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A longitudinal analysis of blockbuster pharmaceutical drugs.

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Abstract

Blockbuster drugs play a key role in the pharmaceutical industry. However, discovery and development alone are not enough to create a blockbuster. Firms must be able to market the drug aggressively to achieve the potential gains from their innovation. The knowledge behind each drug may come from a variety of sources, both large and small: firm size is not a significant advantage at the development stage (Cockburn & Henderson 2001; Danzon et al. 2005). However, larger firms may benefit more financially after a drug is approved (Ciftci & Cready 2011). We argue that while many firms are capable of discovering and developing new drugs, only a handful of firms are capable of successfully commercializing a breakthrough innovation. This commercialization capability is what creates a blockbuster: without this capability, even a major innovation would not reach blockbuster status.

The roots of this study extend to Schumpeter (1942), and ability of large firms to invest in research and development. While asymmetric information in the market for knowledge internalizes R&D activity (Arrow, 1962), it is competitive pressure that forces the firm to maintain a pipeline of innovation. A monopolistic firm will also be under pressure to delay the release of innovations in order to minimize cannibalization and maximize returns from extant products (Scherer, 1965). The nature of the innovative process is such that smaller firms may be better at undertaking radical innovation, while larger firms excel at incremental innovation (Nelson and Winter, 1982). The 'bureaucratized' model of

incremental innovation in big pharma (Nelson and Winter, 1982) led to a larger and larger proportion of returns emanating from a smaller and smaller set of drugs: a highly skewed distribution of market outcomes (Manning et al, 2005). This resulted in a model of drug development, wherein big pharma firms reap the bulk of their profits from a very set of 'blockbuster' drugs (Cutler, 2007).

In this study we examine the complete population of blockbuster drugs from the last three decades, and find that the vast majority were discovered by one firm, and commercialized by a larger (major) firm. Our data sources examine the patenting, licensing, and acquisition of knowledge. We then compile three in-depth case studies of blockbuster drugs that have recently seen their core patents expire. The evolutionary tale that ensues supports our broader claim. Major firms act as gatekeepers, selecting drugs that they attempt to develop to become the top sellers. A firm with a history of successful selection and commercialization develops a rare and inimitable capability. We argue that the pharmaceutical industry resembles creative industries such as movie making, in which successful organizations (or individuals) have a high degree of control over which movies, actors, directors, etc. achieve the most success. Skills are vertically integrated, and while the differences in capabilities between tiers of firms may be small, the financial implications of these differences are quite large (Caves, 2000).

We present evidence that blockbusters have all been marketed by a handful of very large firms, despite having origins in a much larger number of firms. We focus specifically on three case studies to examine the mechanics of licensing, specifically: Lipitor, Plavix, and Actos. In each case, the originator company had limited experience in marketing blockbusters, while the licensee company had significant experience. We use these three cases to explore patterns in the timing of licensing and acquisitions that may shed light on the structure of the pharmaceutical marketplace.

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A longitudinal analysis of blockbuster drugs

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ABSTRACT

‘Blockbuster’ drugs play a key role in the pharmaceutical industry. However, discovery and development alone are not enough to create a blockbuster. Firms must be able to market the drug aggressively to achieve the potential gains from their innovation. The knowledge behind each drug may come from a variety of sources, both large and small: firm size is not a significant advantage at the development stage. However, larger firms may benefit more financially after a drug is approved. We argue that while many firms are capable of discovering and developing new drugs, only a handful of firms are capable of successfully commercializing a breakthrough innovation. This commercialization capability is what creates a blockbuster: without this capability, even a major innovation would not reach blockbuster status.

Introduction

“Blockbuster” drugs¹ play a key role in the pharmaceutical industry. Cutler (2007) shows that between 2000 and 2005, drugs with more than \$1 billion in sales accounted for between 28 and 36 percent of total global sales. Changes in the sales of these drugs can cause large swings in a firm’s profitability. For example, Pfizer’s profits dropped by 19% when the patent for its blockbuster Lipitor expired and the product began experiencing generic competition (Thomas 2012); Novartis’s profits in the first quarter of 2012 fell by approximately 16% due to generic competition with its blockbuster Diovan (Falconi 2012). The term “patent cliff” is often used to refer to the dramatic revenue decline associated with the expiration of intellectual property protection. The pharmaceutical industry anticipates losing \$78 billion in global revenue from the 2010-2013 patent cliff: half of this loss may be due to blockbuster drug patent expirations in 2011 alone (Harrison, 2011).

Blockbuster drugs are usually significant therapeutic breakthroughs compared to previously available therapies. However, greater therapeutic value alone is not enough to create a blockbuster; firms must be able to market the drug aggressively to achieve the potential gains from their innovation. To this extent, firm size may play a role. Studies of firm size in the pharmaceutical industry have shown that larger firms do not necessarily have an advantage in successfully taking a drug through the stages of development (Cockburn & Henderson 2001; Danzon, Wang, & Wang, 2005), but they may have an advantage in achieving greater financial gains following drug approval (Ciftci & Cready 2011).

¹ Consistent with Cutler (2007), Munos (2009), and Lazonick and Tulum (2011), we define blockbuster drugs as those having annual revenue over greater than \$1 billion.

While smaller firms may be at a disadvantage in marketing new drugs, they could potentially mitigate much of this disadvantage by partnering with a larger firm. The standard model of pharmaceutical development begins with discovery and preclinical testing, followed by three phases of clinical trials (DiMasi et al. 2003; FDA 1999). Finally, the company submits the clinical trial data to the FDA for approval and the drug may go to market. While this model suggests that a single firm may perform all of these steps, in fact drug licensing is common. Small firms are particularly likely to enter into licensing agreements. For instance, Danzon et al. (2005) show that between 1988 and 2000, among firms with fewer than 25 compounds in development, about 70 percent of phase 3 clinical trials involved an alliance with another firm. Additionally, these firms partnered with larger firms in the vast majority of cases, suggesting that the firms could gain from the additional resources these large firms could bring to bear.

However, even large firms may benefit from out-licensing. Danzon et al. (2005) also find that alliances are common among large firms. For a major innovative drug, even a large firm may lack the resources to convert the innovation into a blockbuster. In this study we look at the population of blockbuster drugs launched after 1980 that have achieved worldwide sales of greater than \$1 billion (USD). In the majority of cases, blockbuster drugs were marketed by larger firms: many were developed at smaller firms and the knowledge was transferred post-patent filing. Three case studies of blockbuster drugs give greater insight into products that were developed at fairly large firms, but then licensed to even larger firms for marketing. The originating firms we examine are not

small in absolute terms: they are still in the top 30 pharmaceutical firms by revenue. Despite their relatively large size, however, they still licensed their blockbuster drugs to much larger firms, rather than attempt to do the marketing themselves.

In this study, we argue that while many firms are capable of discovering and developing new drugs, only a handful of firms are capable of commercializing a breakthrough drug. Further, this commercialization capability is what creates a blockbuster; without this capability, even a major innovation would not reach blockbuster status. These firms thus act as gatekeepers, determining which drugs become the top sellers. We argue that the pharmaceutical industry therefore resembles creative industries such as movie-making, in which major studios have a high degree of control over which movies, actors, directors, etc. achieve the most success.

