



Key Business Strategy Tools to Survive a Patent Cliff in the Biopharmaceutical Industry

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“Key Business Strategy Tools to Survive a Patent Cliff in the Biopharmaceutical Industry.”

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A Thesis in the Field of Biotechnology Management

for the Degree of Master of Liberal Arts in Extension Studies

Harvard University

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Abstract

This case study presents the research gathered in seeking to identify a number of key business strategy tools that biopharmaceutical companies have used to revitalize their growth following the patent cliff. Consequences on net income post patent expiration of blockbuster drugs from 2007-2012 are examined relative to Biogen, Novartis, and Sanofi and their corresponding oral therapies to treat patients with multiple sclerosis. Research has been gathered from financial statements, clinical publications, corporate press releases, and other articles speculating on the effects of the patent cliff for companies that were able to survive beyond it without collapsing. The business strategy tools most commonly utilized are identified as mergers and acquisitions of companies or products, investing in research and development, academic collaborations, and expanding business exposure in emerging markets. The degree to which each of these key tools, among other select strategies, was utilized and successful varies per company; each company used more than one of these tools during the selected timeframe. The patent cliff examined may be the one with the largest impact on revenues to date, but it will not be the last. Companies must be more strategic and proactive to take steps to ensure their portfolios and pipelines are resilient and suit their business needs.

Acknowledgments

“Unless you try to do something beyond what you have already mastered, you will never grow.”

- RW Emerson

With special thanks to QS

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Chapter I

Introduction

This thesis will present the key tools used by the biopharmaceutical companies Biogen, Novartis, and Sanofi that have survived the often sharp drop in profitability associated with the 21st century patent cliff. The cliff resulted in steep declines in revenue from brand name drugs, compelling companies to seek alternate ways to bolster their revenues without solely relying on blockbuster drug sales. Three pharmaceutical companies that have successfully overcome the patent cliff – Biogen, Novartis, and Sanofi – will be presented and analyzed. Analysis will focus on the development of their oral therapies – Tecfidera (dimethyl fumarate), Gilenya (fingolimod), and Aubagio (teriflunomide), respectively – to treat multiple sclerosis (MS). Developing these new therapies contributed to the companies' triumph during the patent cliff, which occurred during 2009-2013; other companies were not so fortunate. As producers of small molecule therapies to treat common diseases, pharmaceutical companies can be contrasted to today's growing biopharmaceutical industry which has more focus on advanced formulations and biologic therapies for common and also rare diseases. The three companies of interest can be classified at times as biopharmaceutical corporations because they are striving to become a mixture of the revenue-generating business practices of both pharmaceutical companies and the biotech industry to create a more sustainable model.

What Is a Patent and What Is the Patent Cliff?

To further investigate the implications of the aforementioned patent cliff, it is imperative to define patents, exclusivity, and a few relevant laws that pharmaceutical companies follow in the process of bringing medicines from bench to the market. Sponsor companies seek patent authorization from the United States Patent and Trademark Office (PTO) to protect their drugs from being made, used, offered for sale or being imported into the United States by an unauthorized third party company (Barons Pensabene & Gregory, 2013). Drug patents are typically sought for the compound itself if the product is a new chemical entity that is not already approved and patented in the United States. Patents can also be granted for the process (methodology, equipment) used to manufacture that compound, the formulation (dosage form) of the compound, or the method of use of the compound. Market exclusivity and patent terms for drugs are governed by the 1984 drug price competition and patent term restoration act, more commonly known as the Hatch-Waxman Act (Barons Pensabene & Gregory, 2013). This act is held as a federal law aligned with the United States Food and Drug Administration (FDA) drug approval processes. It creates provisions for patent term extensions with exclusivity, expedited FDA approvals for generic drugs, and a simplified patent litigation process tied to generic drug submissions to FDA (Barons Pensabene & Gregory, 2013). Exclusivity can be granted in addition to PTO patent terms following the approval of a drug product by FDA. Exclusivity terms are fixed and defined as seven years, five years,

three years, and six months for drugs with the following attributes: orphan drug designation, classification as a new chemical entity, new clinical studies, or studies in pediatric populations, respectively (Barons Pensabene & Gregory, 2013). Most of the MS drugs relevant to this thesis qualify, at the least, as new chemical entities to be awarded exclusivity. Orphan drug designation can be granted for products defined by FDA as “intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug” (“Developing Products for Rare Diseases,” 2015). Although MS itself is not designated as an orphan condition in the United States, other countries may classify it differently and may incentivize developers in the form of simpler marketing authorization requirements with abbreviated review times and lower fees to register such products in those regions with a population need. The size of the MS market attracts drug researchers to develop drugs for the most common types of MS but also for subsets of MS which are still being clinically characterized and could prevent progression of the disease.

Patent terms, which are typically set for 20 years from the date of filing, can be extended by up to five years to credit the sponsor with the time the product was under development and under review by FDA (Barons Pensabene & Gregory, 2013). The Hatch-Waxman Act gives incentive for sponsors to develop new drugs. The act prevents copies from entering the market for several years after approval of a new drug while allowing consumers to switch to lower priced generic versions of drugs once their

patents have expired to reduce their healthcare costs. Patent exclusivity allows sponsor companies to recoup money that they spent to develop the brand name drug and also money lost on drugs that they failed to bring to market; this exclusivity then requires other companies to invest time and money to develop unique methods to manufacture generic versions of the sponsors' brand name drug.

The patent cliff, the point at which pharmaceutical companies suffered steep losses in revenue due to expired patents on brand name drugs, posed a considerable threat across the biopharmaceutical industry. An expired patent can open the door for generic companies to market copies of innovator products. If a generic is brought to market, the resulting loss in revenue for the innovator company could be quite substantial.

All companies were not affected equally during the patent cliff. Biogen, for example, held patents for biotechnology products that did not see as much revenue loss as did pharmaceutical companies that manufactured less complex drugs for more common disease states. DeRuiter and Holston (2012) note that Novartis was heavily impacted by the patent cliff-related revenue loss from blockbuster drug Diovan (valsartan) as was Sanofi with revenue loss from their blockbusters Plavix (clopidogrel), Avapro (irbesartan), and Lovenox (enoxaparin). These blockbuster drugs were developed to treat or prevent relatively mainstream medical ailments such as high blood pressure and a spectrum of cardiovascular disorders (DeRuiter & Holston, 2012). Sanofi was predicted to lose \$9 billion in revenue through the consequent decade of generic competition just from the 2012 patent loss of Lovenox and Plavix (Harrison,

2011). A loss so great could have been tempered by cutting spending or acquiring new drugs through acquisitions, which is precisely what Sanofi did and will be explained in more detail in the discussion. The benefits of diversifying and concentrating portfolios on non-mainstream therapies and more specialized disease states is a direction many companies are heading toward.

Thesis Question

The nature of this thesis fits a question model compared to a hypothesis model. The question of interest is: What business strategies have pharmaceutical companies employed to revitalize their growth following the patent cliff? To bolster revenues, companies could refocus their internal and external research and development (R&D) efforts toward chronic diseases such as multiple sclerosis, which is a disease still being studied to determine early diagnosis techniques and optimal treatments or cures. In addition to investing in R&D, biopharmaceutical companies have used other tools to help increase their revenue, develop their pipelines, and to diversify or focus their portfolios.

This thesis will examine the apparent shift of pharmaceutical companies toward focusing their efforts on four key business strategies to support long-term, steady revenue streams: mergers/acquisitions of companies or products, investing in R&D, academic collaborations, and focusing on expanding into emerging markets. To narrow the focus, the relationship of three different companies and management of their

individual MS portfolios, which are contemporary blockbusters, have been selected for examination. Figure 1 from Vollmer (2011) has shown how innovative new medicines coming to market, on the vertical axis, dropped gravely during the patent cliff while R&D expenses continued to climb on an annual basis. \$20 billion to \$58 billion in sales were at risk of loss from patent expiry during the pivotal business phase in the pharma industry from 2007-2012 (Vollmer, 2011). This revenue loss is why companies must devise strategies to recover and prevent such a large fall in the future.

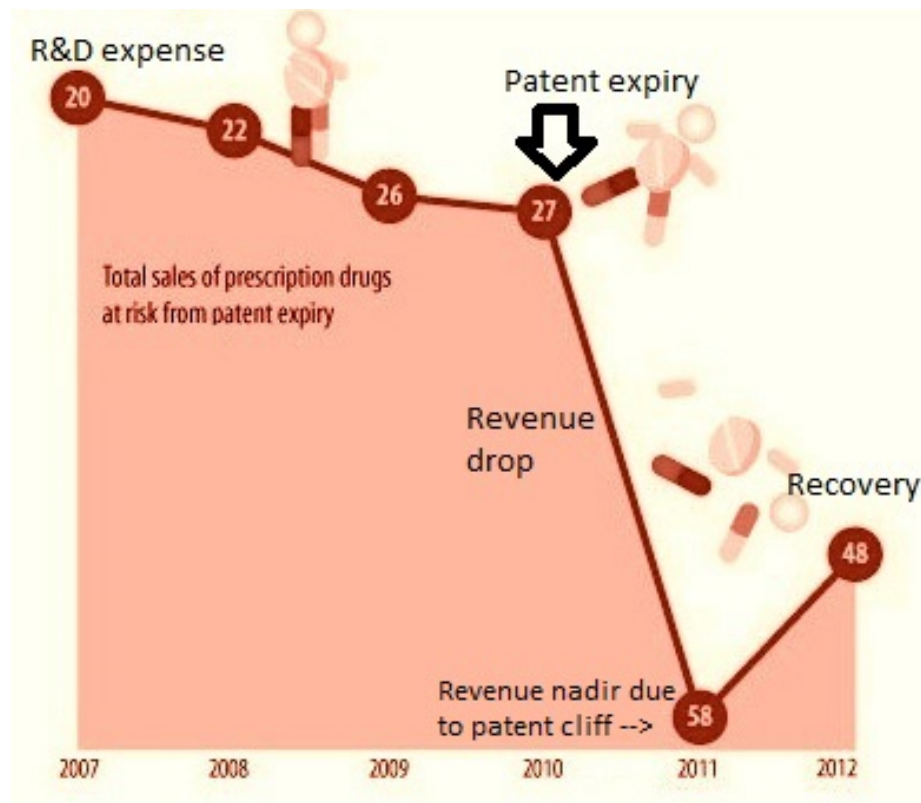


Figure 1: Patent Cliff Events. This graphic shows prescription drug sales at risk during a patent cliff. (Vollmer, 2011)

Figure 1 also represents how sales return tended to fluctuate across the industry for a range of years when patents/exclusivities approach expiry. A period of time following patent expiry shows the entry of generic competition, which is estimated to have eaten away at \$67 billion from top drug companies' annual sales in the US during this 2007-2012 highly active cliff period (DeRuiter & Holston, 2012). During the patent cliff years of 2009-2013, Sanofi and Novartis suffered patent expirations on a top ten selling drug in each of their portfolios (Kaitin, 2012). Sanofi was only affected in 2010 while Novartis was affected three times – in 2011, 2012, and 2013 (Kaitin, 2012). Biogen was able to escape a major revenue loss at this time.

