(108) Abad-Zapatero, C. *Ligand Efficiency Indices for Drug Discovery: Towards an Atlas-Guided Paradigm*; Academic Press: Boston, MA, 2013.
(109) Leeson, P. D.; St.-Gallay, S. A. The influence of the 'organizational factor' on compound quality in drug discovery. *Nat. Rev. Drug Discovery* **2011**, *10*, 749−765.
(110) Perola, E. An analysis of the binding efficiencies of drugs and their leads in successful drug discovery programs. *J. Med. Chem.* **2010**, *53*, 2986−2997.
(111) Oprea, T. I.; Davis, A. D.; Teague, S. J.; Leeson, P. D. Is there a difference between leads and drugs? A historical perspective. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 1308−1315.
(112) Shahzad, A.; McLachlan, C. S.; Gault, J.; Cohrs, R. J.; Wangb, X.; Kohler, G. Global translational medicine initiatives and programs. *Transl. Biomed.* **2011**, *2*, 1−7.
(113) NIH Bench-to-Bedside Program Home Page. http://clinicalcenter.nih.gov/ccc/btb/.
(114) Frank, R.; Hargreaves, R. Clinical biomarkers in drug discovery and development. *Nat. Rev. Drug Discovery* **2003**, *2*, 566−580.
(115) Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin. Pharmacol. Ther.* **2001**, *69*, 89−95.
(116) Strimbu, K.; Travel, J. A. What are biomarkers? *Curr. Opin. HIV AIDS* **2010**, *5*, 463−466.
(117) Day, M.; Rutkowski, J. L.; Feuerstein, G. Z. Translational medicine − a paradigm shift in modern drug discovery and development: The role of biomarkers. In *Pharmaceutical Biotechnology: Advances in Experimental Biology and Medicine*; Guzman, C. A., Feuerstein, G. Z., Eds.; Springer Verlag: New York, 2009; Vol. *655*, pp 1−12.
(118) Lee, C.-M.; Farde, L. Using positron emission tomography tro facilitate CNS drug development. *Trends Pharmacol. Sci.* **2006**, *27*, 310−316.
(119) Kapur, S.; Zipursky, R. B.; Remington, G. Clinical and theoretical implications of 5-HT2 and D2 receptor occupancy of clozapine, risperidone and olanzapine in schizophrenia. *Am. J. Psychiatry* **1999**, *156*, 286−293.
(120) Chawla, S. P.; Grunburg, S.; Gralla, R. J.; Hesketh, P. J.; Rittenberg, C.; Elmer, M. E.; Schmidt, C.; Taylor, A.; Carides, A. D.; Evans, J. K.; Horgan, K. J. Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. *Cancer* **2003**, *97*, 2290−2300.
(121) Keller, M.; Montgomery, S.; Ball, W.; Morrison, M.; Snavely, D.; Liu, G.; Hargreaves, R.; Hietala, J.; Lines, C.; Beebe, K.; Reines, S. Lack of efficacy of the substance P (neurokinin1 receptor) antagonist aprepitant in the treatment of major depressive disorder. *Biol. Psychiatry* **2006**, *59*, 216−223.
(122) Schirmer, M.; Calimia, K. T.; Wenger, M.; Klauser, A.; Salvarani, C.; Moncayo, R. ^{18}F-fluorodeoxyglucose-positron emission topography: A new explorative perspective. *Exp. Gerontol.* **2003**, *38*, 463−470.
(123) Bhatnager, A.; Hustinx, R.; Alavi, A. Nuclear imaging methods for non-invasive drug monitoring. *Adv. Drug Delivery Rev.* **2000**, *41*, 41−54.
(124) Aboagye, E. O.; Price, P. M.; Jones, T. In vivo pharmacokinetics and pharmacodynamics in drug development using positron emission topography. *Drug Discovery Today* **2001**, *6*, 293−302.
(125) Taneja, S. S. ProstaScint® scan: Contemporary use in clinical practice. *Rev. Urol.* **2004**, *6*, S19−S28.
(126) Schettino, C. J.; Kramer, E. L.; Nox, M. E.; Taneja, S.; Padmanabhan, P.; Lepor, H. Impact of fusion of indium-111 capromab pendetide volume data sets with those from MRI or CT in patients with recurrent prostate cancer. *Am. J. Roentgenol.* **2004**, *183*, 519−524.