Several previous studies of the pharmaceutical industry have provided evidence in support of our “gatekeeper” hypothesis. Berndt, Pindyck, & Azoulay (2003) examine the role of “consumption externalities” in pharmaceutical sales—that widespread use of a drug makes it more acceptable to physicians and patients, because they take it as a signal of the drug’s safety and efficacy, or as an indication that use of the drug is in line with standard clinical practices. In such an environment, a drug may achieve dominance despite the existence of higher-quality drugs in the same therapeutic class. Azoulay (2002) shows that both scientific evidence and marketing affect a drug’s sales, which suggests that a major marketing campaign could help lead to a situation in which the dominant drug is not the best alternative in the class.

Direct-to-consumer advertising (DTCA) could provide a way for less-dominant firms to bypass the gatekeepers. However, some evidence suggests that this is unlikely to occur. While Iizuka and Jin (2005) show that DTCA expands the market for a therapy class, they also show in a follow-up study (Iizuka and Jin 2007) that DTCA does not affect brand choice within a therapy class. Likewise, Liu and Gupta (2011) show that in the anti-hyperlipidemia drug market, sales of the leading drug, Lipitor, benefit from the advertising of the other major brands.

We present evidence that over the past 30 years, blockbusters have all been marketed by a handful of very large firms, despite having origins in a much larger number of firms. We begin by focusing on three case studies to examine the mechanics of licensing. We chose three case studies to examine the premise of our study: Lipitor, Plavix, and Actos. Each of these drugs reached peak revenues of over \$4 billion per year. In each case, the originator company had limited experience in marketing blockbusters, while the licensee company had significant experience. We use these three cases to explore patterns in the timing of licensing and acquisitions that may shed light on the structure of the pharmaceutical marketplace more generally.

We then move to a broader examination of commercialization patterns in blockbuster drugs (defined here as drugs having peak annual sales over \$1 billion in constant 2005 dollars). We use data from the FDA, company reports, and several other sources to construct a database containing all drugs meeting the \$1 billion threshold

between 1980 and 2010. Our database includes the originating firm, peak sales, the year of peak sales, the licensing or acquiring firm, the year of licensing or acquisition, and the year of the original patent. We present summary statistics showing that blockbusters originated from many different firms, but almost all of them were commercialized by a handful of “major” pharmaceutical companies. These major companies were already in the top 12 manufacturers prior to licensing or acquiring the blockbuster.

In our conclusion, we examine the implications of our study for the blockbuster model. Numerous articles have predicted the impending demise of the blockbuster model and a resulting shakeup in the industry. We suggest instead that while the blockbuster model may disappear, the top firms in the industry will retain their relative advantage in extracting the value of innovative drugs through commercialization.

The Economics of Innovation and Innovation in the Pharmaceutical Industry

In this section, we describe a conceptual framework of development and marketing in the pharmaceutical industry and relate this framework to creative industries such as movie-making. We use Caves’ (2000) analysis of creative industries as a starting point. The purpose of this framework is to highlight the characteristics of the pharmaceutical industry that lead to returns to scale in commercialization, but not necessarily in research and development.

The pharmaceutical industry was one of the first to initiate large-scale corporate R&D within firm boundaries. As early as the first few decades of the nineteenth century, firms like Merck and Pfizer used their in-house R&D labs to develop products like medicinal grade morphine and tartaric acid. By the twentieth century, commercial R&D was a key competitive feature of the industry; as the scale-intensity of the function rose, internal operations grew in size (Chandler, 2005).

The pharmaceutical industry bifurcated beginning with the antibiotics revolution in the 1940s, into what became the branded and generic strategic groups (Galambos & Sewell, 1997; Lee, 2003). During the 1940s and 1950s, large-scale research and development became increasingly important, as firms rapidly churned out new therapies. The branded groups consisted of the firms that increased the scale of their R&D operations, while the generic firms were those who elected to imitate the products of the branded firms. Lee (2003) also notes that turnover during this period was considerable—the top 5 firms often did not retain their position in the top 5 for long. Despite the rapid changes in market share, however, the antibiotic revolution did not significantly change the number of firms in the market (Munos 2009).

Schumpeter (1942) was one of the early voices arguing that extent of investment necessary for innovation by the 1940s was so large that only large firms could afford to do it. They have the incentive to invest in R&D because they have large revenues over which they can spread them, and quickly recoup their investment. His work was used as the basis for a call for the state to incentivize innovatory activities of these firms.

It has been estimated that for every 10,000 compounds that investigated in the early drug discovery phase, 250 show enough promise to enter pre-clinical testing (Giovannetti and Morrison, 2000; PhRMA, 2008). Of these, 5 compounds survive to enter Phase I, II and III clinical trials and only one of these is likely to result in an FDA approved drug. Finally, of all FDA approved drugs, relatively few eventually generate even enough revenue to cover their development costs.

The industry changed again with the emergence of biotechnology in the 1970s (Galambos & Sturchio 1998). While previous changes in drug discovery had emerged from the large pharmaceutical firms, the biotechnology revolution was led by a number of smaller startup firms. This and other changes to R&D moved drug discovery towards a more targeted approach that did not necessarily favor large R&D operations. In fact, Cockburn & Henderson (2001) showed that large firm size was not an advantage in R&D, while competence in the use of recombinant DNA (a type of biotech) was an advantage. Munos (2009) shows that during this period, the number of pharmaceutical firms increased rapidly, further suggesting that this change in technology resulted in a major structural change in R&D.

In summary, the current structure of R&D in the pharmaceutical industry does not appear to favor large-scale R&D operations. Innovation in the global pharmaceutical industry comes from a range of firms, operating at different points of the innovation funnel. Large numbers of small, specialized firms focus on early stage drug

development. Large pharmaceutical firms have their own drug development operations, but also cooperate with smaller firms as well as with organizations focused on more basic research like universities. Nelson and Winter (1982) argued that small firms have superior capabilities in “search” or radical innovation, while large firms have superiority in “routinized” or incremental innovation. More specifically, a large firm may wish to delay introduction of new products to avoid cannibalizing extant revenue streams (Scherer 1965), while small firms have little fear of cannibalization and thus may undertake highly original projects (*variation*) that thrive in unstructured environments. The small firms that survive have projects that have progressed to significantly lower levels of uncertainty. Large firms are able to acquire or partner with the survivors that best fit their own creative objectives (*selection*). The outcome of this joint creative process results in an outcome that is successful if the market accepts it (*retention*).

We argue that large firms’ advantage comes in the “selection” and “retention” stages of the innovation process. Large firms may have a substantial advantage in the commercialization of the drugs that emerge from R&D, such that only a few very large firms are able to create a blockbuster drug. This type of industry structure is akin to “creative industries” like movies, as analyzed by Caves (2000).