As shown in Figure 2 from Kaitin (2012), Novartis and Sanofi were among the top pharmaceutical companies subject to the patent cliff revenue losses of \$8.8 billion and \$4.6 billion, respectively, and had to immediately act for change to reduce the negative impact while Biogen was relatively unscathed due to no blockbusters losing patent in the same time. Wisely, Biogen still took action to generate steady revenue using several business strategy tools to prevent becoming engulfed in the next patent cliff. Smaller companies, like Biogen, might evade revenue loss due to patent cliff as they are afforded the securities of a more predictable and easier to control narrow portfolio of marketed products. In turn, this may force smaller companies to make more conservative investments compared to the risks that large companies, like Novartis and Sanofi, are able to take and reap the potential benefits of greater increases in revenue over time.

'Industry Leaders' in Lost Revenues Due to Patent Expirations

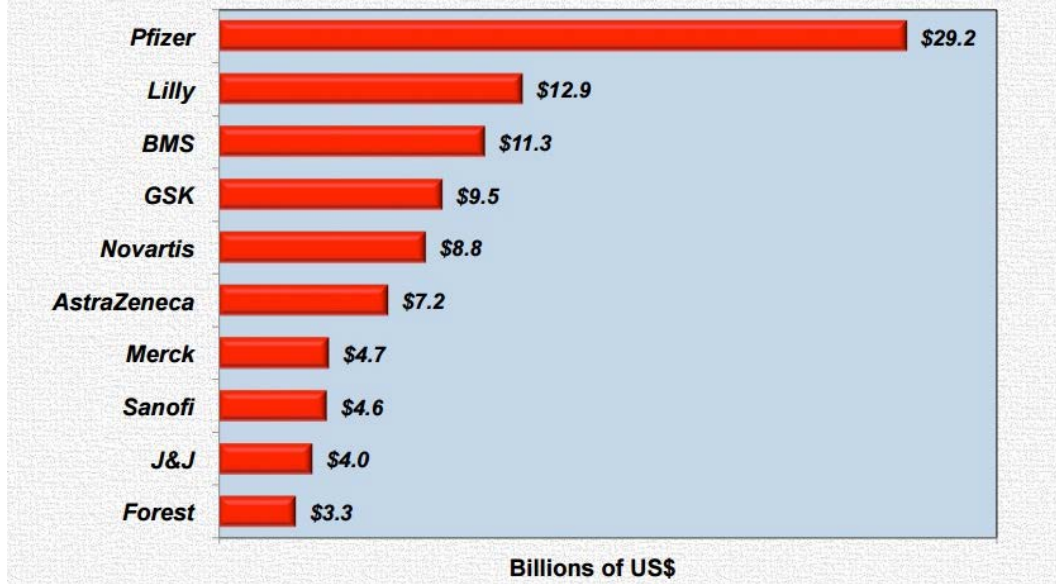


Figure 2: Revenue Loss by Company. This chart shows the biopharmaceutical companies that lost the most revenue due to patent expirations. (Kaitin, 2012)

This research explores bridging science and business in analyzing the various tools used to generate revenue following a patent cliff. This thesis is different than other projects or research on similar topics because it analyzes the before and after effects of the patent cliff according to the same parameters on three different companies. Moreover, three oral medications for the same disease state, one of each owned by these companies, will be reviewed. This type of comparative research has not been published, nor has significant cost consideration been given of these most recently

approved oral MS therapies by Biogen, Novartis, and Sanofi to determine the overall strength of these companies.

What Is MS and How Is It Relevant?

MS is a disease marked by central nervous system (CNS) inflammation, as shown in Figure 3, resulting in lesions and plaques. When the CNS becomes inflamed, the protective myelin sheath that insulates nerves known as axons becomes damaged, resulting in disrupted nerve impulses (Courtney, 2014). This disruption can delay or inhibit transmission of messages from the brain and spinal cord to other parts of the body, leading patients to experience some of the many symptoms of MS. Shown in red (Figure 3), the areas of axonal damage and inflammation are known as lesions, the scar tissue accumulating around the damaged myelin is known as plaques.

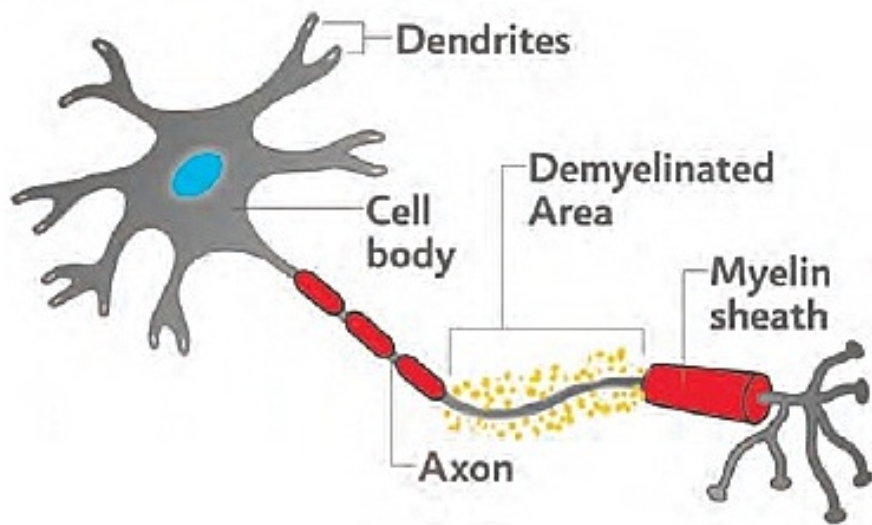


Figure 3: MS Damage to Nerve Cells. This graphic shows the areas of nerve cells affected in patients with MS. (Courtney, 2014)

MS may begin as a clinically silent disease or with patients reporting a range of significant or frequent symptoms; common practice is to initiate treatment as soon as possible after diagnosis. Symptoms vary per patient and can include balance issues, bladder dysfunction, cognitive changes, depression, dizziness, walking issues, numbness, pain, sleep issues, stiffness, speech difficulties, tremor, visual disorders, and weakness (Courtney, 2014). Disease activity is measured based on the size and number of lesions and plaques seen via magnetic resonance imaging (MRI) along with several numerical scales by which patients are assessed for mobility and disability (Courtney, 2014).

Across the biopharmaceutical industry, drugs for MS have gained popularity on a number of corporate pipelines. The competitive spirit of MS drug development is aimed

at spotlighting new therapies creating a contemporary blockbuster effect around drugs for the disease. As scientists build on existing research to better understand the etiology and management of the disease, as well as the actions of the various trial drugs for MS and its comorbid conditions, they are able to create more targeted and more effective treatment options. MS is a lucrative field as the disease is chronic, often not diagnosed until ages 20-50, employs a range of CNS involvement, and is estimated to affect over two million people worldwide (“Multiple Sclerosis FAQs,” n.d.).

As stated by Courtney (2014), MS has become a disease of interest not only because it affects such a large number of patients, but also from a scientific perspective due to the unpredictability of symptom flare-ups and subsiding that are desired to be managed in a better way or eliminated altogether. Initially, treatments for MS would function to reduce the severity and duration of flare-ups or relapses (Courtney, 2014). Now, science has advanced and treatments have been created known as disease modifying therapies (DMTs) which have the added function of slowing disease activity (Courtney, 2014). By slowing disease activity, DMTs may delay the progression of the disease, thereby delaying the associated disability and increasing the lifespan of patients with MS (Courtney, 2014).

As part of navigating the patent cliff, Biogen, Novartis, and Sanofi chose to develop oral therapies to bring to market to compete with the existing injectable therapies for MS. Among marketed therapy options, there are three oral DMTs approved for long term treatment of MS: Aubagio, Gilenya, and Tecfidera, owned by Sanofi, Novartis, and Biogen, respectively. Since MS does not have a homogenous

presentation in the patients it affects, it is most frequently described in stages.

Courtney (2014) cites that most patients, 80-85%, present with relapsing-remitting MS (RRMS) which can progress to secondary-progressive MS (SPMS), about 10% of patients present with primary-progressive MS (PPMS), and about 5% of patients present with progressive-relapsing MS (PRMS). The three oral DMTs of interest are approved to treat relapsing forms of MS.

The recent increased interest in the MS disease state has spawned competition across several companies as they race to complete clinical trials, aiming to be first to launch their product(s) with the broadest indication possible and maximized reimbursement models. Consequently, therapies for MS have rapidly moved from palliative care to disease modifying capabilities. New treatments have the potential to not only slow disease progression, but also reverse some of the symptoms of disease. New disease mechanisms and disease stages are being targeted; funds are being put into place for earlier detection and more aggressive disease management by the companies in the MS space. Having an MS drug on the market spells big revenues due to high drug prices and the relatively large and accessible patient population for companies marketing these products. The revenue potential from these new MS products is helping to offset R&D investments and previous losses from the patent cliff while also building up cash before the onset of the next patent cliff.

The Cost and Revenue from MS Franchises

Historically, patients were diagnosed with MS later in life and given the choice of one of several time consuming infusion therapies. Now, pharmaceutical companies have turned their heads and wallets toward MS and the field is being revolutionized to find ways to diagnose MS earlier and provide alternative treatment options. MS is a costly and burdensome disease without a cure. In 2009, the average annual MS-related health care costs in the US were almost \$24,000 per person taking into account pharmacy costs, both inpatient services and outpatient visits, and emergency room visits (Owens, Olvey, Skrepnek & Pill, 2013). Treatments are now more targeted and are leaving patients with the ability to function more highly in society despite having a diagnosis of MS. In the past, pharmaceutical companies were keen to turn profits by developing many drugs with similar mechanisms of action, but for MS, they have proceeded to manufacturing many new drugs with novel mechanisms of action to help better control the disease. While still hungry for a profit, companies are working with more chronic diseases and investing in the necessary science to raise awareness and spread knowledge about MS.

