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Review Article

Recent trends in specialty pharma business model



Mannching Sherry Ku*

Savior Lifetech Corporation, No. 29, Kejhong Road, Chunan, Miaoli 35053, Taiwan

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ABSTRACT

The recent rise of specialty pharma is attributed to its flexible, versatile, and open business model while the traditional big pharma is facing a challenging time with patent cliff, generic threat, and low research and development (R&D) productivity. These multinational pharmaceutical companies, facing a difficult time, have been systematically externalizing R&D and some even establish their own corporate venture capital so as to diversify with more shots on goal, with the hope of achieving a higher success rate in their compound pipeline. Biologics and clinical Phase II proof-of-concept (POC) compounds are the preferred licensing and collaboration targets. Biologics enjoys a high success rate with a low generic biosimilar threat, while the need is high for clinical Phase II POC compounds, due to its high attrition/low success rate. Repurposing of big pharma leftover compounds is a popular strategy but with limitations. Most old compounds come with baggage either in lackluster clinical performance or short in patent life. Orphan drugs is another area which has gained popularity in recent years. The shorter and less costly regulatory pathway provides incentives, especially for smaller specialty pharma. However, clinical studies on orphan drugs require a large network of clinical operations in many countries in order to recruit enough patients. Big pharma is also working on orphan drugs starting with a small indication, with the hope of expanding the indication into a blockbuster status. Specialty medicine, including orphan drugs, has become the growth engine in the pharmaceutical industry worldwide. Big pharma is also keen on in-licensing technology or projects from specialty pharma to extend product life cycles, in order to protect their blockbuster drug franchises. Ample opportunities exist for smaller players, even in the emerging countries, to collaborate with multinational pharmaceutical companies provided that the technology platforms or specialty medicinal products are what the big pharma wants. The understanding of intellectual properties and international drug regulations are the key for specialty pharma to have a workable strategy for product registration worldwide.

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1. Defining specialty pharma

“What is specialty pharma?” many people question me. Is it in-licensing specialists? Niche marketers? Drug delivery

firms? Will generic drug manufacturers be included? How about biotech companies that move into drug development? Well, depending on whom you ask, they are all of the above [1]. Wall Street's definition is a catch-all, and includes drug delivery, biotech, and generic firms. For instance, Morgan

* Savior Lifetech Corporation, No. 29, Kejhong Road, Chunan, Miaoli 35053, Taiwan.

E-mail address: Kus_98@yahoo.com.

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Stanley coverage of specialty pharma includes: generic companies like Teva, Mylan, and Actavis; over the counter companies like Perrigo and Warner Chilcott; development centric companies like Allergan, Forest, and Valeant (previously Bi-vail); drug delivery companies like Alkermes; and animal healthcare company like Zoetis (formerly Pfizer animal healthcare division) [2]. As the popularity of the specialty pharma business model has expanded, so has its scope. Today, many use the term “specialty pharma” interchangeably with development-centric pharmaceutical or biopharmaceutical companies. Others apply it to companies developing generics, reformulating existing drugs, or targeting niche markets. Some others more often use the term to identify companies that are “not biotech not big pharma”, where big pharma is defined as large-cap pharmaceutical companies. In other words, “specialty pharma” has become such a broad term that it covers just about everything except the big pharmaceutical companies and medical device and diagnostic makers.

2. Specialty pharma business model

After defining specialty pharma is inclusive of all healthcare-related firms that are neither big pharma houses nor medical device and diagnostic makers, the next question is “What is specialty pharma's business model and why it gains so much popularity nowadays?” In order to answer these questions, it is necessary to compare and contrast big pharma with specialty pharma. Big pharma typically follows a vertically integrated business model. It means that big pharma carries out the work from the beginning to the end on a worldwide scale including discovery research, drug synthesis, preclinical research, clinical development, regulatory work, scale up and manufacturing, and worldwide distribution, sales, and marketing. Moreover, big pharma has more breadth by working in four to six therapeutic areas. These may include cardiovascular, antimetabolite (such as antidiabetics), central nervous system (CNS), oncology, and infectious diseases. Specialty pharma, by contrast, acquires drugs from academia, research institutions, or other companies, and seeks to commercialize them in new markets. It selects a core of activities while relying on a network of contract research organizations (CRO), contract manufacturing organizations (CMO), and other preferred pharma partners to accomplish its commercial goal. Specialty pharma focuses most of its efforts on one or two therapeutic areas with specified physician populations. These specialized non-primary care physicians can be managed with a smaller sales force. Specialty pharma often has a small research and development (R&D) organization and contracts out animal and human tastings to CRO and its manufacturing to CMO. It is a business model that has been prevalent in the last years as venture investors seek to find a way around the long, expensive, and risky drug discovery process. The attributes of specialty pharma are “small”, “niche”, “agile”, and “focused” that are popular with Wall Street. The specialty pharma business model is compared with that of traditional big pharma in [Table 1](#).

3. Four categories of specialty pharma

The business model of specialty pharma can be divided into four categories ([Fig. 1](#)). Some companies are experts in the search of compounds for in-licensing; some focus on marketing specialty medicines to a limited number of clients; some started as a generic company; and some with a specific delivery technology knowhow. The world largest generic company, Teva (“Nature” in Hebrew) is on the list of specialty pharma. In fact, the largest product of Teva is a specialty brand medicine, glatiramer (Copaxone), which constitutes nearly 50% of profit and 20% of revenue which is \$20.3 billion in 2012 [3]. Glatiramer, the most popular multiple sclerosis drug, was originally discovered by three professors at the Weizmann Institute of Science in Israel. It is a random polymer (6.4 kD) composed of four amino acids (namely glutamic acid, lysine, alanine, and tyrosine) that are found in myelin basic protein [4]. Administration of glatiramer shifts the population of T cells from pro-inflammatory Th1 cells to regulatory Th2 cells that suppress the inflammatory response. Given its resemblance to myelin basic protein, glatiramer may have acted as a decoy, diverting the autoimmune responses against myelin. Glatiramer was approved in 1996 in the US and in 2000 in the EU. It is currently marketed in 49 countries.

4. Story of Teva and generic glatiramer

Teva's glatiramer patent expires in 2014 and 2015 in the US and Europe, respectively. Two generic glatiramer products from Sandoz/Momenta Pharmaceuticals and Mylan/Natco Pharma partnerships that Teva assumes in a news release for the 2015 budget, will launch in September 2015. Mylan, the first filer of generic glatiramer, is in litigation with Teva which has filed two citizen petitions trying to stop the launch of generic glatiramer. In the meantime, Teva is developing a sustained injection of glatiramer reducing the dosing frequency from 20 mg/day to 40 mg three times/week, which was approved by the Food and Drug Administration (FDA) in January 2014 [5]. The new formulation with a different strength and dose regimen would not be subject to generic competition. Once patients convert, it would be hard for insurers to force them to use a generic that would require them to go back to daily injections. However, if Teva's own history is of any lesson, Teva is unlikely to prevail, albeit with a changed role from a generic aggressor to a brand defender. While the competition in specialty pharma may be fierce, Teva will still be working hard in specialty drugs. It anticipates four specialty product approvals and five submissions next year “which we believe will improve treatment options for patients and add value for all of our stakeholders,” Teva CEO Vigodman said [6].