The “bureaucratized” model of incremental innovation in big pharmaceutical firms led to a larger and larger proportion of returns emanating from a smaller and smaller set of drugs – a highly skew distribution of market outcomes (Manning et al, 2005). This resulted in a model of drug development, wherein big pharmaceutical firms reap the bulk of their profits from a very set of “blockbuster” drugs (Cutler, 2007). This

model of high uncertainty and highly skew revenue and profit distributions has much in common with the production of cultural products like movies, with features like the “nobody knows principle”, the “curse of the superstar”, the “angel's nightmare” and the instability of profit (De Vany and Walls, 2004). This is the position of scholars like Howkins (2001).

Several properties of creative industries relate specifically to the phenomenon we address in this paper—that blockbusters emerge from a very small set of firms. Specifically, the industry combines time constraints (in the form of the patent cliff and first-mover advantage) with considerable demand uncertainty (consumers’ reactions to a product are not well-known beforehand). Additionally, as noted by Berndt *et al.* (2001), new pharmaceuticals show positive externalities in adoption—greater use of a novel drug results in greater acceptance of the drug as safe and effective. This could lead to another property noted by Caves (2000), that small differences in quality may lead to large differences in market share.

The combination of demand uncertainty and the need for rapid diffusion and adoption is likely to favor organizations with the greatest marketing reach. A large-scale marketing operation will be able to more rapidly disseminate information about a new drug, which in turn encourages its acceptance. Larger organizations will also be able to absorb the risk inherent in the high failure rate of investigated compounds and the inability of any firm to determine *a priori* which drug will become a blockbuster. This would explain two patterns identified in previous literature: the high degree of licensing

identified by Danzon *et al.* (2005), and the positive association between firm size and the correlation between R&D intensity and future earnings (Ciftci & Cready 2011).

The importance of scale in commercialization operations also has implications for the analysis of mergers in the pharmaceutical industry. Both Munos (2009) and Grabowski & Kyle (2008) note that mergers in the industry do not increase R&D productivity. However, if scale is important in commercialization, mergers may create organizations that are better able to extract revenues from existing pipelines.

In the remainder of the paper, we provide evidence that scale is necessary in producing a blockbuster drug. Our main contribution is to show that the scale required is considerable: almost all blockbuster drugs were either developed by a top-12 pharmaceutical firm or licensed to a top-12 firm. Only rarely does a blockbuster drug emerge from a smaller firm without licensing.

- a. 'Nobody knows' principle: Demand uncertainty exists because the consumers' reaction to a product are neither known beforehand, nor easily understood afterward. *Ex ante and ex post we don't know which of a class of drugs is the blockbuster.*
- b. Art for art's sake: Workers care about originality, technical and professional skill, harmony, etc. of creative goods and are willing to settle for lower wages than offered by 'humdrum' jobs.

- c. Infinite variety: Products are differentiated by quality and uniqueness; each product is a distinct combination of inputs leading to infinite variety options. This may be seen in works of creative writing, whether poetry, novel, screenplays or otherwise. Similarly in the pharmaceutical industry, each drug has a unique biochemistry.
- d. A list/B list: Skills are vertically differentiated. Artists are ranked on their skills, originality, and proficiency in creative processes and/or products. Small differences in skills and talent may yield huge differences in (financial) success. Similarly,
- e. Time flies: When coordinating complex projects with diversely skilled inputs, time is of the essence. Hence firms rush to patent intellectual property and try to be first to market in any new class of drugs, since the first drug typically garners the largest market share.
- f. *Ars longa*: The industry is heavily reliant on durable intellectual property, since this is the basis upon which firms are able to collect rents.

Blockbuster drug database

While the case studies of Actos, Plavix, and Lipitor explore contextual histories of each drug's commercialization path, pulling our analysis back to the entire population of blockbuster drugs gives a perspective on how pervasive the movement of knowledge is. We have assembled a list of all blockbuster pharmaceutical drugs from 1980 to 2010 and traced the shifts in knowledge control over the life of each product². As with the case

² Note: for this paper, we only consider pharmaceutical innovations, and not those from biotechnology.

study analysis, we define blockbuster drugs as those that reached annual global revenue of greater than \$1 billion (based on constant 2005 dollars) in their peak sales years (Munos, 2009; Lazonick and Tulum, 2011). Pharmaceutical sales tend to build over time, and generally peak just before patent exclusivity expires (See Figures 1-3). We therefore use global sales data from the final five years of a drug's patent protection as a proxy for peak sales, to identify which drugs achieve blockbuster status. Using this filter, we examined a sample of annual reports of every large pharmaceutical firm from the past three decades to identify candidate drugs. Consistent with Munos (2009), we use the database *EvaluatePharma* to gather sales data. Overall, we identified 121 blockbuster drugs, which can be found in Table 1.

To trace the control of a drug's core innovation, we have relied on three sources of data. First, we start with the approval of new drugs by the U.S. *Food and Drug Administration* (FDA). The FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, or *Orange Book*, provides information on when a new molecular entity (NME) is approved, and the core patent underlying the innovation. Second, we use the patent data to identify the date of invention and the original assignee. Third, we use both the licensing data from *Pharmaprojects* (Dunlap *et al*, 2010) and company annual reports to follow the movement of knowledge. This may take the form of licensing, sub-licensing, acquisitions, mergers, or a combination thereof. If the firm identified as marketing and selling the drug during the period in our peak sales data matches that of the innovating firm, then we classify drugs as having been commercialized internally.

For the purposes of analysis, we separated pharmaceutical firms into “major” and “non-major” firms. We considered a firm to be a “major” firm in a particular year if it ranked among the top 12 pharmaceutical firms on the *Fortune 500/International 500* list in that year. For example, we noted in the case studies that when Sanofi licensed Plavix to Bristol Myers Squibb, Sanofi was a relatively small player in the industry, with little experience in commercializing breakthrough drugs. We therefore classified the Plavix agreement as a transfer from a non-major innovator to a major commercializing firm. Sanofi has since merged with Aventis and become a major.

Results

Our population of blockbuster drugs demonstrates that these drugs originate from many sources, but are commercialized through a small set of “major” firms. **Table 1** contains a summary of the relevant figures from our database. Of the population of 121 blockbuster drugs, 87.6% were ultimately commercialized by a “major” firm. Major firms not only end up marketing the vast majority of blockbuster drugs, but they generate higher revenue: drugs marketed by major firms had average late-stage annual revenue of \$2.385 billion, compared to \$1.973 billion for non-major firms. Both licensing and acquisitions are prominent mechanism for the transfer and eventual commercialization of knowledge. Nearly 25% of all blockbuster drugs that were discovered at non-major firms and commercialized by majors were transferred via licensing. 37% of all blockbusters were transferred via merger or acquisition, suggesting that either knowledge portfolios were transferred or that some residual capabilities within the originating firm were of

value to the commercializing firm. Only one drug (Tarceva) was acquired as a standalone entity, and the transaction was part of a broader divestiture related to the Pfizer-Warner Lambert deal. Another five drugs came from institutional sources, such as universities, which did not possess *any* commercialization capabilities. Taken together, our data suggests that while there are many sources of innovation, only a few firms can commercialize breakthrough drugs to the extent that blockbuster rents are earned.