How has so much changed in just a few years? The business and science behind pharmaceutical companies and biotechnology companies is becoming closer and closer to a single product rather than being quite distinct. In the past, big pharma was known for following business models aimed at minimizing investments and maximizing returns. Much of the science stemming from pharmaceutical companies was done via screening and tweaking existing molecules on a chemical basis to find compounds that would treat

common ailments affecting large populations. Biotech companies have been known more for their novel drug development of targeted therapies to treat more complex diseases. Many pharmaceutical companies now have biotechnology components, either from their own targeted research and development or from acquisitions. As presented by Evens and Kaitin (2015), Sanofi leads the field of companies with the highest number of marketed biotechnology products at 23, while Novartis and Biogen fall further down the list with 18 and six, respectively, over the timespan from 1980-2014. Evens and Kaitin note that these years also saw a rise in new marketed products in the neurology discipline, a total of nine, some of which are indicated for MS. One reason why biotechnology became an attractive business model to pharmaceutical companies was its promise of developing drugs that could generate high revenues. Revenues in biotechnology companies increased almost three fold from 1991-1999 with a corresponding six-fold increase in sales (Evens & Kaitin, 2015). As biotech began to grow, so did novel technology to create and support new molecules. During this time, drug regulations from FDA were under continuous development. Regulators began requiring more complex clinical trials and enhanced monitoring for adverse events after a drug was approved, which increased costs to developers and added time to the development cycle until the drug was on the market and bringing in revenue. Despite added costs and time for development of biotechnology products, acquisitions remain prevalent for biotech-derived targeted therapies which can bring in \$100,000 or more for annual treatment cost per patient (Evens & Kaitin, 2015).

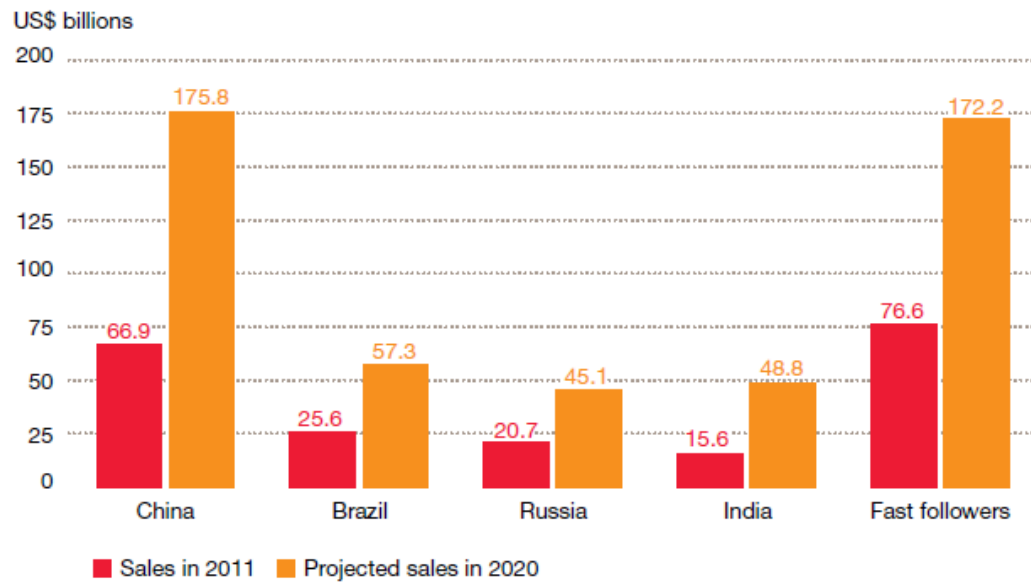
Companies that offer specialized treatments, including biological drugs and drug/device combination products, have faced less immediate revenue loss to generic competition due to the manufacturing complexity of their products. Pharmaceutical companies that solely market small molecule drug products for oral use have a much bigger target on their backs when it comes to copying their products and finding patients who will take those copies. As recently as 2014, it was estimated that pharmaceutical companies would lose approximately \$50 billion in annual revenue from patent expiry – a number less significant than in the height of the patent cliff, however still a representation that companies have work to do to preserve revenues ("Big Pharma's Patent Cliff," 2013). Some companies are choosing to diversify and include biologicals and generics in their portfolios, while others are choosing to narrow their therapeutic focus and deepen their pipelines in select areas.

In the area of development, oral MS therapies with disease modifying capabilities have the potential to reduce overall disease-related costs to the healthcare systems by simply increasing patient adherence to treatment regimens, which should aid in long term efficacy of the treatment and reduced exacerbations that may require intensive intervention. For the time being, efficacy, safety, and convenience of the oral dosing options is fetching a desirable price among oral MS therapy options despite some hesitancy from payers compared to long term real world use data from older injectable therapy options.

Regardless of a company's focus or diversification, many are beginning to supply medicines at demand globally to increase profits after the patent cliff. Not all countries

outside the United States have a pharmaceutical footprint or local manufacturing presence, but they do have patients with many of the same diseases seeking treatment options. In the past, it was difficult to find patients in international markets and subsequently difficult to arrange for the sale and reimbursement of pharmaceuticals in some of those locations. Some specialty pharmaceutical companies have established work histories in global markets depending on the nature of their portfolios, but not the majority prior to the patent cliff. Now, many of these countries are being highlighted as growth markets and are developing their own local healthcare systems with enhanced market access, defined processes to secure reimbursement, and better abilities to diagnose patients, all of which is creating a greater demand for medicines as shown in Figure 4.

Demand for medicines is rising rapidly in the growth markets



Source: *Business Monitor International*

Notes: (1) All sales are expressed in US dollars at constant exchange rates; (2) The fast followers include Argentina, Egypt, Indonesia, Mexico, Pakistan, Poland, Romania, South Africa, Thailand, Turkey, Ukraine, Venezuela and Vietnam.

Figure 4: Pharmaceutical Sales in 2011 and 2020 Projections. This graph shows the potential increase in demand in growth markets. ("Pharma 2020", 2012)

These growth markets and other emerging market countries could become an important source of revenue for companies marketing MS therapies since the disease geographically tends to affect more people living farther from the equator in North America, Europe, and southern Australia (Courtney, 2014).

Chapter II

Materials and Methods

To write this thesis, company financial and clinical histories were obtained and analyzed to determine trends in business strategy tools used during the years of interest in the patent cliff. The sources used in analyzing this position and making the argument are publically available and include clinical trial publications, medical journals, business articles, and corporate press releases. The factual nature of the financial and clinical data was interpreted against news stories and press releases of key milestones at each pharmaceutical company – Biogen, Novartis, and Sanofi. Graphs were imported or created from financial reports from the companies and products of interest to illustrate trends over time in revenue fluctuations impacted by the patent cliff. In spite of their public sources, important information and data are appropriately referenced.

Materials

Multiple sources of materials were used in this research: formal studies, evaluations, news clippings, articles, archival records such as public use files from respected health organizations, disease specific registry data, and interviews with subject matter experts (SMEs). The sources were utilized to examine each of the three

companies of interest prior to, during, and after the patent cliff by analyzing their revenues, their pipelines, and the diversification of their portfolios. Beyond examining the companies of interest, small amounts of data from other companies were gathered and used for benchmarking comparison and additional supporting data in this thesis along with providing more broad background knowledge for the author to convey relevant information to the reader in a proper context.

Most materials for this thesis were readily available with the exception of interviews with SMEs which were externally limited and depended on timing and availability of those SMEs to provide some further context to the development of new therapies in a competitive pharmaceutical market. A limitation of the research materials was evident when researching regulatory strategy and clinical trials published on the products of interest as not all desired information was publically available and extrapolation of trends across trials due to design differences was challenging. Although company financial data was available, verifying the information was a limiting factor to this research. All source data and information were obtained in English. Collecting evidence to support this research also relied upon availability of resources and online subscriptions to journals; these sources facilitated having current versus outdated sources to review.

Methods

To support this case study and provide information on some broader implications, the sample size of three companies was adequate to provide quantitative data, define some common industry tools, and to examine characteristics of high revenue, stable franchises. Pharmaceutical business development and strategy has evolved over time, however, there are repetitive trends which emerge and discount the need to analyze every company to support this case study. As for the number of therapies analyzed, three new drugs approved over several years were selected for study such that they could show or suggest trends and could be analyzed and compared to other products at future periods of time.

Calculating new statistics to support this case study was not necessary. Some statistical figures from previously published research, such as clinical trial endpoints, were cited for emphasis and comparison throughout this thesis. To learn more about the regulatory and clinical development programs for these drugs, history was gathered from the websites of each company as well as the FDA website and related links. Researching the clinical trial designs for these MS drugs helped unveil money invested in each of the drugs of interest and the reported revenues they are now earning. Regarding the revenues, some information on reimbursement was gathered and reported to emphasize that revenue has a dependency on how quickly a company can launch a drug and what prices or discounts are negotiated for those drugs based on the company interactions with public and private payers in healthcare systems.

The resources described here have been pulled together to identify which tools were used by Biogen, Novartis, and Sanofi and are further presented in the results section. Gathering research in the ways described above provided information to develop a meaningful comparison across three different companies and their similar oral MS products.

Chapter III

Results

To offset revenue lost during the patent cliff, Biogen, Novartis, and Sanofi employed a variety of business tools. Figure 5 (“Annual Report 2014,” 2015; “Annual Results 2014,” 2015; “Biogen 2014 Annual Report,” 2015; “Our history,” 2014; Toor & McBride, 2012; “Working to find solutions,” 2015) shows the key tools each company used and further results of the impact of those key tools for each company follow.



Figure 5 – Key Business Strategy Tools. These four tools will be analyzed in their usefulness by the three companies of interest.