5. Defining specialty medicine

The reader now may understand what specialty pharma is but wonder what specialty medicine is. Specialty medicines are those indicated for rare conditions that affect a small number

of patients that are managed by specialty pharmacies, who handle insurance prior to authorization, patient compliance management and patient education since these agents often require special handling, administration, and clinical support. According to EMD Serono, a pharmaceutical company headquartered in Geneva, Switzerland, which resulted from the merger between Merck KGaA and Serono in January 2007, the number of specialty pharmaceuticals on the market has grown from only 10 in 1990 to >250 in 2010. This trend is expected to continue, as there are now >600 specialty pharmaceuticals in the pipeline. It is estimated that costs for these agents will exceed \$160 billion by 2013. Most of the so called “specialty pharma companies” have one or more specialty medicines products.

The other characteristics of specialty pharmaceuticals are high price and high profit margin, consequently also called “niche products”. The growth trend of specialty products is being driven by breakthroughs in genomics, accelerated development of targeted therapeutics and improvements in genetic testing to facilitate personalized medicine approaches. As major nonspecialty brand drugs become available as lower-cost generics, specialty drug spending, according to Catamaran (formerly informedRx) Prescription Management Services, is projected to grow from 18% of total pharmacy costs in 2010 to 43% in 2020 [7].

6. Mylan's EpiPen niche play

Teva is not the only generic company marching into specialty medicine. Mylan, the third largest generic company in the world, has a specialty pharma division which markets EpiPen, an auto-injector with a protected needle to deliver a measured dose of epinephrine (better known as adrenaline) [8]. Epinephrine is used widely to open the trachea in life-threatening allergic reactions (also known as anaphylaxis). EpiPen is the number one prescribed auto-injector with a 90% world market share in the US and worldwide. EpiPen has constituted 27% of Mylan's profit since 2008. Mylan licensed in the EpiPen technology, which was originally developed as the ComboPen, a product developed for the military for treating exposure to nerve agents used in chemical warfare. EpiPen is manufactured by Meridian Medical Technologies, interestingly a subsidiary of Pfizer. Teva has filed an Abbreviated New Drug Application (ANDA) of generic EpiPen and Mylan settled with Teva on June 22, 2012, which allows the launch of Teva's generic version of EpiPen in June 2015 [9].

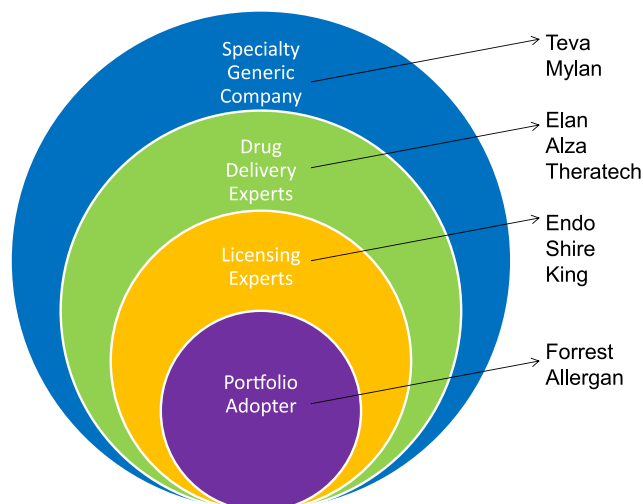


Fig. 1 – Various specialty pharma business models.

EpiPen is not the only specialty medicine in Mylan's treasure trove. Mylan is also big in transdermal drug delivery systems. Mylan acquired Vermont based Bertek Inc. in 1993, and in 1999 renamed the company Mylan Technologies Inc. (MTI). MTI is the first company to receive approval for generic nitroglycerin, estradiol, clonidine, and fentanyl transdermal patches. MTI also does contract manufacturing work for others. MTI is the CMO for the brand EMSAM (selegiline) transdermal patch [10].

7. Actavis on a merging spree

Teva and Mylan each have a major presence in drug delivery alternative sectors, although they are not yet dominant in any individual area. Teva's liquids and inhalants (i.e., budesonide) account for 13% of the US generic inhalant business and Mylan's transdermal products account for 13% of the US generic transdermal business. Actavis (previously Watson), is another major transdermal technology company. Actavis acquired Theratech Inc. for \$300 million in stock in 1998 [11]. Theratech is a small company in Salt Lake City near the University of Utah, which was founded by Professor William Higuchi, a pioneer in transdermal technology. On July 1, 2014, Actavis completed the acquisition of Forest Laboratories,

Table 1 – Comparison of business models between specialty and traditional pharma.

Category	Traditional pharma	Specialty pharma
Strategy	Blockbuster drugs mostly oral solid products	Specialty medicines mostly injectable cold chain products
Organization	Vertically integrated	Networked
Research and development	Large size fully supported internally divided by Therapeutic Silos	Small size with help from contract research and partnership
Manufacturing	Many sites worldwide	Contract manufacturing
Marketing	Clinician physician network	Direct to patients
Sales distribution	Intensive detailing	Patient advocacy groups
Pricing	Based on differentiation of competing medicines	High price based on life saving or improved quality of life

another specialty pharma company with branded skin products. The merged company now markets a slew of topical skin products including testosterone patch (Androderm), estradiol cream (Estrace), progesterone gel (Crinone) and nitroglycerin ointment (Rectiv). Watson's first-to-file status on generic Lidoderm is to add significant revenue to its transdermal franchise. On November 17, 2014, Actavis announced yet another merger plan to acquire Allergan for \$219/share, a valuation of about \$66 billion [12]. Allergan is best known for Botox, but it has a long history of developing pharmaceuticals. Completion of the deal would mean that Actavis has increased its market capitalization from < \$5 billion to \$100 billion in 5 years [13].

8. The race to dominate the alternative drug delivery sector

While Teva is also a leader in liquids (~\$1.4 billion market) and inhalants (~\$1.2 billion market), it lacks critical mass in injectable, dermatological cream and ointment, and transdermal. In 2010, Teva was fourth in injectable (10% share). Separately, we note Mylan's impressive 51% share in the \$1 billion generic transdermal market, but it lacks significant exposure to other alternative dosage forms including inhalation and injectable. As a result, Mylan acquired the privately-held Bioniche Pharma Global Injectable Pharmaceuticals Business in September 2010 [14]. Mylan acquired again in November 2011, the rights from Pfizer to make generic versions of two GlaxoSmithKline respiratory drugs: Advair Diskus (fluticasone propionate) and Seretide Diskus (fluticasone propionate and salmeterol) using Pfizer's proprietary dry-powder inhaler delivery system [15]. The underlying reason for the expansion into the nonoral solid area is the better profitability of specialty medicines and is also because of the rise of biotech protein and peptide drugs that require alternative routes of administration such as injection. The fourth big generic player, Sandoz, is already big in biosimilar credited for the US launch of growth hormone Omnitrope using the 505(b)(2) pathway back in May 2006 [16]. The big four: Teva, Sandoz, Mylan, and Actavis are poised to compete in the specialty biosimilar pharma space.

Oral solid sales of ~\$27 billion in 2010 represented 71% of the total US generics market (excluding branded generics). However, the number of players in oral solids is huge with intense competition. According to 2010 IMS sales figures, there are 33 players in oral solids with revenue exceeding \$100 million, while there are only three players in transdermal [17]. The 2010 US generic market specialty pharma players in each of the niche dosage form areas are presented in Table 2.