Commercializing firms face both product and market uncertainty when choosing which drugs to acquire or license. However, the further that a drug moves along the path of clinical trials, the greater the probability of its approval and launch. The timing of acquisitions and licensing deals is therefore of interest with respect to our analysis of blockbuster drugs. The pursuit of knowledge prior to patenting is likely to have fewer transfer mechanisms. However, because early stage knowledge may be more tacit, it is also likely be more difficult to value. With this in mind, we focus our analysis on the timing of licensing and acquisitions *after* the knowledge has been patented. In the population of blockbuster drugs out-licensed by the originating firm, 43% were in later stages of development or post-launch.

Given that the vast majority of blockbuster drugs were commercialized by major firms, an exploration of which firms were significant players is warranted. **Table 2** contains the list of so-called major firms, and the periods in which they had attained this status. It can be seen from this list that different majors pursue different portfolio strategies with respect to blockbuster drugs. Pfizer has acquired eleven blockbuster drugs,

while in-licensing three and developing three. Eli Lilly and Merck have retained a focus on internal development, while GlaxoSmithKline has exclusively growth out of mergers and acquisitions. Bristol-Myers Squibb on the other hand, has relied heavily on licensing. Others have adopted more balanced approaches.

What the data discussed above show is an imbalance between the *sources* of pharmaceutical innovation and those firms that *commercialize* that innovation. Blockbuster drugs have come from major firms, non-major firms, and institutions. As the Lipitor case showed, discovery is often serendipitous. However, the capabilities required to generate blockbuster revenue are the scarce resource in the pharmaceutical industry.

The Actos, Plavix, and Lipitor cases all saw firms positioning to gain additional rents from blockbuster drugs late into their patent exclusivity. As Figures 1-3 show, the sales period of a blockbuster drug is short and punctuated. Therefore, the moves to extract additional rents from the final few years of a drug's exclusivity are non-trivial. We observe similar patterns in our broader database, with many firm acquisitions coinciding with the later stages of blockbuster drugs' lives. To this extent, major firms are willing to forgo substantially all of the product *and* market risk in order to apply superior commercialization capabilities. It is at this stage that we observe vigorous legal defenses against early generic infringement, applications for pediatric exclusivity, delivery mechanism innovation, and cross-indication drug combinations (such as Lipitor and Norvasc to form Caduet).

Blockbuster Drug Case Histories: Lipitor, Plavix, and Actos

Lipitor

Originating Firm: Warner Lambert

In early 1990s, Warner Lambert was diversified firm with interests in a variety of confectionery and consumer health categories, in addition to pharmaceuticals. Portfolio brands included Visine, Listerine, and Schick Tracer (Simons, 2003). Pharmaceuticals were not the primary focus of the firm: 67% of Warner Lambert's revenue and 70% of its profits came from non-prescription products in 1991 (Weber, 1991). The Parke Davis division had developed a series of pharmaceutical innovations since its 1970 acquisition, however only one drug, Lopid was anywhere near blockbuster status by 1991. It wasn't until Lipitor launched that the Parke Davis unit gained some degree of prominence within the organization. A Warner Lambert annual report from 1997 noted that Parke-Davis had "returned to the forefront of the global pharmaceutical industry" on the back of Lipitor (Warner Lambert, 1998).

Prior to the Lipitor launch, Warner Lambert possessed limited experience in commercializing breakthrough pharmaceutical innovations. The implications of this inexperience would soon become clear, however. The details of the Lipitor story are outlined below, and demonstrate a movement of knowledge from non-major pharmaceutical player to a major. A parallel story contributes additional emphasis. In 1995, Warner Lambert in-licensed Rezulin, an anti-diabetes drug (Warner Lambert, 1998). The drug was rushed to market in the United States and ultimately withdrawn, due

to safety concerns (Hazaray, 2007). Two new drugs, Lyrica and Neurontin, were in the pipeline at that time, and ultimately reached blockbuster status under Pfizer's ownership.

Commercializing Firm: Pfizer

Unlike Warner Lambert, Pfizer had an established track record of the discovery, development, and commercialization of breakthrough innovation in the pharmaceutical industry. One of Pfizer's early successes actually came from what may have been termed an early generic drug market: penicillin. In the 1950s, Pfizer released Terramycin, an unpatented antibiotic, and competed on the basis of price (Miller, 1967). It wasn't until the 1980s that Pfizer truly set out of the path of pharmaceutical research and commercialization. 1982 marked the launch of Feldene, an arthritis drug that had been patented a decade earlier (U.S. Patent 3,591,584). Feldene was Pfizer's first modern near-blockbuster, and it served notice to the company's leadership that pharmaceutical R&D could be a going concern (Lombardino, 2000). Other blockbuster drugs emerged in Pfizer's pipeline in the 1980s and became blockbusters, including Zoloft, Norvasc, and Viagra. Zyrtec was in-licensed from UCB Belgium in 1987 and approved by the FDA in 1995.

At the time that Lipitor was progressing through clinical trials at Warner Lambert, Pfizer had amassed a significant amount of experience commercializing blockbuster drugs. While many of the drugs had emerged from the traditional model of research and development, Pfizer had also engaged successfully with UCB in bringing Zyrtec to the U.S.. The significance of the pipeline of drugs at the time of the Lipitor deal cannot be

understated: Pfizer was in the process of scaling up to bring at least four other blockbuster drugs to market at roughly the same time: a rarity by any standard in the pharmaceutical industry.

Lipitor: Discovery, Development, and Commercialization

In 1985, Warner Lambert's Bruce Roth had discovered atorvastatin, which became Lipitor (Li, 2006). Atorvastatin, as with its statin predecessors, was effective in lowering cholesterol. As a second generation of statin, it differed from earlier forms in that it was synthetically derived (Li, 2006). Initially, it was just as effective as Merck's lovastatin (trade name: Mevacor), and Roth wasn't sure that he had developed anything more than a decent imitation (Simons, 2003). Lipitor went into clinical trials, and Warner-Lambert worked on its market projections and distribution plans. In 1987 the Lipitor project was nearly cancelled (Simons, 2003), with three other statins (Zocor, Pravachol, Mevacor) having launched already and Merck (Mevacor) holding a commanding market share (Li, 2006). Even second-generation statins were in development, with Fluvastatin (Sandoz) achieving patent approval in 1988 (U.S. Patent No. 4,739,073). Despite the developing statin market, testing moved forward at Warner Lambert. As testing progressed from animals to humans, Roth realized that what made this drug unique was its remarkable efficiency (Li, 2006): the lowest dose of Lipitor was more effective than the highest dose its in-market competitors (Simons, 2003). The patent application for Lipitor (atorvastatin) was filed in 1987, and granted in 1989.