(127) Krishna, R.; Nerman, G.; Wagner, J. A. Accellerating drug development using biomarkers: A case study with sitagliptin, a novel DPP4 inhibior for type 2 diabetes. *AAPS J* **2008**, *10*, 401−409.
(128) Velonas, V. M.; Woo, H. H.; dos Remedios, C. G.; Assinder, S. J. Current status of biomarkers for prostate cancer. *Int. J. Mol. Sci.* **2013**, *14*, 11034−11060.
(129) Guidance for Industry: S7B nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals. U.S. Food and Drug Administration, Oct 2005; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074963.pdf.
(130) Hampel, H.; Frank, R.; Broich, K.; Teipel, S. J.; Katz, R. G.; Hardy, J.; Herholz, K.; Bokde, A. L. W.; Jessen, F.; Hoessler, Y. C.; Sanhai, W. R.; Zetterberg, H.; Woodcock, J.; Blennow, K. Biomarkers for Alzheimer's disease: academic industry and regulatory perspectives. *Nat. Rev. Drug Discovery* **2010**, *9*, 560−574.
(131) Rosen, C.; Hansson, O.; Blennow, K.; Zetterberg, H. Fluid biomarkers in Alzheimer's disease − current concepts. *Mol. Neurodegener.* **2013**, *8*, 20-1−20-11.
(132) Ravine, B.; Marek, K.; Eberly, S.; Oakes, D.; Kurlan, R.; Ascherio, A.; Beal, F.; Beck, J.; Flagg, E.; Galpem, W. R.; Harman, J.; Lang, A. E.; Schwarzschild, M.; Tanner, C.; Shoulson, I. Dopamine transporter imaging is associated with long-term outcomes in Parkinson's disease. *Mov. Disord.* **2012**, *27*, 1392−1397.
(133) Hong, Z.; Shi, M.; Chung, K. A.; Quinn, J. F.; Pesking, E. R.; Galasko, D.; Jankovic, J.; Zabetian, C. P.; Leverenz, J. B.; Baird, G.; Montine, T. J.; Hancock, A. M.; Hwang, J.; Pan, C.; Bradner, J.; Kang, U. J.; Jensen, P. H.; Zhang, J. DJ-1 and α-synuclein in human cerebrospinal fluid as biomarkers of Parkinson's disease. *Brain* **2010**, *133*, 713−726.
(134) Baselga, J.; Norton, L.; Albanell, J. Recombinant humanized anti-HER-2 antibody (Herceptin) enhances the antitumor activity of paclitaxel and doxorubicin against HER2/neu overexpressing human breast cancer xenografts. *Cancer Res.* **1998**, *58*, 2825−2831.
(135) Schilsky, R. L. Personalized medicine in oncology: The future is now. *Nat. Rev. Drug Discovery* **2010**, *9*, 363−366.
(136) Chiang, A.; Million, R. P. Personalized medicine in oncology: Next generation. *Nat. Rev. Drug Discovery* **2011**, *10*, 895−896.
(137) Sadigh-Eteghad, S.; Talebi, M.; Farhoudi, M. Association of apolipoprotein E epsilon 4 allele with sporadic late onset Alzheimer's disease. A meta-analysis. *Neuroscience* **2012**, *17*, 321−326.
(138) Harrison, P.; Weinberger, D. Schizophrenia genes, gene expression and neuropathology: on the matter of their convergence. *Mol. Psychiatry* **2005**, *10*, 40−68.
(139) Abou-Gharbia, M. A.; Childers, W. E. The discovery of Effexor® and Pristiq®. In *Analogue-Based Drug Discovery II*; Fischer, J., Ganellin, C. R., Eds.; Wiley-VCH: Weinheim, Germany, 2010; pp 507−524.
(140) Nelson, J. C. Managing treatment-resistant major depression. *J. Clin. Psychiatry* **2003**, *64*, 5−12.
(141) Deecher, D. C.; Beyer, C. E.; Johnston, G.; Bray, J.; Shah, S.; Abou-Gharbia, M.; Andree, T. H. Desvenlavaxine succinate: a new serotonin and norepinephrine reuptake inhibitor. *J. Pharmacol. Exp. Ther.* **2006**, *318*, 657−665.

(142) Yardley, J. P.; Husbands, G. E. M.; Stack, G.; Butch, J.; Bicksler, J.; Moyer, J. A.; Muth, E. A.; Andree, T.; Fletcher, H. F., III; James, M. N. G.; Sleleck, A. R. 2-Phenyl-2-(1-hydroxycycloalkyl)ethyl)amine derivatives: Synthesis and antidepressant activity. *J. Med. Chem.* **1990**, *33*, 2899−2905.