9. Big pharma productivity crisis

The business model of specialty pharma all started with the downfall of big pharma and the rise of the generic industry. It is no secret that the pharmaceutical industry has been grappling with diminishing R&D productivity [18]. R&D investment more than doubled over the last decade, while new molecular entity (NME) approvals plummeted [19]. At the same time, the

ability of big pharma to sustain an investment return on the NME development has greatly diminished with patent cliff and generic competition. Innovator's product peak sales revenues of > \$200 billion had lost to generic by 2010 and \$142 billion more will be at risk from patent expiration by 2015 according to IMS Health. Big pharma, in response, has been closing down of facilities and cutting back on the number of scientists so to save the money it spends on R&D. According to OrbiMed Advisors, employment in the 14 big pharma multinational companies is to fall ~20% between 2009 and 2015. That means some 200,000 jobs are disappearing not only in research, but also in sales and back office functions.

Facing diminishing R&D productivity and the threatening generic entry due to patent cliff, the brand companies employed several defense strategies. The first strategy is to delay generic entry by intensive life cycle management of existing products [20]. The second strategy is aggressive in-licensing of new products/projects [21]. In-licensing has brought many blockbusters to big pharma, especially those new chemical entities sourced from Japanese companies back in the 1980s. At one time, new chemical entities which originated in Japan constituted > 50% of the US FDA approvals in a year. The outflow of pharmaceutical scientists from big pharma to specialty houses, including the ones in the emerging market, could accelerate new drug development overall in the next few years. The third strategy is for brand companies to fight aggressively to retain the market share post generic entry, such as recently seen with Pfizer on Lipitor [22]. Brand companies used to abandon off-patent drugs and turn their attention to the development of NMEs such as the early case of Prozac by Lilly. With the lackluster record to develop new blockbuster drugs, brand companies became more aggressive in protecting the revenue from blockbusters that face generic competition. The recent case of Lipitor by Pfizer is an eye-opening demonstration of generic aversion strategies.

10. Patent cliff: the story of Lilly and Prozac

The patent cliff scenario is generic to all big pharma, albeit to a different degree. Pfizer, the largest pharmaceutical company worldwide, lost ~32% revenue to generic in the 5 years leading to 2013 while the midsize big pharma, Lilly fared worse and lost ~42% in the same period [23]. The expiration of Prozac

Table 2 – Number of players in US generic market by specialty medicine area.

Dosage forms	IMS sales 2010	No. of players >\$100 million
Oral solid	27.0	33
Injectable	4.6	9
Dermatology	1.4	3
Liquids	1.4	3
Inhalants	1.2	3
Transdermal	1.0	3
Nasal spray	0.6	2
Ophthalmics	0.6	2

(fluoxetine) patents in 2001 provides a telling example of the impact of patent expiration on brand company revenue [24]. The original compound patent on Prozac was to have expired February 2, but the FDA extended it for 6 months because Lilly was conducting research on using the drug in children. Five pharmaceutical companies received FDA approval letters with first-to-file exclusive rights to sell a different version of fluoxetine for 6 months. Barr Laboratories, which went to court to end the patent, will have exclusive rights to produce 20 mg capsules, which account for \$2.2 billion of the current \$2.7 billion Prozac market. Dr. Reddy's Laboratories will produce 40 mg capsules, Teva Pharmaceuticals will produce 20 mg liquid fluoxetine, Geneva Pharmaceuticals will manufacture 10 mg capsules, and Pharmaceutical Resources will make 10 mg and 20 mg tablets. Within 1 year of expiration, generic fluoxetine was available from > 10 generic companies at 2% of the price of Prozac brand product. Upon generic entry, Prozac revenues fell from \$1.3 billion in the first half of 2001, to \$380 million in the first half of 2002 [25].

11. Lipitor: the biggest generic entry in history

The patent on Lipitor (atorvastatin calcium tablet), Pfizer's \$12 billion-a-year blockbuster cholesterol medicine with lifetime sales of > \$131 billion, expired on 29 November, 2011. Pfizer did not invent Lipitor but bought it through the merger with Warner-Lambert at a price tag of \$90.2 billion [26]. Pfizer, unlike Lilly, did not lay down and die but employed an unprecedented aggressive strategy to protect and extend Lipitor sales both pre- and post-patent expiration. In a report by the Public Policy Institute of Association of American Retired Persons, Pfizer's strategies are summarized as below [22].

- 1) "Pay-for-Delay" agreement with first-to-file Ranbaxy Laboratories. Ranbaxy was the first-to-file for generic Lipitor in 2003 [27]. In 2008, Pfizer and Ranbaxy reportedly entered into an agreement that Pfizer would stop trying to block Ranbaxy's efforts to launch its product if Ranbaxy delayed introduction until November 2011. In return, Ranbaxy gained the right to sell a generic version of the significantly less popular drug Caduet, a combination pill of Lipitor and the blood pressure drug Norvasc, 7 years earlier than would have otherwise been possible. Several major US retailers have filed lawsuits against Pfizer and Ranbaxy that accuse them of violating antitrust laws by striking a deal that kept generic versions of Lipitor off the market.
- 2) "Authorized Generic" agreement with Watson Pharmaceuticals. Watson marketed and distributed an authorized generic of Lipitor that launched at the same time as Ranbaxy's generic version of atorvastatin. In return, Watson gave about 70% of its Lipitor-related profits to Pfizer, allowing Pfizer to protect some of the revenue it would have lost to Ranbaxy. After Ranbaxy's 180-day exclusivity period ended on May 31, 2012, other generic manufacturers' versions of atorvastatin entered the market, and atorvastatin's price dropped dramatically. The May 2012 date is not incidental. Pfizer did receive a 6-

month patent extension in the EU after developing a pediatric version for children with high cholesterol, allowing Lipitor to maintain exclusivity in most EU countries until May 2012.

- 3) Coupon to patients and rebates to the insurance plans and pharmacy, especially mail-order pharmacies, which account for almost one-half of all Lipitor prescriptions. Pfizer's efforts to minimize the impact of Lipitor's patent expiration have been effective. Lipitor maintained 33% of the US market nearly 4 months after generic entry (early March 2012), which is much better than the usual drop of around 10% [28]. Lipitor worldwide sales maintained at 40% from \$9.6 billion in 2011 to \$3.9 billion in 2012, a decrease. Given the present difficulties of big pharma, Pfizer's aggressive strategies could become a model for other brand name drug manufacturers in future, although Pfizer's strategy is not without legal repercussions. Pfizer and Ranbaxy are facing multiple class action and anti-trust lawsuits [29]. In the meantime, generic drug companies, when faced with the prospect of being unable to gain market share during the first-to-file 180-day exclusivity period, may decide not to challenge brand name drug patents in the future [30]. This decline in competition would slow the entry of generic drugs and represents a lost opportunity in the reduction of health care spending.

12. NME licensing trends

In-licensing has brought many blockbusters to big pharma. Current licensing trends include: (1) rising in biologics deals, cancer being the most popular category; (2) favoring later stage development compounds; and (3) increasing complex deals with cascading milestone payment, and opt-out clauses for risk sharing [31]. In general, deals made in later phases of development tend to be more strategic and therefore more complex, involving multiple categories of development with cascading milestone payments. One of the purposes of a later stage deal is to share risks and opt-out clauses are frequently inserted based on the expectation of the risks becoming clear at future time points. The Medtrack data shows that the complex deals with multiple categories increased from 10% in 2005 to 33% in 2009 [32].