The challenges that Warner Lambert faced did not disappear with the successful testing of Lipitor in early clinical trials, however. Bruce Roth, despite having synthesized the drug, did not have a process developed to manufacture it (Simons, 2003). In 1996, as the drug was nearing the end of clinical trials, Warner Lambert struck a marketing agreement with Pfizer, seeking to leverage the distribution channels of a much larger firm (Dunlap *et al*, 2010). Lipitor was approved by the FDA in December of 1996, and launched three months later in the U.S. (Warner Lambert, 2000). Lipitor was licensed to Yamanouchi in early 1997 (Dunlap *et al*, 2010), and subsequently launched in the Japanese market in 2000. Other licensing agreements were struck over the next five years to cover the markets of Spain, Argentina, India, South Korea, and Italy (Dunlap *et al*, 2010), however Pfizer retained a significant portion of global distribution for itself.

At the time of launch, both firms did not quite know the extent to which Lipitor would be a success. Initial projections of the marketing alliance suggested that Lipitor would generate \$300 million in worldwide revenue (Li, 2006). Pfizer added the key positioning argument to help market Lipitor to the medical community: its relative efficiency allowed doctors to prescribe lower overall doses (Simons, 2003). Within the first year on launch, Lipitor had reached 18% market share (Simons, 2003). Both Warner Lambert and Pfizer were enjoying the success of what had quickly become a blockbuster drug. In November of 1999, Warner Lambert agreed to be acquired by American Home Products Corporation (AHP) (Warner Lambert, 2001). By this time, Pfizer had a clearer picture of what Lipitor could be, and sought to acquire Warner Lambert for itself. In February 2000, some three months after the AHP deal was announced, Warner Lambert

canceled the AHP deal, incurring a \$1.8 billion penalty (Warner Lambert, 2001). On the same day, Pfizer announced that it was acquiring Warner Lambert in its entirety for \$90 billion (Simons, 2003).

With Warner Lambert and Lipitor under its control and a little more than a decade of patent protection left, Pfizer moved extract as much revenue as it could from its new acquisition. Maximizing global revenue from Lipitor was the company's top priority (Pfizer, 2003). Some strategic moves that followed were defensive in nature, and others were more aggressive. Pfizer applied for patent re-issues to extend the period of exclusivity (Boston Globe, 2009), agreements with Ranbaxy ensured limited competition for initial period after the patent expired (Matsuyama, 2011). Similarly, Pfizer successfully sought a pediatric extension on Lipitor to gain an additional six months of exclusivity (Dunlap *et al*, 2010). Other moves leveraged Pfizer's broad knowledge network to add value in the delivery of multiple drugs. In 2004, it combined its hypertension drug Norvasc with Lipitor to create Caduet, a singular product to treat multiple related indications (Li, 2006). Once the patent cliff appeared, revenues dropped off. By early 2012, Pfizer was beginning to phase out all Lipitor marketing efforts.

Plavix

Originating Firm: Sanofi

The Sanofi of the late 1980s presents a much different firm than the Sanofi of 2012. Sanofi was founded in 1973 as part of the French state-owned Elf Aquitaine, grew via acquisition over the subsequent three and a half decades (Anwar, 2008). Up until the

late 1980s however, Sanofi had only discovered, developed, and commercialized one blockbuster drug. Ticlid, an anti-platelet medication, was patented in 1982 (U.S. Patent 4,321,266) released in markets other than the U.S. in 1978 (Anwar, 2008). The FDA eventually approved the drug in 1991 (Jacobsen, 2004). Despite its limited overall experience in commercializing breakthrough innovation, Sanofi did have two strong candidates in the pipeline: Plavix and Avapro.

Commercializing Firm: Bristol-Myers Squibb

Bristol-Myers approached the late 1980s with a strong background in commercializing new products, but with a weak research and development pipeline. A series of cancer drugs, including Blenoxane and Mutamycin, was discovered and developed in the 1970s, and by 1991, had generated \$1.2 billion in aggregate for the company (Bristol-Myers Squibb, 1992). In 1989, a \$12 billion deal saw Bristol-Myers merge with Squibb, a competing firm with a much deeper research expertise and stronger overall drug pipeline (Freudenheim, 1989). Two blockbusters in particular stand out. Capoten, a blood pressure drug, was patented by Squibb in 1977, and approved by the FDA in 1981. Pravachol, a cholesterol-lowering drug, was patented post-merger in 1991 and approved by the FDA the same year. The newly formed Bristol-Myers Squibb introduced one drug via licensing 1992: Taxol. Taxol was an unpatented drug that was licensed from the National Cancer Institute and became the merged company's first blockbuster (Chabner and Roberts Jr., 2005). By the time that the Plavix and Avapro deals emerged, Bristol-Myers Squibb had established a track record of commercializing

three blockbuster drugs, as well as a portfolio of cancer treatments that together, breached the \$1 billion threshold.

Plavix: Discovery, Development, and Commercialization

Plavix is a drug that treats atherothrombosis, a common link between stroke, heart attack, and vascular death (Sanofi, 1998). Prior to the discovery of clopidogrel, the primary treatment for this indication was Aspirin, which was known to be effective, but not very efficient (Sanofi, 1998). Other anti-platelet drugs have since hit the market, but Plavix's efficiency has ensured a dominant market position for a substantial proportion of its patent-protected life.

The initial patent for clopidogrel was granted in 1985, to a scientist named Daniel Aubert. Subsequent patents for extensions or manufacturing processes being granted in 1989, 1996, 2002, and 2003. Aubert worked for what was Elf-Sanofi, which at the time was a subsidiary of the state-held chemical giant Elf Aquitaine (Montalban and Leaver, 2010). Plavix was fast-tracked through the FDA approval process, on account of its therapeutic need in the market (Sanofi, 1998). Plavix was one of two drugs from the Sanofi pipeline that was approved by the FDA in 1997: Irbesartin (marketed as Avapro in the U.S., and Aprovel in the rest of the world) was approved at the same time (Sanofi, 1998). This placed enormous pressure on Sanofi to commercialize both drugs globally and maximize revenue under the temporary monopoly afforded by the underlying patents. Thus, Sanofi sought partners to bring clopidogrel and irbesartin to market.

The first clopidogrel licensing agreement undertaken by Sanofi was not, in fact, in the U.S. The Japanese rights to Plavix were initially licensed to Daiichi Seiyaku in 1990 (Dunlap et al, 2010), and spent the next several years in clinical trials. However, when Daiichi Seiyaku merged with Sankyo in 2005 to form Daiichi Sankyo, Plavix was in conflict with a Sankyo competitor, Effient (Thomson Reuters, 2011). As a result, the licensed were discontinued that year, and Plavix ended up being launched by Sanofi itself (Dunlap et al, 2010).

Given the speed and breadth with which Sanofi sought to bring Plavix to market, the U.S. was a key region for the company to have in order. However, it was a market in which Sanofi, by its own admission, lacked distribution and marketing capabilities (Sanofi, 1998). As a result, Sanofi signed a development and marketing agreement with Bristol-Myers Squibb (BMS) in 1993 (Dunlap *et al*, 2010). The agreement was for BMS to develop, market, and sell both clopidogrel (as Plavix) and irbesartan (as Avapro) in the U.S. (Sanofi, 1998). Under the terms of the agreement, Sanofi would receive a 15% royalty on total U.S. sales, in addition to a share of the profits that was proportional to relative marketing expenditures (Moore, 1996). Part of the development agreement was to share the cost of clinical trials in the United States. Clinical trials for Plavix were among the largest in history, costing more than \$100 million and testing nearly 20,000 patients (Moore, 1996). This arrangement allowed Sanofi to incur less of the product development risk, while absorbing none of the market risk in the world's largest pharmaceutical-consuming country: the United States.