Assessing Success

The overall health of these publically traded biopharmaceutical companies can be evidenced by the quantity of their new drug approvals during and after the patent cliff, as well as looking at trends in their net income over the years prior to, during, and just after the cliff. As has been found by Bernard (2015), during and immediately after the patent cliff years of 2010-2014, Biogen, Novartis, and Sanofi saw a total of four, five, and four new drug approvals, respectively. These numbers are especially positive and among the mid to upper range of approvals received by any company during those years, with only two companies reporting a higher number of new drug approvals in the same four-year span (Bernard, 2015). Figure 6 (“Biogen 2011 Annual Report,” 2012; “Biogen 2014 Annual Report,” 2015), Figure 7 (“Annual Report 2008,” 2009; “Annual Report 2010,” 2011; “Annual Report 2012,” 2013; “Annual Report 2014,” 2015), and Figure 8 (Annual Results 2012,” 2013; “Annual Results 2014,” 2015; “Sanofi-aventis Delivers 2008 Results,” 2009; “Solid results in 2010,” 2011) the net income of Biogen, Novartis, and Sanofi from 2007-2014, illustrate the primary effect of the patent cliff. This financial data shows that Biogen, considered a small-medium biotechnology company, has been most stable in their business model compared to Novartis who faced a transient loss in income during the patent cliff and compared to Sanofi who

appeared to suffer most during their years as a big pharma company prior to their biotech acquisitions.

Net Income During and Around the Patent Cliff

The net income of Biogen, Novartis, and Sanofi was researched and compared during the broad patent cliff years of 2007 – 2014. This selection of years shows the most pivotal point of the cliff as well as the fluctuations, or lack thereof, immediately prior to the onset of patent expiry.

Biogen

Biogen's net income, shown in Figure 6 ("Biogen 2011 Annual Report," 2012; "Biogen 2014 Annual Report," 2015), has been on an upward trajectory throughout the years of interest, with somewhat of a plateau early in the patent cliff years (2010-2012) relative to the gains the company has been reporting in more recent years. Although Biogen was not strongly affected by the patent cliff, the company did take steps to fortify its pipeline from a later onset patent cliff. Biogen has experienced a growth of approximately 29% and 8% in 2013 and 2014, respectively, in their MS product revenues ("Biogen 2014 Annual Report," 2015).

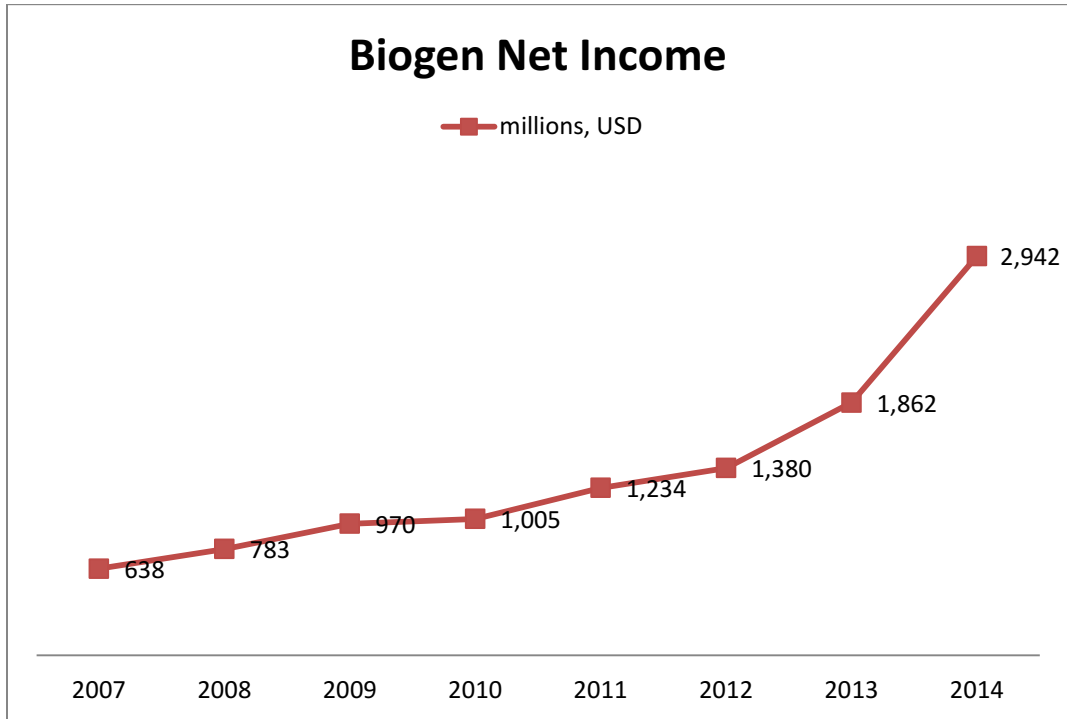


Figure 6: Net Income of Biogen During the Patent Cliff. This graph illustrates Biogen’s net income from 2007-2014.

Novartis

Novartis’s net income, shown in Figure 7 (“Annual Report 2008,” 2009; “Annual Report 2010,” 2011; “Annual Report 2012,” 2013; “Annual Report 2014,” 2015), has been on a modest upward trend, with small declines in the patent cliff years (2011-2013) and only a recent growth spurt in 2014.

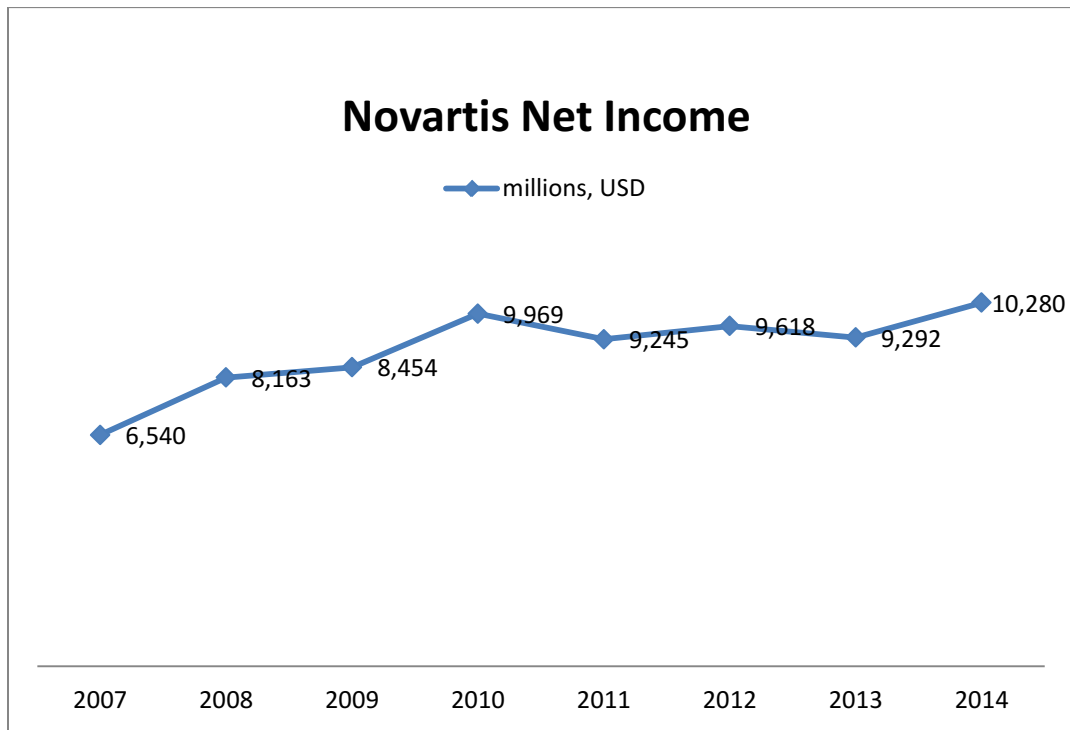


Figure 7: Net Income of Novartis During the Patent Cliff. This graph illustrates Novartis's net income from 2007-2014.

Sanofi

Sanofi's net income, shown in Figure 8 (Annual Results 2012," 2013; "Annual Results 2014," 2015; "Sanofi-aventis Delivers 2008 Results," 2009; "Solid results in 2010," 2011), has been on a downward trajectory over some years of the patent cliff (2011-2014) which the company seems to only recently show mild recovery from in 2014. This modest gain in revenue has greater than proportional effects on the overall

income of the company because the corresponding loss that was avoided would have been quite substantial and taken a long time to recover.

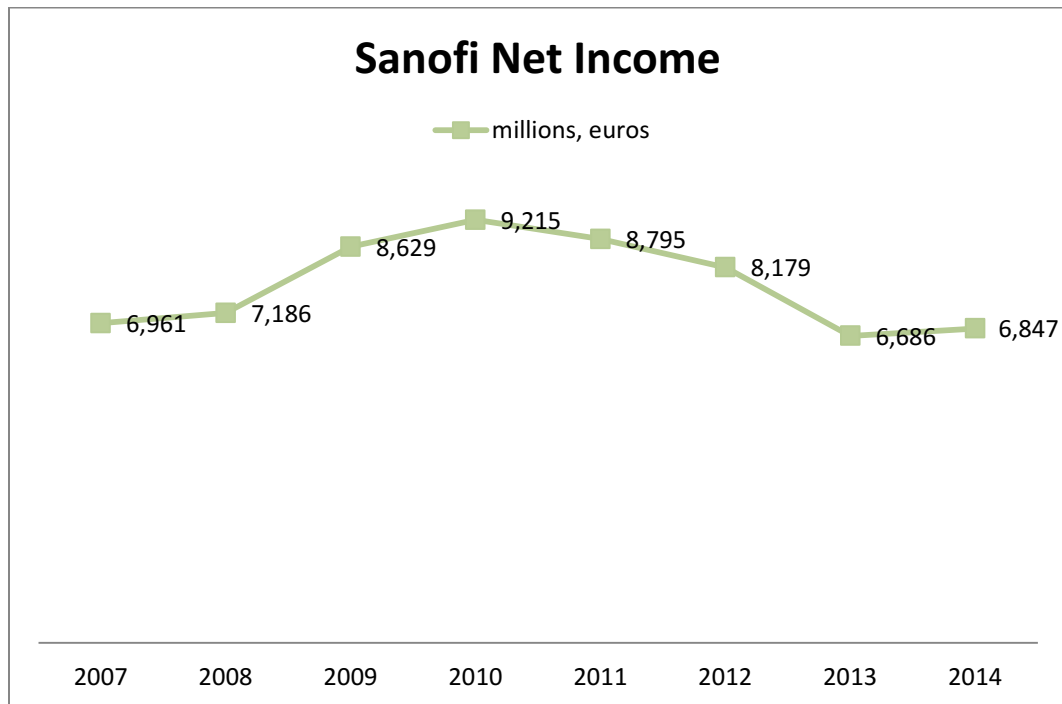


Figure 8: Net Income of Sanofi During the Patent Cliff. This graph illustrates Sanofi's net income from 2007-2014.

Chapter IV

Discussion

Each of the four key business strategy tools identified in the results will be presented in this section and analyzed according to the three reference companies for comparative analysis.