13. Valuation of clinical leads by clinical trial phases

Similarly, biopharmaceutical company equity valuation varies by clinical stage. Fig. 2 shows statistics of value creation by biopharmaceutical initial public offering. The initial public offering valuation minus the venture capital investment represents the increase of value created by the progress of NME from preclinical to clinical phases [33]. The biggest jump is at Phase II with \$162.5 million/Phase II compound. This is one of the reasons why most emerging pharma target to carry their compounds through Phase 2 proof-of-concept (POC) [34] before licensing them to large pharma.

14. High value and high success rate of biologics

Biologics such as therapeutic proteins and monoclonal antibodies are high value medicines typically costing patients > \$100,000/year. They are also relatively immune to generic competitions. Although US congress passed a biosimilar law in 2009 [35], there is a lack of FDA approval pathway and final guidance on any specific product yet to be issued. The EU remains the only market where a number of biosimilars are approved for use. So far, only a couple of biosimilars have been submitted for FDA review: Sandoz's copy of Amgen's white blood cell booster Neupogen, and a biosimilar version of Johnson and Johnson's blockbuster anti-inflammatory Remicade from South Korea's Celltrion [36]. Sandoz is already marketing Zarzio, the top-selling copy of Neupogen in > 40 countries where regulations for generic biologics follow mostly that of small molecules. In the meantime, Amgen itself has six biosimilar molecules in development including a Phase III candidate, ABP 501, a knockout of Humira (adalimumab) in patients with moderate-to-severe plaque psoriasis [37].

The success rate for biologics to reach commercialization is higher than chemical drugs. The 2003 Federal Trade Commission (FTC) report [38] compared the success rate between biologics and small molecules according to the phases of drug development (Fig. 3). The success rate for small molecules increases from 12% to 38% as the compound progresses from clinical Phase I to Phase III clinical stage. Comparatively, biologics has a higher success rate of 53% compared to 38% for small molecules at Phase III. As a result, biologics at a later stage have become hot properties, with bidding wars among large pharma.

15. High attrition at clinical Phase II POC

The other reason most emerging pharma target out-licensing upon completion of Phase II POC is the high attrition/low success rate of Phase II compounds into Phase III clinical trial [39]. Fig. 4 presents the data from the Pharmaceutical

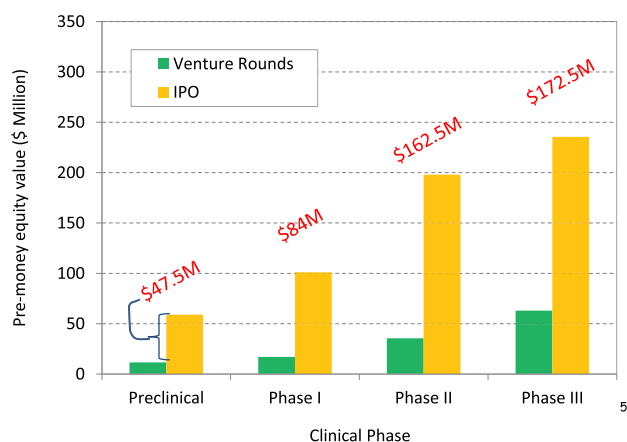


Fig. 2 – How much is your compound worth? Biopharmaceutical company valuation by clinical stage.

Benchmarking Forum [40] on R&D compound survival rates by development phase for 14 large pharmaceutical companies: Abbott, AstraZeneca, Bayer, Bristol-Myers Squibb (BMS), Boehringer-Ingelheim, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, and Schering-Plough. Overall, 24 preclinical leads are needed to enter clinical development in order to yield one commercial product. These data highlighted that compound attrition in Phase II is the key industry challenge. Only one of four compounds entering Phase II was able to proceed through into full Phase III clinical studies. Thomson Reuters Life Science Consulting in 2011 analyzed the 87 reported reasons for Phase II failures from 2008 to 2010: 51% (44 out of 87) were due to insufficient efficacy; 29% (25 out of 87) were due to strategic reasons; 19% (17 out of 87) were due to safety reasons; and only 1% due to pharmacokinetic/bioavailability reasons [41]. Future improvement of success rates in Phase II will depend on the better understanding of target disease relationship or in other words, a leap of faith in translational medicine [42].

16. Open innovation model

The term 'open innovation' was coined by Henry Chesbrough of Harvard Business School in 2003 to describe the increasingly widespread of knowledge and technology such that integration of knowledge and expertise from multiple sources is the key for success [43]. Chesbrough made the point again in 2006, suggesting the only way for a high tech business to thrive is to embrace open innovation [44]. With falling R&D productivity, increasing regulatory scrutiny, and patent expirations eroding a substantial amount of revenues, big pharma realized the need to look beyond their own walls for innovation. Many companies shifted R&D expenditures externally for in-licensing of technology platforms or drug ideas, or even discovery lead compounds for further development.

By the turn of the 21st century, most companies had revenue derived from in-licensed compounds exceeding that which originated from the organic growth of internal R&D.

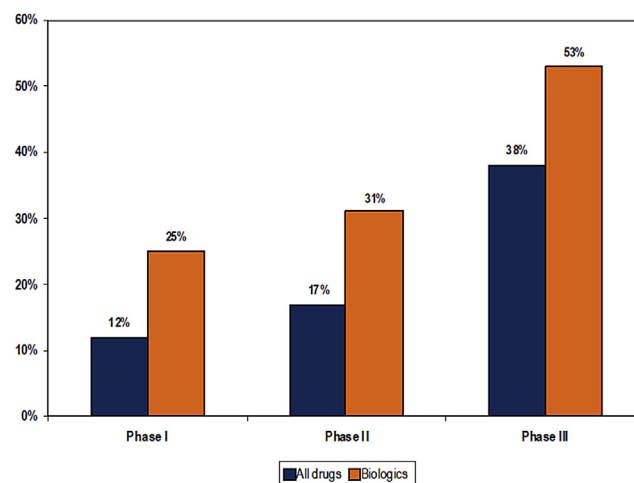


Fig. 3 – FTC 2003 report on probability of US commercial entry of clinically developed drugs from phases of development.

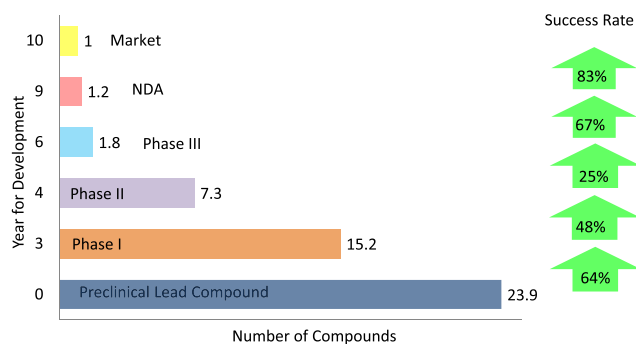


Fig. 4 – Success rate by development stage of new molecular entity drugs.

AVOS Life Sciences has analyzed the revenues from drugs at least \$500 million in annual sales from the top 14 pharma companies. Contribution of organically developed products declined from 45.3% of revenue in 2008 to 39.7% in 2013, whereas the proportion of revenue from licensed products grew from 29.2% to 30.8%, and that from acquired products grew from 22.4% to 25.8% [45].