Sanofi's role in the growth of Plavix/Iscover around the world gave it the resources to pursue greater scale and scope. The decade after the Plavix launch in the U.S saw Sanofi involved in two mergers of significant size. In 1999, Sanofi merged with its cross-town rival Sythelabo, which had been owned by L'Oreal (Sanofi-Sythelabo, 2001). In its pursuit of "major" status within the pharmaceutical industry, Sanofi finally cracked the top 20 global pharmaceutical firms, by market capitalization, in 2002 (Anwar, 2008). Then, in a bid to gain ever-greater scale, Sanofi-Sythelabo launched a hostile takeover attempt of Aventis in 2004. Sanofi-Sythelabo's initial takeover bid was comprised of a mix of stock and cash (Sanofi-Synthelabo, 2005). The resulting company would be the third largest pharmaceutical firm in the world. The newly formed Sanofi-Aventis soon believed it had the reach and capabilities to extract maximum revenue from Plavix in the U.S. market, despite the clock running out on patent protection. In 2007, Sanofi-Aventis made a takeover bid for Bristol Myers Squibb at a rumored value of \$28 per share (Pritchard, 2007). The deal ultimately fell through, purportedly on the inability of both parties to agree to a value on Plavix (Pritchard, 2007).

Actos

Originating Firm: Takeda

Takeda has long played the role of product specialist, primarily discovering drugs and licensing out the knowledge to a commercializing firm. Takeda was cognizant of its marketing and distribution limitations early on, and formed a beachhead in the United States in the form of a partnership. In 1977, Takeda formed a joint venture with Abbott Laboratories, which they called Takeda Abbott Pharmaceuticals (Ando, 2005). The focus

of this joint venture was drug development and marketing, with Takeda serving as the discovery engine (Ando, 2005). TAP's first near-blockbuster was Lupron, a prostate cancer drug, in 1985. It was followed by Prevacid, a blockbuster ulcer-treating acid-indigestion drug, in 1995 (Simon and Kotler, 2003). In both cases, Takeda was the patent holder, despite the TAP joint venture commercializing the drug. A third drug, Atacand, was discovered internally at Takeda and subsequently out-licensed to Astra (the Swedish precursor to AstraZeneca) in 1995 (Dunlap et al, 2010).

Commercializing Firm: Eli Lilly

Eli Lilly had commercialized nine blockbuster drugs by the time it in-licensed the Actos knowledge from Takeda. While Lilly's history extends to the late 1800s, its first pseudo-blockbuster drug was the antibiotic Erythromycin, which was developed internally and patented in 1953 (U.S. Patent No. 2,653,899). Lilly occasionally drew on external knowledge to commercialize drugs, relying on Stanford University to discover Humulin and Princeton University to discover Alimta. However, Prozac, Zyprexa, and others were discovered and commercialized internally.

Actos: Discovery, Development, and Commercialization

Actos is an anti-diabetes drug that improves insulin sensitivity and reduces blood glucose levels in patients with Type II diabetes (Takeda Pharmaceutical Company, 2009). The first class of Type II diabetes drug to emerge was Sulphonylureas, which induced higher levels of insulin production (Takeda vs. Mylan, 2006). However, because the condition is one of insulin efficiency, this class was inherently flawed.

Takeda was not alone in developing Actos. In the early 1980s it was engaged in a research partnership with the American firm Upjohn (which was acquired by Pharmacia in 1995 and ultimately Pfizer in 2003 (Pfizer, 2004)). Takeda and Upjohn were involved in the testing of Ciglitazone, in an effort to find a similar compound that was safe for human consumption (Takeda vs. Mylan, 2006). In September 1982, Takeda Chief Scientist Kanji Meguro synthesized Pioglitazone, which ultimately became Actos (Takeda vs. Mylan, 2006). Meguro is listed as the inventor on Actos' key patent (U.S. Patent No. 4,687,777), which was filed in 1986 and granted a year later. Upjohn, lacking confidence in the initial Pioglitazone test results, pulled out of the research agreement with Takeda before Actos entered into clinical trials (Takeda vs. Mylan, 2006).

Type II diabetes medication benefited from a new class of drug, introduced in the 1990s, called thiazolidinediones, or TZDs (Takeda vs. Mylan, 2006). TZDs, which enhance the uptake of insulin at the muscular level, were initially discovered by Takeda Pharmaceuticals in the 1970s (Takeda vs. Mylan, 2006). Takeda's initial discovery was a compound called Ciglitazone, which was first synthesized in 1978 (Takeda vs. Mylan, 2006), and patented in 1979 (U.S. Patent No. 4,287,200). Ciglitazone was never deemed safe for human use, but served as the basis for additional drug research in the TZD field. In the United States, Pfizer was the first to market with a TZD drug, launching Rezulin in 1997. GlaxoSmithKline launched Avandia in May of 1999, with Takeda following with Actos two months later (Takeda vs. Mylan, 2006). Pfizer pulled Rezulin from the market

in 2000 over safety concerns, leaving Avandia and Actos with roughly the same market share in a highly concentrated segment (Takeda vs. Mylan, 2006).

Actos was marketed outside of the TAP arrangement with Abbott Laboratories. Takeda pursued an agreement with Eli Lilly in 1998 to market Actos in the U.S. and Canada, where it launched a year later (Dunlap *et al*, 2010). Per the original deal, the marketing arrangement with Lilly was terminated in 2006, leaving Takeda some six years to market Actos itself in the United States before the patent expired (Smith, 2005). Lilly was not the only licensing deal that Takeda pursued for Actos. It connected with Abbott Laboratories in 2000 to market the drug in Argentina, Brazil, Chile, Colombia, Ecuador, Paraguay, Peru, Uruguay, and Venezuela, and brought in Pfizer to market to the Chinese market in 2009 (Dunlap *et al*, 2010). Takeda and Danish firm Novo Nordisk struck an agreement in 1999 to combine diabetes drugs to be marketed in the Japanese market (Dunlap *et al*, 2010). Takeda markets Actos in-house in other parts of Asia (including Japan), and Europe (Takeda Pharmaceutical Company, 2009).

Takeda's run with Actos did not come to a smooth conclusion: in mid 2011, it was discovered that Actos could cause bladder cancer (Feeley, 2011). By the end of the year, as many as 10,000 lawsuits were being prepared, and the drug was being pulled from shelves in Germany and France (Feeley, 2011). While Lilly was involved in the ongoing legal proceedings (Feeley and Fisk, 2012), Takeda was unable to seek maximum market penetration in the final patent-protected years.