Mergers and Acquisitions

Biogen, Novartis, and Sanofi all utilized this tool; however, a greater uptake was seen by the latter two companies as a way to earn revenue during and after the patent cliff years. Biopharmaceutical companies continue to participate in full mergers with companies, acquisitions of single drugs, and deals to acquire or exchange entire portfolios of therapies in various stages of clinical development to better suit their business needs.

Biogen has utilized the tool of mergers or acquisitions, but not to the same degree as Novartis and Sanofi, particularly in the MS space. According to Biogen's 2014 annual report (2015), the company has fully acquired the rights to Tysabri (natalizumab), an infusion therapy for patients with relapsing forms of MS, from Elan Pharmaceuticals to help focus and grow their MS franchise. This drug acquisition was

completed in 2013 and contributed to the rise in Biogen's net income from 2013-2014 ("Biogen 2014 Annual Report, 2015"). Specifically in the MS space, Biogen has entered into a development and commercialization partnership with AbbVie Biotherapeutics, Inc. and is currently under regulatory review in the United States and Europe for an injectable RRMS product, Zinbryta (daclizumab) ("Biogen 2014 Annual Report, 2015").

Novartis has made several moves to acquire or license products in their oncology portfolio as well as acquiring the remaining rights to Arzerra (ofatumumab) from GlaxoSmithKline Pharmaceuticals (GSK) in 2015 ("Novartis acquires all remaining rights," 2015). This monoclonal antibody is being developed beyond its oncology indications as a treatment for RRMS ("Novartis acquires all remaining rights," 2015). In addition to the GSK deal, Novartis is working with XOMA Corporation ("XOMA announces," 2015) in developing first-in-class immuno-oncology antibodies as well as AVEO Oncology ("AVEO announces," 2015) to develop and commercialize a first-in-class growth factor antibody. In a quest to focus their business, Novartis completed a three part transaction with GSK, positioning them to acquire a portfolio of oncology products from GSK, to divest their vaccine division to GSK, and for both companies to merge their over the counter (OTC) product portfolios in a joint venture to create a large consumer healthcare company of which Novartis will own 36.5% ("Annual Report 2014," 2015).

When Sanofi's blockbuster products including Plavix, Avapro, and Lovenox started coming off patent during the cliff, critics waited for the company to make an acquisition to benefit its pipeline, and the company did not disappoint. In 2011, Sanofi

acquired Genzyme Corporation which had been reputed in the R&D and manufacturing of rare disease biotechnology products (“Sanofi-aventis to Acquire,” n.d.). At that time, Genzyme’s portfolio included at least one investigational drug product under development for MS (“Sanofi-aventis to Acquire,” n.d.). This strategic acquisition enabled Sanofi to establish a formidable MS franchise containing both oral and infusion products. This acquisition set forth shareholder rewards contingent upon the success of one of the MS products owned by Genzyme (“Sanofi-aventis to Acquire,” n.d.). Sanofi’s acquisition offered strong global reach and an additional oral MS drug to add to their portfolio. Aubagio (teriflunomide) is an oral MS drug marketed by Sanofi, who now owns Genzyme, and Genzyme had owned Lemtrada (alemtuzumab) which is a recently FDA-approved injection therapy for MS (Edney & Bennett, 2014). This type of collaboration between pharmaceutical companies in a shared space such as MS is not only a win for the company, but also for patients. Part of the strategy behind Sanofi’s acquisition of Genzyme was to establish a competitive MS portfolio and be recognized by patients and healthcare professionals as a leader in the field; Sanofi’s two approved MS treatments now serve 60% of global MS patients according to the company (Edney & Bennett, 2014). Despite a slower recovery than some other companies, Sanofi appears to be doing well beyond their small net income climb shown in 2014, boasting 26.6% growth rates for Genzyme and sales that more than doubled for their multiple sclerosis franchise in the second quarter of 2015 (Sagonowsky, 2015). Strategic use of this tool allowed Sanofi to avert a greater impact from the patent cliff, evidenced by the plateau in their net income (Figure 8) compared to the overall upward trend exhibited

by Biogen (Figure 6) and Novartis (Figure 7). Without merging and acquiring, Sanofi's income from blockbuster drugs could have plummeted more sharply, putting the company in a more difficult position from which to recover.

Investing in R&D

Across the biopharmaceutical industry, spending on R&D has been hovering around the same amount since the primary years of the patent cliff effects, from \$47.9 billion in 2007 to \$49.6 billion in 2012 as reported by members of a lead biotechnology organization representing research and innovation ("2015 biopharmaceutical research industry profile," 2015). As companies make use of different business strategy tools, investment in R&D from one company may increase while that from another company decreases, resulting in an overall plateau.

Biogen, Novartis, and Sanofi all strategically invested in R&D to increase their revenues around the time of the patent cliff, with Novartis being the most enthusiastic about this tool (Kaitin, 2012). All three companies are among the members of PhRMA, an advocacy organization of biopharmaceutical companies that promotes research for new treatments. PhRMA (2015) has found that "biopharmaceutical companies on average invest as much as six times more in R&D, relative to their sales, than the average U.S. manufacturing firm. In 2014, PhRMA member companies invested nearly 24 percent of domestic sales into R&D" ("PhRMA Member Companies Invested," 2015). This tool of investing in R&D shows that companies that spend additional money to develop more drugs will bolster their revenue streams when successful compounds

come to market over the next decades, indicating the reward from this type of early investment favors companies that are not risk averse in pursuing development opportunities ("PhRMA Member Companies Invested," 2015). To reduce some of the risk associated with failed R&D ventures, more biopharmaceutical companies are collaborating with one another and also academic centers.

Already holding a strong MS franchise, Biogen continues to work internally on R&D efforts in MS and also the related yet broader field of neurology to find drugs for diseases including Alzheimer's and amyotrophic lateral sclerosis (ALS) ("Neurology," 2015).

During the patent cliff years, Novartis was identified as the top pharmaceutical spender in R&D in 2010 as shown in Figure 9. These R&D efforts led to "13 major approvals in key markets in 2014 and advance[s in their] pipeline" ("Annual Report 2014," 2015). Von Schaper (2010) notes that Novartis owns claim to having the first FDA approval for an oral MS therapy, Gilenya, helping to boost annual sales since 2010.

Top Ten R&D Spenders in 2010

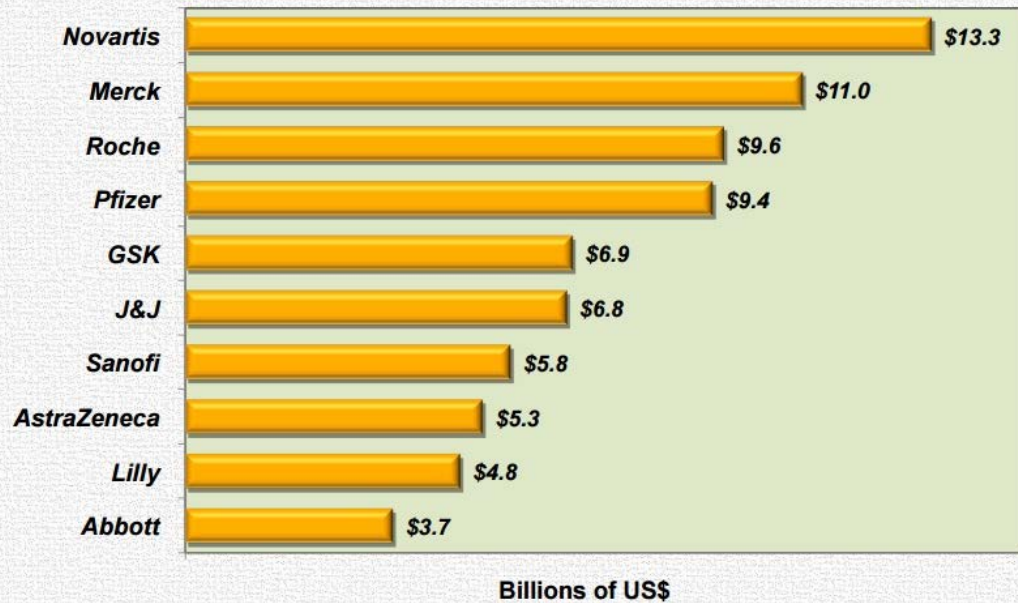


Figure 9: Companies with Greatest R&D Expenditures in 2010. This graph shows the amount of money spent on R&D. (Kaitin, 2012)

Also among the top spenders in R&D in 2010 shown in Figure 9, Sanofi has extended itself internally and externally into early stage collaborations with other pharmaceutical companies to further their stake in specialized medicines and make an investment in the very active field of RNAi therapies. These R&D efforts are projected by the company to produce a total of 18 new product launches over 6 years leading up to 2020 ("Annual Results 2014," 2015). Biogen was notably not included in this figure as the company did not have as much money to invest in R&D, nor did they need to at that time.

Academic Collaborations

Biogen, Novartis, and Sanofi all utilized the tool of collaborating with academic institutions, with Biogen being the most devout. Institutions are free to enter multiple partnerships with pharmaceutical companies that are best suited for the projects they are currently seeking funding. Between 2008 and 2013, of the top twenty academic institutions that had partnerships, all twenty had deals with at least three pharmaceutical companies with the top institutions having up to twelve deals during this patent cliff time (Larkin, 2014). This tool may be underused by some of the larger pharmaceutical companies as the revenue from investing in these types of collaborations could take the longest of any of the tools to be realized.

Biogen formed an academic collaboration with MIT's Whitehead Institute for an overall commitment of \$5.25 million over three years that the company will contribute to research projects in neurology and several other areas ("Whitehead Institute and Biogen," n.d.). In addition to internal research, Biogen has academic partnerships and collaborations with Massachusetts Institute of Technology (MIT), Harvard Medical School (HMS), Duke University, Columbia University, University of Connecticut, and several consortiums to further scientific fields of interest and to potentially develop novel therapies in their early stages in the lab ("Working to find solutions," 2015).

Novartis maintains an academic collaboration with the University of Pennsylvania for novel cancer immunotherapies (Toor & McBride, 2012).

Sanofi has academically collaborated outside the area of MS with University of California at San Francisco for diabetes, brain trauma, and oncology, Harvard Medical School with a focus on diabetes, and Texas A&M University for the development of drug therapies for tuberculosis (Toor & McBride, 2012).