In a Price Waterhouse Coopers 2009 Special Report: Pharma 2020: marketing the future, a detailed breakdown of R&D cost is presented [46]. The cost leading to clinical Phase II POC constitutes 43.2% of the total R&D budget. This allocation is before the days of open innovation, when 60% of R&D budget is devoted to the discovery and development of internally originated compounds. This cost distribution of large pharma is not different from that of biotech companies [47]. The author's own large pharma experience through the transformation of the traditional business model to the open innovation model has seen firsthand that the internal R&D expenditure shrunk substantially to about 30% of the total R&D budget, evident from the large number of R&D staff layoffs. Instead, the R&D money is re-allocated, to a less extent in-licensing lead compounds and novel target platforms, and to a larger extent the acquisition of late phase assets and further development of these assets into late clinical phases followed by regulatory registration. These collaborative efforts can take up to 50% of the budget, while the remaining 20% may be reserved for life cycle management of blockbuster compounds facing generic threats (Fig. 5). We know the old blockbuster innovation model is unsustainable. We will have to see whether the new open innovation model will work for the pharmaceutical industry in the next 10 years.

17. The license of Taxol from the National Cancer Institute to BMS

In the years that followed, universities and research institutes such as the National Institute of Health (NIH) became the major sources of innovation for new drugs. One of the most successful stories is the license of paclitaxel from the National Cancer Institute (NCI), a division of the NIH to BMS. Paclitaxel was discovered in 1962 as a result of NCI screening program

[48]; Monroe Wall and Mansukh Wani isolated the drug from the bark of the Pacific yew, *Taxus brevifolia*, and named it "Taxol". In 1977, Dr. Susan Horwitz, Albert Einstein College of Medicine, identified the mechanism of Taxol as stabilizing the microtubules and slow cancer cell division and growth. In 1984, the NCI began Phase 1 clinical trials against a number of cancer types. In 1989, investigators at Johns Hopkins reported partial or complete responses in 30% of patients with advanced ovarian cancer. In August 1989, the NCI decided to out-license the drug because of the practical difficulties in semi-synthesis of Taxol from Yew tree extract and the large financial scale of the program. Four companies responded including the American firm BMS, which was selected as the partner in December 1989. BMS submitted Taxol NDA within a period of 18 months and Taxol was approved in 1992. The choice of BMS later became controversial and was the subject of Congressional hearings in 1991 and 1992. While it seems clear the NCI had little choice but to seek a commercial partner, there was also controversy about the terms of the deal, eventually leading to a report by the General Accounting Office in 2003, which concluded the NIH had failed to ensure value for money [49].

18. Externalization of R&D: academia versus specialty pharma

Most big pharma have long standing collaborations with academic institutions. However, the collaborative innovation model suffers from, for the most part, the lack of common languages bridging the basic research and clinical development [50]. The traditional conflicts between public and corporate collaborations are confidentiality, publishing, and intellectual property rights and ownership. With respect to confidentiality and publishing, most parties recognize the nature of competition and accommodate reasonable delays in publication in order to allow time for patent filing. Intellectual property rights, however, continue to pose a challenge since at least three parties are involved: the inventor(s), the institution, and the commercial corporation. Companies need to understand that many universities are limited by federal and state laws with respect to ownership rights of the intellectual property generated by their faculty. Successful negotiations will have to be based on the fact that the value process is equitable, that all parties receive a return on their investment, and that the collaborators receive equity on the basis of their contributions.

Frustrated with the limitations imposed by law or institution regulations, professors of industrial entrepreneurship have come out and founded a crop of small specialty pharma backed by venture capital. The "small" or "niche" or "focused" specialty pharma without the overblown bureaucratic systems seem more adapted to close the gap between basic research and clinical development. Two separate analyses comparing small biotechnology companies with large pharma companies have concluded that company size is not an indicator of success in terms of R&D productivity [51]. A more recent survey conducted of 842 clinical Phase II compounds from 419 companies from 2002 to 2011 by the Boston Consulting Group, again found no correlation between

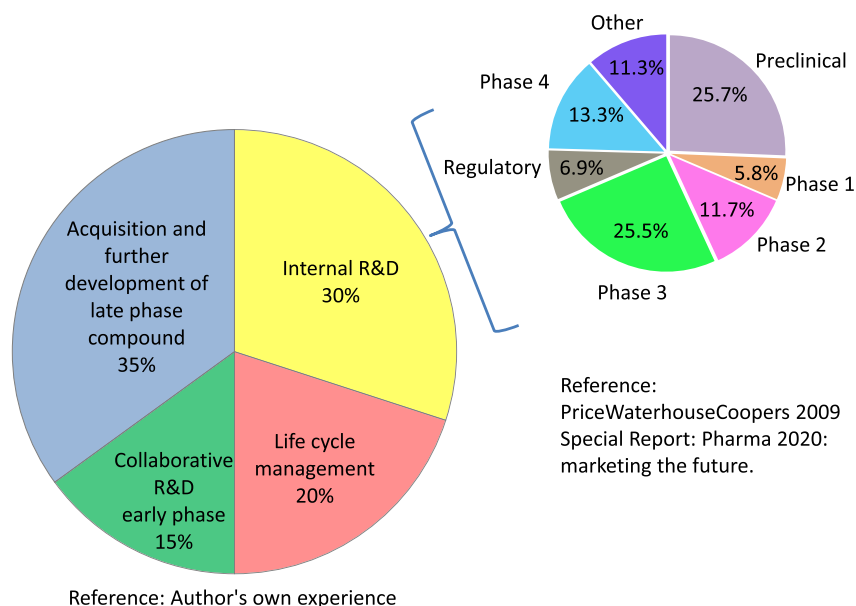


Fig. 5 – Open innovation model.

company size and the likelihood of R&D success [52]. Instead, scientific acumen or good judgment and proximity of location to a science hub such as Cambridge or the San Francisco Bay area were found to correlate significantly with success. In fact, the decision to advance a compound in a large pharma is often influenced by a progression-seeking behavior motivated by self-interest of the team responsible for the project. A recent publication from Pfizer showed that two-thirds of the company's Phase I assets that were progressed could have been predicted to fail [42]. It is no wonder with the poor decision making that the low R&D productivity follows suit. The fact that size does not matter is an encouraging sign to many small specialty pharma companies, especially in the pharmerging countries such as Russia, India, Mexico, Korea, and Taiwan.

19. Pharma's corporate venture

Externalization of R&D is nothing new but the systematical externalization of R&D by corporate venture of big pharma is new. Externalization used to occur through product licensing, program partnerships, or company acquisitions. The problem has been that these activities have not fundamentally changed the economics of R&D or dramatically improved the return on R&D investments. The challenge is to increase the number of drug programs to which a pharmaceutical company has access without increasing, to the same degree, the capital or resource investment required to access these R&D programs. The quickest way to enlarge one's pipeline is through merger. However, more and more post-merger analysis showed that merger does not necessarily benefit R&D [53]. Instead, a growing number of companies have begun corporate venture investments. Venture money is invested in a specialty pharma company in exchange for preferential rights to an R&D program and, in this process preferential access to the data may lead to an early decision on whether to exercise those rights.

This way, options can be purchased to license future successful programs without day-to-day operational responsibilities and the associated commitments of resources and management time which also free up the smaller niche players from bureaucratic interferences from the big corporation.