Conclusion

Our analysis shows that size is an advantage in the pharmaceutical industry. However, the advantage does not come from R&D capabilities—small firms are capable of producing highly innovative drugs. Instead, the advantage comes from the very large firms' ability to commercialize the new drug. It appears that only a few firms are capable of the large-scale marketing required to turn a major innovation into a blockbuster. Specifically, we showed that over the past thirty years, blockbuster drugs emerged from firms of varying sizes, but were funneled into a small number of paths to market dominance. Small- to medium-sized firms with major innovations either pursued licensing agreements with larger manufacturers, or were acquired by large manufacturers. Surprisingly, even relatively large firms pursued licensing agreements with the same very large manufacturers.

Our case studies showed that large firms' acquisition of the rights to market a major innovation could occur in several ways. In the case of Actos, the originator company, Takeda, engaged in a joint venture with Abbott Labs for the full duration of the drug's patent life. In the case of Lipitor, on the other hand, the patent owner Warner Lambert first entered into an alliance with Pfizer. Three years later, Pfizer acquired Warner Lambert, possibly due to concerns that Warner Lambert was engaged in talks with other companies over the licensing of Lipitor. Finally, in the case of Plavix, originator Sanofi entered into an alliance with Bristol-Myers Squibb because Sanofi lacked the capability to market the drug in the United States. Sanofi later merged with Synthelabo and Aventis to become the 3rd largest pharmaceutical company in the world.

At this scale, Sanofi had the capability to bring Plavix back in-house and attempted to buy BMS. While the particular paths taken were unique, each of our three case-study drugs shared a common thread in their histories: each was licensed to a much larger firm because the originator firm lacked the capability to market the drug. Our larger analysis of blockbuster drugs shows that this thread is common across blockbusters that originated with smaller firms. The largest firms appear to hold a significant advantage in commercialization—they are highly effective at extracting the value of innovative drugs.

With the anticipated end of the blockbuster era, several articles have questioned the financial viability of the major drug manufacturers. Our study suggests some qualified reasons for skepticism that the end of the blockbuster era will bring a major upheaval in the industry. Large firms' advantage in commercialization suggests that they may maintain their dominant position. Marketing of pharmaceuticals may move from broad-based to targeted approaches, but a company with a broad reach may still have an advantage in identifying markets for niche drugs and commercializing the drugs within those more narrow markets.

References

Amselem, A., Eloy, F., and Maffrand, J.P. 1982. U.S. Patent 4,321,266. Washington, DC: U.S. Patent and Trademark Office.

Ando, K. 2005. *Japanese Multinationals in Europe: A Comparison of the Automobile and Pharmaceutical Industries*. Edward Elgar: Cheltenham.

Arrow, K. 1962. Economic welfare and the allocation of resources for invention. Pp. 609-626 in *The Rate and Direction of Inventive Activity: Economic and Social Factors*, National Bureau of Economic Research: Princeton University Press.

Aubert, D. 1985. U.S. Patent No. 4,529,596. Washington, DC: U.S. Patent and Trademark Office.

Azoulay, P. 2002. Do pharmaceutical sales respond to scientific evidence? *Journal of Economics and Management Strategy* 11(4): 551-594.

Berndt, E.R., Pindyck, R.S. and Azoulay, P. 2003. Consumption externalities and diffusion in pharmaceutical markets: Antiulcer drugs. *Journal of Industrial Economics* 51(2): 243-270.

Bell, A.S., Brown, D., and Terrett, N.K. U.S. Patent 5,250,534. Washington, DC: U.S. Patent and Trademark Office.

Boston Globe. 2009. ***Pfizer wins extension of Lipitor patent***. Boston Globe (Boston.com). Accessed at http://www.boston.com/business/healthcare/articles/2009/01/07/pfizer_wins_extension_of_lipitor_patent/ on May 15th, 2012.

Bristol-Myers Squibb Company. 1992. Annual report 1991. Retrieved from EDGAR Online database: <http://www.sec.gov/edgar.shtml>.

Caves, R. 2000. *Creative Industries: Contracts between Art and Commerce*. Boston: Harvard University Press.

Chabner, B.A., and Roberts Jr., T.G. 2005. Chemotherapy and the war on cancer. ***Nature Reviews Cancer*, 5: 65-72.**

Chakrabarti, J.K., Hotten, T.M., and Tupper, D.E. 1993. U.S. Patent 5,229,382. Washington, DC: U.S. Patent and Trademark Office.

Chandler, A. 2005. *Shaping the Industrial Century: The Remarkable Story of the Evolution of the Modern Chemical and Pharmaceutical Industries*. Harvard University Press: Cambridge MA.

- Ciftci M. and Cready, W.M. 2011. Scale effects of R&D as reflected in earnings and returns. *Journal of Accounting and Economics* 52(1): 62-80.
- Cockburn I and Henderson K. 2001. Scale and scope in drug development: Unpacking the advantages of size in pharmaceutical research. *Journal of Health Economics* 20(6): 1033-1067.
- Cohen, S.N., and Boyer, H.W. 1980. U.S. Patent 4,237,224. Washington, DC: U.S. Patent and Trademark Office.
- Cooper, R.M. 1993. Legislative Patent Extensions. *Food & Drug Law Journal*, 48:59-63.
- Creger, P.L. 1972. U.S. Patent 3,674,836. Washington, DC: U.S. Patent and Trademark Office.
- Cutler, D. 2007. The demise of the blockbuster? *New England Journal of Medicine* 356: 1292-1293.
- Danzon, P.M.; Wang, Y.R.; and Wang, L. 2005. Productivity in pharmaceutical-biotechnology R&D: The role of experience and alliances. *Journal of Health Economics* 24 (2): 317-339.
- Davinson, E., and Wells, J.I. 1989. U.S. Patent 4,879,303. Washington, DC: U.S. Patent and Trademark Office.
- De Vany, A.S. and Walls, W.D. 2004. Motion picture profit, the stable Paretian hypothesis, and the curse of the superstar. *Journal of Economic Dynamics and Control*, 28(6): 1035-1057.
- Dunlap-Hinkler, D., Kotabe, M., and Mudambi, R. 2010. A story of breakthrough versus incremental innovation: corporate entrepreneurship in the global pharmaceutical industry. *Strategic Entrepreneurship Journal*, 4(2) 2010: 106-127.
- Falconi, M. 2012. Novartis profit hit by Diovan. *The Wall Street Journal*. <http://online.wsj.com/article/SB10001424052702303592404577363072539802622.html>, accessed 8/30/2012.
- Feeley, J. 2011. Takeda May Face 10,000 U.S. Suits Over Actos Cancer Claims. *Bloomberg Business Week* (1 December 2011). Accessed at <http://www.bloomberg.com/news/2011-12-01/takeda-may-face-10-000-u-s-suits-over-actos-cancer-claims.html> on August 24, 2012.