Emerging Markets

Expansion into emerging markets is a major tool used by Biogen, Novartis, and Sanofi during the patent cliff years and still today, particularly by the latter two companies, to aid in earning more revenue in the wake of the patent cliff. Entering into these markets can happen both at the clinical trial preapproval stage by enrolling patients at local trial sites and later in development when submitting and seeking marketing authorization to sell the drug in foreign countries. Following the patent cliff, the value of global marketing authorizations was closely examined along with the potential of treating diseases on a global basis rather than solely focusing on the more established United States and European markets. Expanding access to other markets provides a larger group of patients whom could be considered for enrollment into clinical trials and reaching out to these other countries helps to identify subpopulations that may respond differently to therapies. Emerging markets could be the key to creating next generation products targeted to a certain aspect of a disease or even

expanding indications of existing products to reach populations that do not have as many locally approved treatment options. Particularly interesting in the MS space is the approval of oral therapies since some patients in these markets do not have access to infusion centers to receive injection-only MS therapies. Expanding into emerging markets may offer an easier way to gain revenue from sales of products where competition is not as abundant ("Pharma 2020," 2012).

As shown in Figure 10, companies are rapidly trying to adopt global practices as they bring new products to market to tap into additional revenue. The reimbursement and regulatory processes to gain authorization to market drugs in some emerging and growth markets (China, Brazil, Russia, India, Mexico, Turkey, Poland, Venezuela, Argentina, Indonesia, South Africa, Thailand, Romania, Egypt, Ukraine, Pakistan, Vietnam), which are second to emerging markets in economic advancement but not far behind, are still being developed ("Pharma 2020," 2012). It is a particularly critical time for biopharmaceutical companies to have a presence in these markets so they can gain a better understanding of the quality and quantity of data required to secure drug approval and gain sales in these markets which will continue to exhibit potential over at least the next several years. Sales in growth markets are projected to exceed that of the United States market as soon as 2020 as illustrated in Figure 10. Regulatory approval is typically first sought in the United States or Europe where timelines to approval and reimbursement are often transparent and the pathway is well understood by sponsors. In emerging markets, regulatory approvals can happen as quickly as 3 months or take several years to be granted without much precedence for sponsors to leverage to

navigate these often confusing pathways. Some countries do not require local clinical trials therefore they are important to consider in trying to gain fast market entry for new therapies when prioritizing markets to register new products.

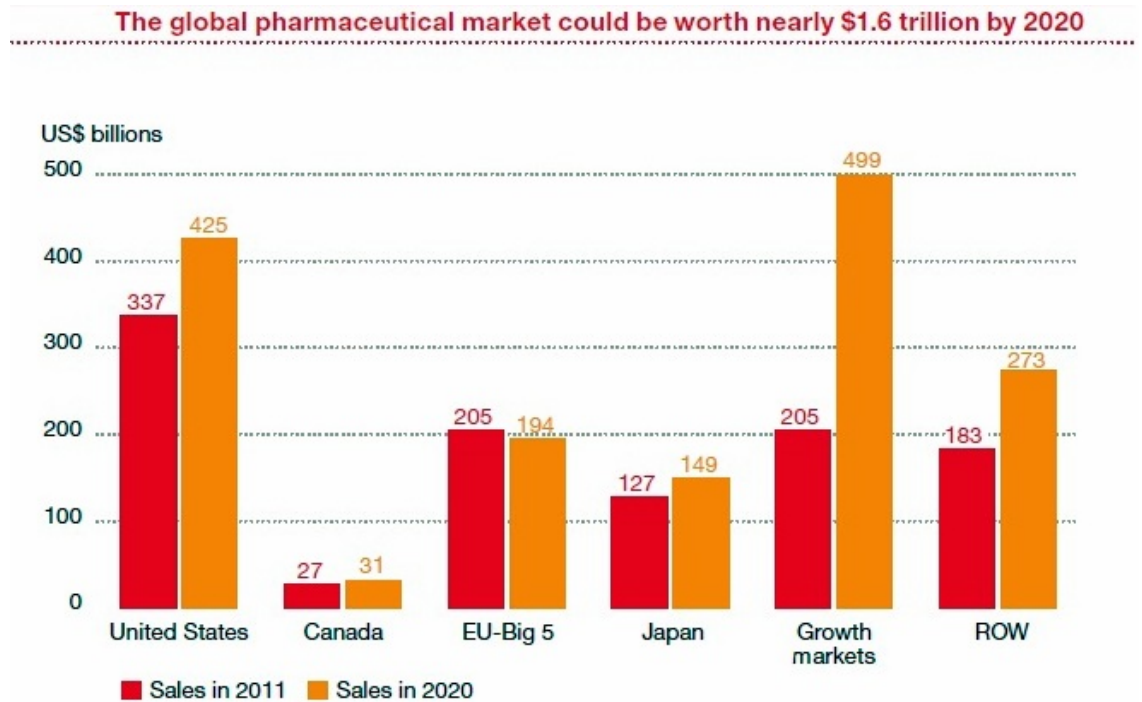


Figure 10: Rest of World (ROW) Pharma Sales Potential. This graph shows how much sales could grow in the global market over the next decade. ("Pharma 2020," 2012)

Biogen has been seeing increased demand for Tecfidera in emerging markets which has served to offset revenue loss of less favored, older injectable MS therapies that Biogen also markets ("Biogen 2014 Annual Report," 2015).

Novartis has made an effort to expand sales of their patent-protected products internationally into emerging markets in Asia, Africa, and Latin America, resulting in 4% net sales increase in 2013 (“Novartis Delivers,” 2014) and 11% sales increase in 2014 which helped offset the impact of generic competition for products subject to the patent cliff (“Annual Report 2014,” 2015).

For Sanofi, expansion into emerging markets has led to a 9.3% increase in sales in 2014 as the company promotes growth in Africa, Middle East, Eastern Europe, Russia, Turkey, Asia, and Latin America (“Annual Results 2014,” 2015).

Other Considerations

Use of any combination of these key business strategy tools has resulted in the ability of Biogen, Novartis, and Sanofi to increase their revenue, develop their pipelines, diversify or focus their portfolios, and accelerate science. For example, competition for new MS drugs has helped accelerate the science as several companies publish their findings to create unique treatments. Biogen boasts what they call the world’s leading portfolio of MS treatments including Avonex (interferon beta-1a), Fampyra (fampridine prolonged-release tablets), Plegridy (peginterferon beta-1a), Tecfidera, and Tysabri (“Our therapies,” n.d.). Having multiple products indicated for a range of MS diagnoses, Biogen has gained a wealth of knowledge of the disease state and has formed relationships with key opinion leaders and influencers in the field, which, combined with

their in-house scientific expertise, has helped to establish the company as an authority in the MS field as they continue to develop new products.

Pharmaceutical companies should be willing to spend the time to develop more oral treatments to continue to increase patient adherence and decrease long term disease costs when they decide which compounds they pursue. The reward for companies spending time and money to develop such compounds is that the return may be higher as patients and payers are willing to pay more for therapies that are effective and don't require special trips to a site to receive medication infusions, disrupting their work and home lives.

It is difficult to isolate the effect of MS portfolios on Biogen, Novartis, and Sanofi – change in their revenue areas of neuroscience and CNS may be the best correlation to the research and development of the companies' MS drug franchises. According to sales revenue earned in 2014, Biogen was the most successful in CNS sales totaling \$8007 million, followed by Novartis with \$5769 million, and Sanofi with \$1457 million ("Top 25 pharma companies," 2015). The revenue from CNS sales shows 46%, 7%, and 18% growth, respectively, from 2013 to 2014 ("Top 25 pharma companies," 2015). This growth implies that Sanofi will eventually become more of a contender in the field of companies with high earning MS portfolios once their collaborations and acquisitions are fully recognized. Fluctuations in income of biopharmaceutical companies are likely to be prolonged as effects of the patent cliff linger, despite the many strategies companies are employing to mitigate their revenue and patent losses.

Aside from utilizing the key tools identified to varying degrees of success, each company has used other strategies to survive. One additional strategy is the diversification of their portfolios and pipelines. Several pharmaceutical companies have sold or traded some or all of their portfolios and primary business areas of expertise to diversify in an effort to maximize profits and realign niches in today's highly competitive market. As an example, Novartis chose to combat reduced revenues from blockbuster patent expiry by allocating funds toward other internal divisions, Sandoz in this case, to increase launches of generic drugs and keep the company portfolio diversified ("Annual Report 2012," 2013). Sandoz contributed \$8,702 million in net sales to Novartis in 2012 from their retail generics, biosimilar products, and differentiated product sales on a global scale ("Annual Report 2012," 2013).

A second additional strategy is the creation of focused growth platforms which include select markets and portfolios a company has identified as having high potential to increase overall revenue. For many companies, the patent cliff was not just a one quarter or one year loss of revenue, it spanned several years depending on how many drugs are involved. For example, according to their 2012 annual results (2013), Sanofi's sales throughout 2008-2012 continued to grow year over year during the patent cliff until its oppressing effect was exhausted around 2013 according to the plateau (Figure 8) in loss of brand name revenue from key products sold in the United States and Europe. Sanofi has focused on increasing sales in selected growth platforms which have doubled from 2008-2012, keeping the company's income relatively stable ("Annual Results 2012," 2013).

A third additional strategy used in helping companies gain revenue is extending efforts toward patient outreach and building community presence. To help patients with MS manage their medications, companies have developed social business initiatives including targeted education programs and expanded access programs. In a novel way, Novartis has created active online communities explained by Helfand (2014) where patients can gather and share their experiences, providing insight back to the company on lifestyle modifications these patients voluntarily make for better outcomes. Reaching out to patients in these ways is aimed to help create additional use of the company's approved MS therapies and also continue to drive the need to develop better medications (Helfand, 2014). The number of patients that can be reached through these initiatives is extensive, as shown in Figure 11. For patients participating in these initiatives, it is possible that the outreach creates an alliance toward the company and their therapy options would be preferred to those patients after experiencing a more personal connection with the company.