(143) Preskorn, S.; Patroneva, A.; Silman, H.; Jiang, Q.; Isler, J. A.; Burczynski, M. E.; Ahmed, S.; Paul, J.; Nichols, A. I. Comparison of the pharmacokinetics of venlafaxine extended release and desvenlafaxine in extensive and poor cytochrome P450 2D6 metabolizers. *J. Clin. Psychopharmacol.* **2009**, *29*, 39−43.
(144) Abou-Gharbia, M. Discovery of innovative small molecule therapeutics. *J. Med. Chem.* **2009**, *52*, 2−9.
(145) Abou-Gharbia, M.; Childers, W. Targeting neurodegenerative diseases: Drug discovery in a challenging arena. *Pure Appl. Chem.* **2012**, *84*, 1543−1556.
(146) Graziani, E. I. Uncoupling neuroprotection from immunosuppression: The discovery of ILS-920. In *Accounts in Drug Discovery*; Barrish, J. C., Carter, P. H., Cheng, P. T. W., Zahler, R., Eds.; RSC Publishing: Cambridge, UK, 2011; pp 316−331.
(147) Saunders, R. N.; Metcalfe, M. S.; Nicholson, M. L. Rapamycin in transplantation: A review of the evidence. *Kidney Int.* **2001**, *59*, 3−16.
(148) Faiver, S.; Kroemer, G.; Raymond, E. Current development of mTOR inhibitors as anticancer agents. *Nat. Rev. Drug Discovery* **2006**, *5*, 671−688.
(149) Skotnicki, J. S.; Leone, C. L.; Smith, A. L.; Palmer, Y. L.; Yu, K.; Discafani, C. M.; Gibbons, J. J.; Frost, P.; Abou-Gharbia, M. A. Design, synthesis and biological evaluation of C-42 hydroxyesters of rapamycin: The identification of CCI-779. *Clin. Cancer Res.* **2001**, *7*, 3749S−3750S.
(150) Rini, B.; Kar, S.; Kirkpatrick, P. Temsirolimus. *Nat. Rev. Drug Discovery* **2007**, *6*, 599−600.
(151) Choi, J.; Chen, J.; Schreiber, S. L.; Clardy, J. Structure of the FKBP12-rapamycin complex interacting with the binding domain of human FRAP. *Science* **1996**, *273*, 239−242.
(152) Summers, M. Y.; Leighton, M.; Liu, D.; Pong, K.; Graziani, E. I. 3-Normeridamycin: A potent non-immunosuppresive immunophilin ligand is neuroprotective in dopaminergic neurons. *J. Antibiot.* **2006**, *59*, 184−189.
(153) Ruan, B.; Pong, K.; Jow, F.; Bowlby, M.; Crozier, R. A.; Liu, D.; Liang, S.; Chen, Y.; Mercado, M. L.; Feng, X.; Bennett, F.; van Schack, D.; McDonald, L.; Zaleska, M. M.; Wood, A.; Reinhardt, P. H.; Magolda, R. L.; Skotnicki, J.; Pangalos, M. N.; Koehn, F. E.; Carter, G. T.; Abou-Gharbia, M.; Graziani, E. I. Binding of rapamycin analogs to calcium channels and FKBP52 contributes to their neuroprotective activities. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 33−38.
(154) Dinleyici, E. C.; Yargic, Z. A. Current knowledge regarding the investigational 13-valent pneumococcal conjugate vaccine. *Expert Rev. Vaccines* **2009**, *8*, 977−986.
(155) Sucher, A. J.; Chahine, E. B.; Nelson, M.; Sucher, B. J. Prevnar13, the new 13-valent pneumococcal conjugate vaccine. *Ann. Pharmacother.* **2011**, *45*, 1516−1524.
(156) Gruber, W. C.; Scott, D. A.; Emini, E. A. Development and clinical evaluation of of Prevnar 13, a 13-valent pneumococcal CRM_{197} conjugate vaccine. *Ann. N.Y. Acad. Sci.* **2012**, *1263*, 15−26.
(157) Brant, A. 20 top selling vaccines − H1, 2012. *FierceVaccines*, Sept 25, 2012; http://www.fiercevaccines.com/special-report/20-top-selling-vaccines/2012-09-25.
(158) Mullin, R. The future is now. *Chem. Eng. News* **2013**, *91*, 12−17.