20. The success story of Lilly Ventures

Lilly Ventures is probably the oldest and largest corporate venture endeavor among the big pharma [54]. The Chorus group, small and relatively independent from the Lilly R&D headquarter, conducts only critical path experiments to address POC questions. The other necessary (but costly and time-consuming) early-development work, such as formulation, delivery, and manufacturing scale-up, comes after Chorus decides to advance a program. To date, Chorus has advanced two dozen compounds into early development, and half of the 10 compounds that have completed POC studies have advanced to full development. Chorus's success has inspired Lilly to seek ways to replicate the model in low-cost countries by entering into risk-sharing partnerships in India and China. Vanthys, a joint venture with India-based Jubilant Organosys, was created for the low-cost company to take on development responsibilities for specified programs through POC. Lilly has the option to regain rights to the compound in exchange for milestones, royalty payments, and in some instances, co-promotion rights in local home geographies. A prelude to Vanthys is the deal Lilly made with Suven, an Indian active pharmaceutical ingredient (API) manufacturer, to bring a limited set of CNS candidates into POC. Lilly then forged a deal with Piramal, a large India pharma to take compounds contributed by Lilly through Phase 3 development. The Lilly Asia Ventures fund is thus born.

Lilly had then taking it to a next level in accessing more Phase III clinical operation capacities from clinical contract

research laboratories that operate globally, with a significant presence in China, India, Russia, and Eastern Europe. Lilly moved two Alzheimer's compounds to Quintiles, the premier clinical CRO, to conduct the development work while enlisting TPG-Axon Capital to finance up to \$325 million of development expenses in exchange for milestones and royalties on the products. Through these deals, Lilly gained access to Quintiles' Alzheimer's clinical expertise while it transferred much of the financial risks to TPG-Axon. Lilly can thus approach Phase III development more aggressively in maintaining control over both Alzheimer programs, while freeing up internal resources and capital for other candidates in its pipeline. Lilly remains dedicated to new drug discovery and development, with R&D spending among the highest, close to 20% of sales, while the industry giant Pfizer spent around 15.5% in 2010 [55].

21. The “first-generation” specialty pharma

This open innovation paradigm has been used by the “first-generation” specialty pharma themselves. These include, among others, King Pharmaceuticals, Allergan, Forest Labs, and Shire Pharmaceuticals; the latter two have managed to build successful businesses on a pure in-licensing strategy. The UK-based Shire plc has a product portfolio composed of acquired molecules deprioritized by big pharma, with a strategic focus on the CNS and the gastrointestinal disorders. It became so successful that AbbVie attempted in 2014 to buy Shire, but withdrew the \$55 billion merger offer and paid Shire a breakup penalty of \$1.7 billion [56]. AbbVie withdrew the offer in lieu of heightened attention of US congress on inversion legislation. The Tennessee-based King Pharmaceuticals, following a similar strategy with the pipeline, consists of Phase III products from big pharma in the areas of hypertension and pain. King boosted its sales potential so much that King ended up being bought out by Pfizer in 2010. All four companies have a small R&D unit relative to their revenue, but a large business development budget for in-licensing of development candidates.

22. Repurposing of big pharma leftovers

Acquisition of late-stage product candidates or even marketed products from big pharma is a clever strategy, but not without its limitations. There are several reasons why big pharma put compounds up for sale can be several folds. It could be either because they have performed unremarkably in clinical trials or because their market potential is not compelling enough to pursue. Also, big pharma might have a number of small marketed products that do not really add much to the bottom line. Plus, newly merged big pharma have an assortment of marketed products and product candidates that no longer fit the strategic direction of the combined company. All of these products, it seems, are there for the picking, as long as the specialty pharma can pay the price. As the competition to bid on the left-over compounds between the specialty pharma heats up, product acquisition from big pharma is likely to get more and more expensive. Moreover, data shows that big

pharma is not an endless source of compound acquisition for the smaller players. A 2004 survey of the top 20 global big pharma that had products filed or approved for marketing in the US with sales potentials of \$5–100 million, found a fair number of those compounds; very few, however, had a remaining patent life of > 3 years [57]. In the end, less than a half dozen patent-protected products were found suitable for out-licensing. The sourcing of late stage compounds is getting more and more difficult, unless one can form a special alliance with a specific big pharma such as Singapore's Aslan with Lilly.

23. Shire's orphan drug strategy

As a result of the scarcity of late stage acquisition targets, some specialty pharma are headed upstream forming their own research units in discovery and early development of new compounds. Of the first-generation specialty pharma, Allergan and Forest Labs have built their own discovery operations, while Shire [58] purchased the R&D capability through the 2006 acquisition of Human Genome Therapies (HGT). HGT is a small company focused on genetic diseases that are very rare and have a very high unmet need, i.e., orphan drug indications. An orphan disease is one that hits anywhere between 2000 and 200,000 people in the US [59]. According to the NIH, there are close to 7000 such rare diseases. The HGT portfolio of orphan drug products focuses on the very rare end of the orphan diseases with target populations between 2000 and 3000. What this means is that the development programs have to be global in nature in order to bring products to the market [60]. By focusing on a niche area of patient care, Shire must trawl the world to find patients to complete its clinical studies, and as a result, Shire now operates in 43 countries to create a viable business model. The capability to commercialize products in a global scale to reach each patient is the important last step to complete the business model. The success of such a strategy can be seen in two of the company's currently marketed products, Elaprase and Replagal, which are used in over 43 countries as enzyme replacement therapies. Shire's example is a reality check for specialty pharma companies in the emerging countries interested in orphan drug indications, but which do not have the infrastructure to perform global clinical trials, not to mention recruiting rare disease patients worldwide.

24. Celgene's transformation of orphan drug into blockbuster

More curious yet, orphan drug status for very very old drugs has been a gold mine for some specialty pharma companies. The most outstanding cases are Celgene's thalidomide (Thalomid), lenalidomide (Revlimid), pomalidomide, and apremilast [61]. Thalidomide, a drug designed as an antiemetic agent that fell out of favor after it was linked to birth defects in Europe in the 1960s, was approved in 1998 as an orphan drug for the treatment of leprosy and in 2006 for the treatment of multiple myeloma. The second generation lenalidomide is

about 1000 times more potent than thalidomide in the *in vitro* tumor necrosis factor- α (TNF- α) inhibition assay, an indication of anti-inflammatory properties [62]. Pomalidomide is about 10 times more potent than lenalidomide. The inhibition potency of apremilast in TNF- α production is similar to lenalidomide but with additional Phosphodiesterase-4 (PDE4) inhibition activities. Lenalidomide costs \$164,000/patient/year and is expected to exceed \$4 billion in revenue in 2013 [63]. The third and fourth generation pomalidomide and apremilast will follow suit. Perhaps one will say the key reason for the success of the thalidomide family of four products is because of Celgene's persistent improvement in the chemistry and pharmacology, where Celgene has been able to grow the products on multiple indications.