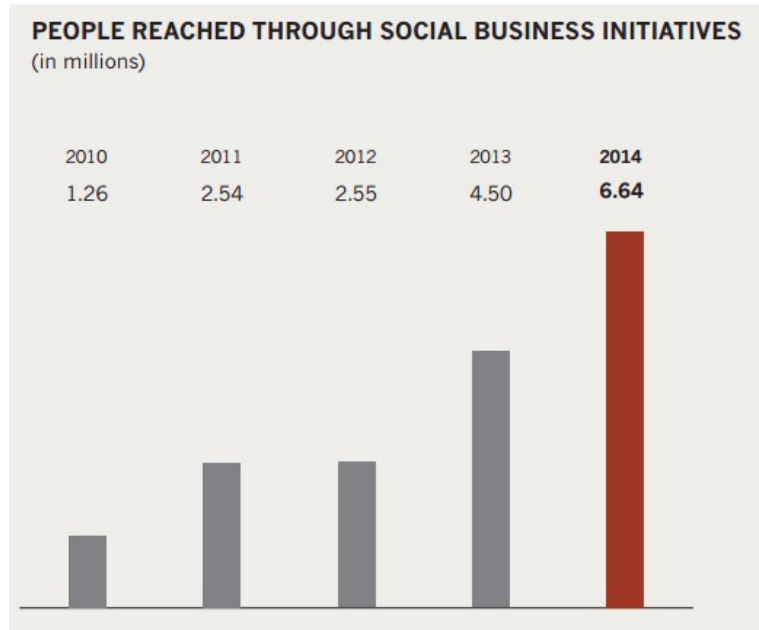


Figure 11: Social Business Impact on Novartis Pharma Customers. This graphic illustrates the growing trend of social business programs. ("Annual Report 2014," 2015)

A fourth additional strategy used by biopharmaceutical companies is to optimize their regulatory strategy to accelerate review times and access incentives in patent and exclusivity extensions. This can be done by streamlining clinical development phases and trial design with health authority input and applying for additional authority feedback and collaboration, when possible, to reduce review times. To combat increased regulatory requirements and lengthy development timelines, these companies have cultivated creative regulatory programs to secure approval of their oral MS therapies and are likely doing so for other products. Approved for similar indications, Novartis has had the most success utilizing this strategy to gain approval more quickly for their oral MS drug compared to the other companies because they

were able to secure priority review, a process set out to expedite FDA review by 4 months, and be the first to market oral MS drug. Dunn (2013) states that Biogen submitted Tecfidera to FDA on February 27, 2012. The drug efficacy and safety were evaluated in relatively standard clinical development program comprised of two phase three trials, one phase two dose-finding study, and an ongoing open-label extension study (Dunn, 2013). Tecfidera was approved by FDA in approximately 13 months on March 27, 2013 to be taken orally, twice daily, for “relapsing forms of [MS]” (Dunn, 2013). Katz (2010) states that Novartis submitted Gilenya to FDA on December 18, 2009 under the time-saving priority review process as it was the first oral MS treatment submitted to FDA. The drug efficacy and safety was evaluated in two pivotal trials and was approved by FDA in approximately nine months on September 21, 2010 to be taken orally, once daily, by patients with “relapsing forms of [MS] to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability (“Efficacy,” 2015)” (Katz, 2010). Dunn (2012) states that Sanofi submitted Aubagio to FDA on August 12, 2011 under the standard review process for a new molecule. The drug efficacy and safety was evaluated in just one phase 3 trial, three phase two studies, and an additional ongoing phase three study (Dunn, 2012). Aubagio was approved by FDA in approximately 11 months on September 12, 2012 to be taken orally, once daily, for “relapsing forms of [MS]” (Dunn, 2012).

Three new, oral MS therapies approved in just three years by FDA shows an impressive interest in this space. Faster clinical development with fewer required trials, expedited regulatory review pathways (FDA’s standard review is 10 months compared

to priority review is only six months), and unique statements in approved indications coming from the strategy behind the clinical trial development can be key to differentiate one company from another in the MS space, to secure preferential reimbursement, and to gain broad exclusivity and patent protection. The regulatory strategies analyzed above only take into consideration the FDA process; it is important for companies to consider global regulatory strategies when determining which countries they desire to submit their marketing applications to and in what order if they want to maximize the revenue of their global MS franchises. In addition to regulatory strategy, these companies undertook individualized drug development pathways. Development considerations include creation of new molecular entities versus scientifically modifying an already approved product, differentiation of mechanism of action which can lend one product to have a superior tolerability for patients compared to other similar products and ultimately gain favor in the marketplace, and testing varying formulations and strengths in the clinical stage so a most appropriate dose and formulation can be offered to patients once the drug is approved.

Limitations

One finding from this analysis is the apparent, and uncharacteristic, persistence of high prices for MS products despite increased competition. As previously proposed, setting high prices on MS drugs is a method of overcoming a patent cliff for some companies, yet it seems that costs continue to rise in this field to everyone that has a

drug on the market, which could actually delay the onset of another patent cliff for those companies invested in this new blockbuster field. It is difficult to identically assess the costs of these therapies to one another and to comparative products marketed globally due to various payer systems and pricing indexes (Hartung, Bourdette, Ahmed, & Whitham, 2015). For this reason, this research focused on entire company net incomes rather than analyzing specific drug prices and revenues. Further analysis could be done to compare wholesale price of one drug to another in the United States or to determine if there are similar constant price indicators for other countries.

Another aspect to consider in this type of research is an overall difficulty to access true company business information. Data available for analysis are a few quarters old and have primarily been sourced from the prior year annual shareholder report; new development strategies are kept confidential while in progress and take some time for new business models to be announced, put into effect, and be evaluated. Taking this into consideration, this research focused on two US-based companies and primarily relied on annual financial reports so the level of detail for data analysis could be represented in a way to illustrate trends. Sanofi, a company based out of France, reported many figures in euros rather than US dollars, which illustrated the impact of the patent cliff but did not allow trend lines from all three companies to be compared in a single image or in a more specific financial manner.

Broader Implications

This case study is the next step in the field of inquiry because it predicts future trends in pharmaceutical business strategy. Drawing attention to strategies previously and currently used in the MS space for profitable companies provides examples for how other companies might want to apply similar strategies to avoid being greatly impacted by future patent cliffs.

As companies mature beyond the patent cliff, more potent and targeted drugs are being developed and marketed to patients globally at competitive costs. It is important across the biopharmaceutical industry for companies to strike a balance in their use of business strategy tools – if too many companies were to reduce R&D spending in favor of other business strategy tools, drug development and discovery or growth portfolios in less lucrative therapeutic areas or expansion into less populated markets could come to a halt without further incentives.

Pharmaceutical companies are not only acting on the business and investor front, they are also working to create supportive environments for those affected by MS. Patient groups for MS are very active, and they lobby to ensure funds are made available for MS research and that patients with MS are aware of the costs of the disease, their choices for treatments, and accessibility to care (“Current Advocacy,” n.d.). Several times these patient groups have advocated allowing drugs to be approved so that patients can have a choice, so it behooves companies to listen to their concerns and work with them in the future to better understand how to have a positive impact.

For now, it seems that the result of surviving the patent cliff for Biogen, Novartis, and Sanofi has led to the positive outcome of creating more treatment options for patients with MS. This same concept applies to many other clinical areas, as shown in Figure 12, as other companies over the past decade have chosen to pursue differentiating clinical specialties, advancing science while generating revenue after the patent cliff.

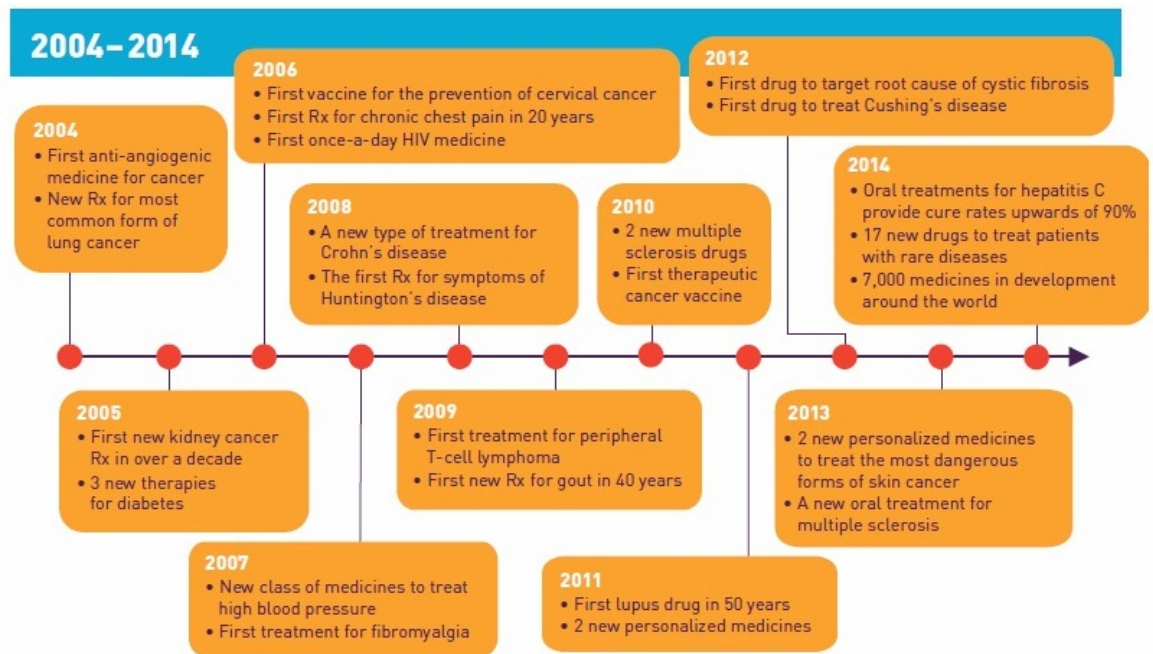


Figure 12: Pharma Industry Advances 2004-2014. This graphic shows the great number of pharma accomplishments in the past decade. ("2015 biopharmaceutical research industry profile," 2015)

Although we are beyond the crux of this patent cliff as we see company revenues plateauing or returning to show annual increases, innovation of new drugs and more targeted therapies shows no signs of stopping according to persistence in interest from sponsors and demand from patients. In MS, despite having a good understanding of the disease, patients are still seeking options to improve their quality of life with more effective therapies, fewer side effects, and more convenient dosing regimens ("2015 biopharmaceutical research industry profile," 2015). Sponsor companies must be patient throughout this process – it can take years for the drug development process and it can take years for consumers to see the realized value of those drugs, particularly if they are already stabilized on an alternative therapy. Uptake of these new products may not be immediate as the educated patient population waits to see long term safety and efficacy data before they switch from a tried and true treatment to something highly innovative.

Innovation and Bolstering of MS Pipelines

To survive a patent cliff, companies now must continuously strive to develop new products within their therapeutic areas of interest. Despite all of the new therapies on the market for MS, there is still a large unmet medical need including medications that cure the disease rather than reducing relapses or providing palliative remedies which will continue to drive interest in this field. By employing an array of tools, each biopharmaceutical company offers a pipeline filled with derivations of current products

and new drug products that allow them to secure new patents and exclusivities, driving revenue. Maintaining a robust pipeline is important for the success of a company both for its investors and to ensure its viability as a potential target for a merger or acquisition if that is in its best interests. In the neurology area, Biogen currently has four products in their pipeline – one that has been filed to FDA and is under review, one in phase three, one in phase two, and one in phase one to strengthen their MS franchise ("Our pipeline," 2015). Novartis has only one product in their robust pipeline under a potential MS indication. ("Clinical Pipeline," 2015) Sanofi has two products potentially indicated for MS in early phase development in their pipeline ("Annual Results 2014," 2015). These companies are not only looking to add MS products to their pipeline, but also to expand indications of therapies to other disease states as mechanisms of the drugs become better understood.

Pricing

Another implication of the patent cliff is aggressive pricing strategies sponsors are implementing for new therapies. Taking into account the high costs of MS, biopharmaceutical companies have responded with charging high prices for their treatment options and associated therapies. To expedite growth, industry has made an effort to raise drug prices and increase profits on MS therapies. On a global level, this practice has the potential to revolutionize healthcare systems to implement pricing controls if efforts become too aggressive.

One of the ways these companies are able to charge more for these new drugs is by developing easy to administer oral therapies, compared to older injection therapies, because people are willing to pay for convenience of the formulation regardless of the complexity costs incurred by the company manufacturing the product. Are newer, more expensive treatment options available in oral formulations truly worth the increased cost over traditional MS medications? It will take time to see if the high cost of these new oral MS therapies is truly cost effective; economic analysis cannot be completed in a useful manner until these therapies have been marketed for a substantial time. Cost to the patient is typically subsidized by private or public insurance, and lately insurers are a bit more skeptical about allowing every newly approved treatment on their formularies, analyzing cost effectiveness data if more than one drug is approved for the same indication. For instance, Canada has developed a preferred monotherapy treatment algorithm with regard to effectiveness and quality-adjusted life years (QALYs), however, there is not enough clinical evidence to support inclusion of combination therapy in the health economic model. The cost effectiveness of combination therapy in RRMS remains unknown. Regarding new and emerging treatments, Lemtrada, an infusion therapy for MS, was identified as a cost-effective treatment while Aubagio, an oral therapy for MS, was not (“Comparative clinical,” 2013). Results from a systematic review suggest that reductions in relapse rate on an annual basis are greatest with Tysabri or Lemtrada, both newly approved infusion therapies for MS, followed by oral therapies Gilenya or Tecfidera at 50% (“Comparative clinical,” 2013). It was also shown that treatment, compared to placebo, was less costly

and more effective depending on the willingness to pay threshold (“Comparative clinical,” 2013). Pharmacoeconomic analysis across disease states is becoming an important tool for payers across the globe in deciding the fate, via reimbursement of new therapies. Biopharmaceutical companies will have to factor this type of analysis into their development plans for a product when choosing clinical trial comparators and when setting the cost per dose of their therapy to ensure it is warranted. Interestingly, as new MS treatments come to market with high prices, it seems that previously approved drugs in the MS space are benefiting and increasing their prices:

“In the specific case of multiple sclerosis, the research looked at first generation drugs which became available in the 1990s at prices ranging from \$8,000 to \$10,000 a year. More competition from other drugs then entered the field. But instead of the price of the original drugs staying about the same or going down, as classic economic theory might dictate, their price soared. One drug that originally cost \$8,700 now costs \$62,400 a year” (“Drug Prices to Treat Multiple Sclerosis,” 2015, ¶11).

As generic entry looms in 2019 for Gilenya, Novartis along with the other MS product companies are reminded that they must continue innovating and strategizing to protect themselves in the competitive MS world from the losses they will inevitably face from patent loss (Staton, 2015). The patent cliff of the MS products can have a domino effect on the MS franchises and could affect pricing across the industry if data is not continuously gathered to express the benefit each treatment option has to offer for

particular sets of patients to justify the cost of the therapy and allow sales profits to be internally allocated to develop new products.

Related Recommendations

This research of just three companies can be extrapolated into overall recommendations for business strategies for biopharmaceutical companies to earn revenue. Given a broader scope, it would be worthwhile for manufacturers to investigate the effects of the patent cliff on more companies and other disease states to see if similar outcomes are seen. Additionally, taking a look at some US-based companies versus only internationally headquartered companies would provide another angle for comparison that could be taken into consideration. As seen in the results section, the four key business strategy tools identified and utilized by the three companies led to relatively modest net income growth during this particular patent cliff. Comparing the net income to stock prices over the past ten years for Biogen, Novartis and Sanofi as shown in Figure 13, it appears that the two have a direct correlation for Biogen and Novartis, but not for Sanofi. The net income of Sanofi was nearly a plateau, yet the stock price shows an early plateau with a small increase over the past few years. One potential explanation for this recognized increase would be the acquisition of Genzyme in 2011 which has resulted in positive reactions from investors and has added to the company's bottom line. To better understand the correlation, if any truly exists, between stock price, net income, and patent cliffs, it is recommended to analyze these

financial indicators during other patent cliff timeframes and also outside of a patent cliff timeframe to see what relationship trends might emerge.

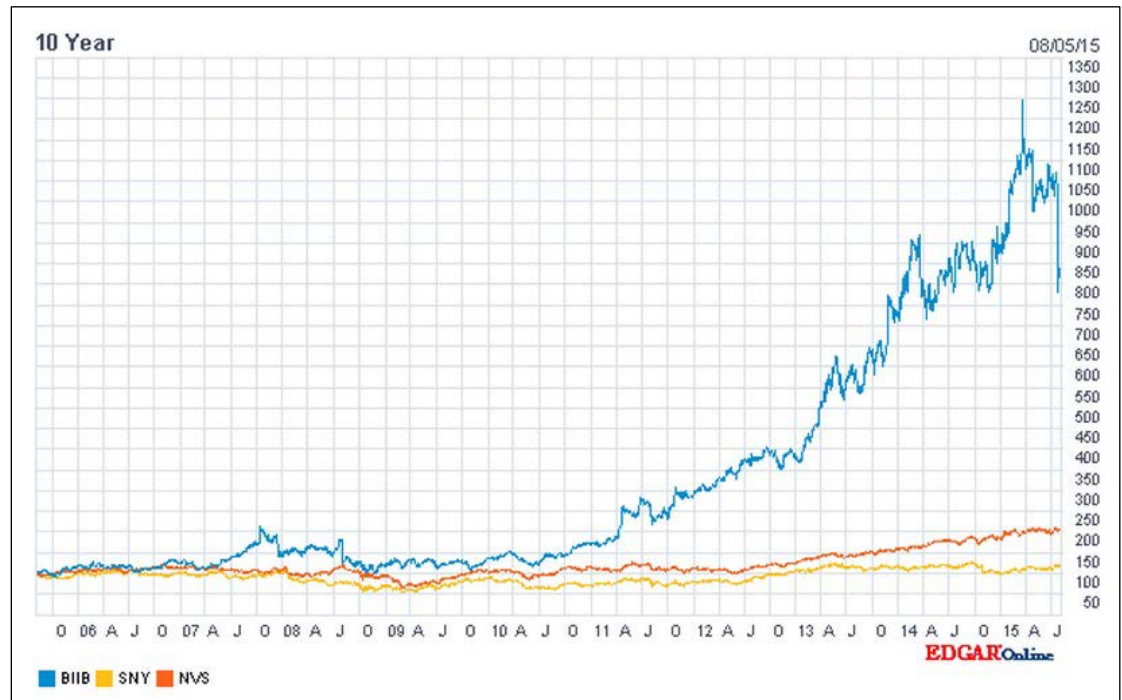


Figure 13: 10 Year Stock Price of Biogen (BIIB), Sanofi (SNY), Novartis (NVS). This chart shows the change in stock prices over the past decade. ("10 Year," 2015)

Conclusion

What business strategies have pharmaceutical companies employed to revitalize their growth following the patent cliff? This question has been answered and supported by the research presented throughout the thesis. Among biopharmaceutical

companies, Biogen, Novartis, and Sanofi used a mixture of business strategy tools to revitalize their growth following the patent cliff. Biogen's efforts were primarily concentrated on academic collaborations and R&D investment, Novartis's around R&D, mergers and acquisitions, and emerging markets, and Sanofi's around mergers and acquisitions, R&D, and emerging markets. This resulted in varying degrees of success, evidenced by the upward trend in net income of the companies, and will take some time to fully be realized as revenue generated from employing these tools adds to the overall strength of the companies, considering all of the other variables that may affect net income over time. Some of these tools may be easier than others to implement, but the success of these companies suggests that using more than one tool at a time can contribute to good health in the evolving biopharmaceutical landscape. To remain competitive, biopharmaceutical companies should internally develop aggressive strategies for clinical development and marketing potential for each of their products and portfolios so they can be proactive rather than reactive in taking steps to stabilize their net incomes. If a biopharmaceutical company was to do nothing to proactively stabilize their net income, a patent cliff could set them up to lose a significant portion of revenue in a short time, becoming a target for acquisition. This lends companies to employ the tool of mergers and acquisitions to bolster their own revenues and fortify their pipelines. If the company promoted themselves to be partially acquired, this could result in their earning additional cash to employ another one of the tools, investing in R&D, to stay in business with a portfolio to better suit their needs.

Thus far, this research shows the various reactions of pharmaceutical companies to the revenue lost to the patent cliff as well as highlighting some proactive measures that could be taken to avoid these situations in the future. With these strategies, if another patent cliff did occur, companies may see less revenue loss or a shorter period of plateau in net income. Companies seem to have learned to invest in R&D of novel next generation products, valuable partnerships with other companies and academic research facilities, and take stake in emerging markets as part of their plans to guarantee long term profitability across products and therapeutic specialties. It is essential for biopharmaceutical companies to understand the historical lesson that revenue loss due to patent expiry was concentrated in mainstream treatments. In the future, a patent cliff could repeat itself by impacting a franchise of contemporary blockbuster drugs concentrated around a specific disease state such as MS. Therefore, it is advisable for biopharmaceutical companies to incrementally invest in R&D of a diversified pipeline for sustainability.

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