25. Genzyme's focus on rare disease

Another great example is Genzyme's Cerezyme (imiglucerase) for the treatment of Gaucher's disease [64]. Gaucher's disease is a genetic disorder leading to a hereditary deficiency of the enzyme glucocerebrosidase. The enzyme acts on the fatty acid glucosylceramide. When the enzyme is defective, glucosylceramide accumulates, particularly in white blood cells, most often macrophages (mononuclear leukocytes) and in the spleen, liver, kidneys, lungs, brain, and bone marrow creating blood and bone disorders. Cerezyme is extremely effective – but it is also extremely expensive with annual treatment costs as high as \$300,000/patient. As a result of this high price, Cerezyme's 2010 sales were over \$700 million [65], a respectable number for any drug. Genzyme's success in the rare disease area attracted the attention of big pharma. Genzyme was subsequently acquired by Sanofi in 2011 [66]. At the time of merger, Genzyme was the world's third largest biotechnology company, employing > 11,000 people around the world. As a subsidiary of Sanofi, Genzyme has a presence in approximately 65 countries, including 17 manufacturing facilities and nine genetic testing laboratories; its products are sold in 90 countries. The combined company employed two strategies that should be familiar with the readers by now: (1) corporate venture capital to enlarge early clinical lead pipeline; and (2) patient advocacy group dedicated to rare diseases with Genzyme orphan drug programs. Sanofi-Genzyme BioVentures, different from traditional venture capital firms, only invest in early-stage life science companies developing innovative products that may become future Sanofi products. The current portfolio contains venture investment on 13 companies. Genzyme Rare Community has been established since 2001 with patient advocacy teams around the world.

Companies like Pfizer, Novartis, and GlaxoSmithKline have not only looking for orphan drug candidates outside, but also established their own research units exclusively devoted to seeking cures for rare diseases. According to lifesciencenation.com, five of the 20 pharma-licensing deals publicly announced in the first 4 months of 2014 involve an orphan or rare disease asset. The accelerated approval pathway for these drugs is driving pharma merging strategies toward small biotech that have cultivated expertise and assets in these rare diseases. Consequently, drug research into rare

diseases was no longer exclusive to biotech but expanded to large and small pharma.

26. Old drug new money: the curious case of colchicine

Perhaps the most amazing story in recent years on old drug making big bugs is URL Pharma's colchicine [67] (Colcrys). The colchicine plant was used as a therapeutic agent for gout more than 3000 years ago, since ancient Greece time. Colchicine tablets are widely available as a generic prescription drug in the US since the 19th century. In July 2009, the FDA approved URL Pharma's version of colchicine with 3 years of market exclusivity. The NDA submission contains some pharmacokinetic studies and a randomized controlled clinical trial in 185 patients with acute gout that somewhat reproduced a previous clinical trial in the literature. The study showed that lower doses of colchicine with fewer side effects are as effective as high doses, facts which are known from experiences among the practitioners. On the basis of this new trial, combined with the previously published evidence, Colcrys approval is technically interpreted by the FDA as a new indication 505(b)(2) approval that the Waxman–Hatch Act stipulates 3 years of market exclusivity [68].

The financial reward of market exclusivity is substantial. After the FDA approved Colcrys, URL brought a lawsuit seeking to remove any other versions of colchicine from the market and raised the price by a factor of > 50, from \$0.09/pill to \$4.85/tablet. According to the Centers for Medicare and Medicaid Services, the cost increased from approximately \$1 million to as much as \$50 million for about 100,000 prescriptions/year. The financial reward appears to be out of proportion to the level of investment and the FDA is under attack for its action in an article in the *New England Journal of Medicine* in 2010. Dr. Janet Woodcock, the FDA director of Center for Drug Evaluation and Research (CDER) in an article to the editor, defended FDA's approval of Colcrys quoting 117 deaths associated with colchicine and the improved label of Colcrys for the safer lower dosage [69]. The authors in an Author/Editor Response responded back and suggested that the FDA modifies the statutory languages so that future legislation will provide more flexibility to reward advancements only when they are optimally useful to the public health [70]. Nevertheless, the taxpayer is bearing considerable costs for a poorly executed legislation by the FDA.

URL Pharma was subsequently acquired by Takeda in 2012 [71]. Takeda has another gout drug, Uloric (febuxostat). The acquisition of Colcrys complements and strengthens Takeda's position on Uloric in the gout marketplace, by providing patients with multiple options to treat and prevent gout flares. It is a strategy of portfolio play with additional drugs added to the existing portfolio while maintaining the same size sales and increasing utilization of the marketing infrastructure.

27. The bumpy road for the antiobesity drug Qsymia

Obesity is a serious chronic health problem affecting > one third of US adults (35.7%), according to the US Centers for

Disease Control. The medical costs associated with obesity had already reached \$147 billion back in 2008. However, the development of antiobesity compounds has been a tough area since the fen-phen diet pill litigation in 1997 after one of the medication's components was linked to heart valve damage. More failure followed in 2007 with the FDA's rejection of Sanofi's Acomplia on concerns that the drug increased the number of suicidal events among users. Also, Merck and Pfizer scrapped plans in 2008 to continue developing similar drugs.

Vivus submitted Qsymia (older name as Qnexa) NDA to the FDA on December 29, 2009. Qsymia is composed of two generic drugs, phentermine (an appetite suppressant) and topiramate (a seizure and migraine medication). The FDA disapproved the NDA on October 29, 2010 based on the potential teratogenic effect of topiramate seen in animal studies, although of the 19 pregnant patients carried to term in the Qsymia clinical study, no birth defects were seen. Vivus resubmitted the NDA with the addition of a strict risk evaluation and mitigation strategy (REMS) to assess comprehensively Qsymia's teratogenic potential [72]. This includes a detailed plan and strategy to evaluate and mitigate the potential teratogenic risks in women of childbearing potential taking the drug for the treatment of obesity [73]. The FDA subsequently approved Qsymia on July 17, 2011. Vivus changed the drug name from Qnexa to Qsymia presumably to shake off the bad public press.

Topiramate is an anticonvulsant, sold by Johnson & Johnson as Topamax since 1996. It is known to have the potential to cause birth defects and suicides [74]. It does not seem important as an anticonvulsant drug, but becomes critical as a diet pill with a target patient population of women of child bearing age. This incidence was viewed as a calamity at the time, but the FDA required a REMS program which later became a reason for doctors not to substitute the more expensive Qsymia with the generic version of phentermine and topiramate. The difference in monthly bills is \$160 against \$90.

Qsymia was initially touted by Wall Street analysts with a peak sale of \$3.6 billion/year. With the potential of generic substitution with the individual drug, the peak sales estimate dropped to \$1.2 billion/year. Although Vivus was successful in securing FDA approval, it foundered without a marketing partner, an issue that ignited shareholder unrest that led to a boardroom overhaul in the summer of 2013. Worse yet, Actavis filed an ANDA for Qsymia with the FDA just months after the product launch. Actavis claimed in a letter to Vivus in May 2014 that the seven US patents Vivus holds are either invalid, unenforceable, or will not be infringed by Actavis' knockoff [75]. The peak sales estimate dropped again to \$400 million/year. In fact, among the three diet pills approved recently, Wells Fargo's analyst Matthew Andrews forecasted \$1.2 billion for Contrave, \$481 million for Belviq, and \$396 million for Qsymia in spite of Qsymia's first-to market timing and best efficacy data [76].

Looking back, Vivus invested on Qsymia heavily with two main clinical studies of 3700 patients for 56 weeks (2200 patients taking three doses of Qnexa to about 1500 on placebo) [77]. It delivered excellent efficacy data with a weight loss of 10.6% for the highest dose, 8.6% loss for the middle dose, and 5.1% for the lowest dose; the value was 1.7% for patients on

placebo. However, the side effect of topiramate was overlooked in the mist of clinical development. The potential of generic substitution is dismissed, and the poor execution of marketing strategies further cut into the profit. Indeed, the success in any specialty pharma product demands full consideration in every aspect of the development activities and eventual commercialization.

28. Innovator's life cycle management opportunities

Life cycle management of on-patent pharmaceuticals has become increasingly important to big pharma since it is more and more difficult to replace off-patent drugs with new blockbusters, as they are challenged to meet revenue and profit growth expectations. Given this environment, companies have started and been successful not only internally, but also at in-licensing technology or projects from specialty pharma for the protection of the life cycles of their blockbuster drug franchises. The study of life cycle management consequently becomes the focus for a subset of specialty pharma specializing in drug delivery platforms and for another subset of specialty pharma concentrating on old drug, new use, especially if the old drug is a blockbuster from a large pharma. The innovator, relying on their own proprietary preclinical and clinical data in the original NDA, can supplement the original NDA and obtain a license for an improved version of their own drug [10]. Whereas for the specialty pharma working on an improved version of the other's drug, the regulatory filing route is NDA 505(b)(2) that requires patent certification of non-infringement to the innovator's patent, in order to rely on the safety and efficacy data filed in the original NDA for the approval of the improved version of the old drug [78]. In this process, inefficiency may kick, in since the specialty pharma is not privy to the innovator's database leading to possible erroneous assumptions and repetitive guesswork. Therefore, it is beneficial to approach the potential customers for one's technology and project ideas before investing significant money in the type of life cycle management projects. The other advantage for the specialty pharma to collaborate with the innovator is to capitalize on the innovator's infrastructure of marketing and sales. It is resource intensive if not impossible, to launch a product when the innovator holds fast to the target patient population. The key to secure the innovator's interest in one's technology would be the demonstrable clinical advantages of the improved version over the old version.

29. Intellectual property strategies

In assessing different technology approaches to old drug, new use, companies need to consider several factors on a molecule-by-molecule basis. First and foremost, they will have to be confident that there is a potential for clinical improvement of the original molecule through reformulation and/or chemical modification. Companies must also consider their tolerance for risk and willingness to invest in either less-proven technologies and/or radical modifications of the

original molecule, as the old saying the idea of being able to achieve rewards without the risk is not sustainable. Finally, the distinctiveness of the technology, including the intellectual property situation, must be carefully assessed. The patents derived from product life cycle management are called ancillary patents, which are distinct from the basic compound patents. The ancillary patents range from polymorph, salt, formulation, prodrug, delivery device, new indication, alternative route of administration, to new method of use. In general, the ancillary patents, particularly if the new product patent expires later than the original patent, are weaker and attract more patent challenges from generic competitions.

30. Regulation and regulatory strategy

The regulatory pathways for the projects described herein may follow three different filing routes: NDA 505(b)(1), NDA 505(b)(2), and ANDA 505(j). The Hatch-Waxman Amendment of 1984 amended the Food, Drug, and Cosmetic Act of 1938 that created a regulatory pathway for the FDA to approve an identical or improved version of a brand drug based on the Agency's previous finding of safety and/or effectiveness for the brand drug [79]. The generic drug, being an identical copy, is filed under ANDA while 505(b)(2) is for an improved version, both of which require patent certification of noninfringement to the brand patents. Consequently, the brand patents need to be consolidated in a place to facilitate the process of patent certification. The Orange Book is the place to gather all brand patent listings. Both NDA and 505(b)(2) are considered brand name products subject to generic challenge and therefore require patent listing in the Orange Book. In short, the NDA requires patent listing, ANDA requires patent certification, and 505(b)(2) requires both patent listing and patent certification.

There are four types of patent certification: Paragraph I is no brand patent listing; Paragraph II is the brand patent(s) has expired; Paragraph III is a commitment not to market one's drug until brand patent expires; Paragraph IV is to challenge the brand patent(s) as a means to secure early market entry [80]. Paragraph IV certification by a generic firm is to assert that relevant innovator's patents are invalid or not infringed by the new product, albeit a new generic product or a new 505(b)(2) product by a company other than the innovator. The basic chemical compound patents are seldom challenged, since it is difficult if not impossible to bypass the basic compound patent. Other patents filed by either the brand name drug maker for the purpose of prolonging the product life cycle by making an improved version of the drug product, or a 505(b)(2) filer also making an improved version of the drug product, are called ancillary patents. These ancillary patents with incremental inventions developed internally or purchased externally are otherwise a frequent target of patent challenges.

It is important for specialty pharma to identify a regulatory filing route at the outset of project initiation so that the required data can be collected in a way suitable for the type of filing. It is a no brainer to select an NDA for an NME or to select an ANDA for an identical copy of a brand product. It is tougher to select 505(b)(2), which encompasses a variety of situations.

A 505(b)(2) is most suited for those who are doing an improved version of a brand drug, which can have its own patents and may not be comparable to a reference labeled drug (RLD). The selection of RLD is necessary for 505(b)(2) filings, so that the FDA may reference the safety and efficacy data on the RLD. This way, a 505(b)(2) filing may need less preclinical and clinical data. However, the 505(b)(2) filer needs to certify no infringement on the RLD patent and the new version of the similar product must be superior to the RLD. Therefore careful selection of RLD, should there be several, may mean product approval or disapproval by the FDA in the end.

A 505(b)(2) application may itself be granted 3 years of Waxman-Hatch exclusivity if one or more of the clinical investigations, other than Bioavailability/Bioequivalence (BA/BE) studies, was essential to approval of the application and was conducted or sponsored by the applicant. A 505(b)(2) application may also be eligible for orphan drug exclusivity (21 CFR 314.20-316.36) or pediatric exclusivity (section 505A of the Act). For blockbuster products, there may be several firms looking for copycat development with perhaps not identical formulation. Once one firm obtains a 505(b)(2) approval, the second runner up is left with no approval until after 3 years, when the market exclusivity is expired for the first filer. In this case, a full NDA may be advantageous, should one's product differ enough from the RLD.

In addition, an applicant may submit a 505(b)(2) application for a change in a drug product that is eligible for consideration pursuant to a suitability petition under section 505(j)(2)(C) of the Act (ANDA generic filing). For instance, one's formulation for intravenous injection (IV) is not identical but you think superior to the innovator. An ANDA cannot be filed even if the formulation is bioequivalent to the innovator's product. This is because the FDA requires a generic IV formulation to be identical to that of the innovator. In this case, one may file 505(b)(2) followed by a suitability petition. A 505(b)(2) is indeed a versatile route of regulatory filing used preferentially by the specialty pharma companies.

31. Conclusion

The global trends of open innovation, fast growing emerging markets, and patent cliff threat provides ample opportunity for smaller specialty pharma companies to gain the upper hand provided that the technology platforms or specialty medicinal products is what the big pharma wants. The easy around the clock internet telecommunication also provides the specialty pharma in emerging countries with opportunities to merge or work with western big pharma on the wide-spanning niche products and the opportunity to improve the use of old drugs. It takes one to evaluate one's own strength and weakness to strategically select partners with complementing strengths, in order to maximize the probability of success. However, this vast opportunity is not endless. The rise of densely populated countries such as India and China is going to accelerate the competition in the pharmaceutical industry worldwide. Smaller players in smaller countries with no domestic demands will eventually lose out to the big players in big countries, except for the ones with the vision to collaborate with the stronger to make themselves strong.

Conflicts of interest

The author declares no conflicts of interest.

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