- Feeley, J., and Fisk, M.C. 2012. Takeda Actos Judge Names Lead Attorneys in Cancer Suits. *Bloomberg Business Week* (13 March 2012). Accessed at <http://www.businessweek.com/news/2012-03-13/takeda-actos-judge-names-lead-attorneys-in-u-dot-s-dot-bladder-cancer-lawsuits> on August 24, 2012.
- Freudenheim, M. \$12 Billion Merger Is Planned By Bristol-Myers and Squibb. *New York Times*, (28 July 1978): A1.
- Galambos, L. and Sewell, J.E. 1997. *Networks of Innovation: Vaccine Development at Merck, Sharp and Dohme, and Mulford, 1895-1995*. Cambridge University Press: Cambridge and New York.
- Galambos, L., and Sturchio, J. 1998. Pharmaceutical firms and the transition to biotechnology: A study in strategic innovation. *Business History Review* 72 (2): 250-278.
- Giovanetti G.T., and Morrison, S.W. 2000. *Convergence: The Biotechnology Industry Report*. Ernst & Young: Palo Alto, CA.
- Harrison C. 2011. The patent cliff steepens. *Nature Reviews Drug Discovery*, 10: 12-3.
- Hazaray, N.F. 2007. Do the Benefits Outweigh the Risks - The Legal, Business, and Ethical Ramifications of Pulling a Blockbuster Drug Off the Market. *Indiana Health Law Review*, 4: 115-150.
- Howkins, J. 2001. *The Creative Economy: How People Make Money From Ideas*, London: Penguin.
- Iizuka, T and Jin, G.Z. 2005. The effect of prescription drug advertising on doctor visits. *Journal of Economics and Management Strategy* 14(3): 701-727.
- Iizuka, T and Jin, G.Z. 2007. Direct to consumer advertising and prescription choice. *Journal of Industrial Economics* 55(4): 771.
- Jacobsen, A.K. 2004. Platelet ADP receptor antagonists: ticlopidine and clopidogrel. *Best Practice & Research Clinical Haematology*, 17(1): 55-64.
- Kawamatsu, Y., and Fujita, T. 1981 U.S. Patent 4,287,200. Washington, DC: U.S. Patent and Trademark Office.
- Kathawala, F.G. 1988 U.S. Patent 4,739,073. Washington, DC: U.S. Patent and Trademark Office.
- Lazonick, W., and Tulum, O. 2011. US biopharmaceutical finance and the sustainability of the biotech business model. *Research Policy*, 40: 1170-1187.

- Lee, J. 2003. Innovation and strategic divergence: an empirical study of the U.S. pharmaceutical industry from 1920 to 1960. *Management Science*, 49(2): 143-159.
- Li, J.J. 2006. *Laughing Gas, Viagra, and Lipitor: The Human Stories Behind the Drugs We Use*. Oxford University Press: New York, NY.
- Liu, Q. and Gupta, S. 2011. The impact of direct-to-consumer advertising of prescription drugs on physician visits and drug requests: Empirical findings and public policy implications. *International Journal of Research in Marketing* 28(3): 205-217.
- Lombardino, J.G. 1971. U.S. Patent 3,591,584. Washington, DC: U.S. Patent and Trademark Office.
- Lombardino, J.G. 2000. A brief history of Pfizer central research. *Bulletin for the History of Chemistry*, 25(1): 10-15.
- Manning, W.G., Basu, A. and Mullahy, J. 2005. Generalized modeling approaches to risk adjustment of skewed outcomes data. *Journal of Health Economics*, 24(3): 465-488.
- Mcguire, J.M. 1953. U.S. Patent 2,653,899. Washington, DC: U.S. Patent and Trademark Office.
- Meguro, K. 1987. U.S. Patent No. 4,687,777. Washington, DC: U.S. Patent and Trademark Office.
- Miller Jr., H.D. 1967. Patent license restrictions in the prescription drug industry. *Virginia Law Review*, 53(6): 1283-1312.
- Molloy, B.B., and Schmiegel, K.K. 1986. U.S. Patent 4,626,549. Washington, DC: U.S. Patent and Trademark Office.
- Munos, B. 2009. Lessons from 60 years of pharmaceutical innovation. *Nature Reviews Drug Discovery* 8: 959-968.
- Naka, T., Nishikawa, K., and Kato, T. 1993. U.S. Patent 5,196,444. Washington, DC: U.S. Patent and Trademark Office.
- Nelson, R. and Winter, S. 1982. *An Evolutionary Theory of Economic Change*. The Belknap Press of Harvard University Press: Cambridge MA.
- Nohara, A., and Maki, Y. 1986. U.S. Patent 4,628,098. Washington, DC: U.S. Patent and Trademark Office.
- Ondetti, M.A., and Cushman, D.W. 1977. U.S. Patent 4,046,889. Washington, DC: U.S. Patent and Trademark Office.

PhRMA. 2011 Pharmaceutical Industry Profile 2011. PhRMA website. Accessed at http://catalyst.phrma.org/wp-content/uploads/fromPhrma/phrma_profile_2011_final.pdf on December 7, 2012.

Pfizer Company. 2004. Annual report 2003. Retrieved from EDGAR Online database: <http://www.sec.gov/edgar.shtml>.

Roach, M., and Sauermann, H. 2010. A taste for science? PhD scientists' academic orientation and self-selection into research careers in industry. *Research Policy* 39 (3): 422-434.

Roth, B.D. 1987. U.S. Patent No. 4,681,893. Washington, DC: U.S. Patent and Trademark Office.

Sanofi. 1998. Annual report 1997. Retrieved from Mergent Online database.

Sanofi-Synthelabo. 2001. Annual report 2000. Retrieved from Mergent Online database.

Sanofi-Synthelabo. 2005. Annual report 2000. Retrieved from Mergent Online database.

Scherer, F. 1965. Corporate inventive output, profits and growth. *Journal of Political Economy*, 73(3): 290-297.

Schumpeter, J. 1942. *Capitalism, Socialism and Democracy*. New York: Harper and Row.

Simon, F., and Kotler, P. 2003. ***Building Global Biobrand: Taking Biotechnology to Market***. Free Press, Simon & Schuster Inc.: New York.

Simons, J. 2003. Pfizer's \$10 billion pill. *Fortune* (6 January 2003). Accessed at http://money.cnn.com/magazines/fortune/fortune_archive/2003/01/20/335643/index.htm on July 23, 2012.

Smith, A. 2005. Diabetes split could shake up market. CNN Money. Accessed at <http://money.cnn.com/2005/06/24/news/fortune500/actos/index.htm> on June 10, 2012.

Stern, S. 2004. Do scientists pay to be scientists? *Management Science*, 50(6): 835-853.

Takeda Pharmaceutical Company. 2010. Annual Report 2009. Accessed from Takeda Pharmaceutical website: http://www.takeda.com/pdf/usr/default/ar2009e_35417_1.pdf on September 9, 2012.

Takeda Chemical Industries, Ltd. vs. Mylan Laboratories, Inc. 2006. 417 F.Supp.2d 341.

Tartari, V. and Breschi, S. 2012. Set them free: scientists' evaluations of the benefits and costs of university–industry research collaboration. *Industrial and Corporate Change*, 21 (5):1117-1147.

Taylor, E.C. 1994. U.S. Patent No. 5,344,932. Washington, DC: U.S. Patent and Trademark Office.

Thomas, K. 2012. Pfizer races to reinvent itself. *The New York Times*. <http://www.nytimes.com/2012/05/02/business/pfizer-profit-declines-19-after-loss-of-lipitor-patent.html>, accessed 8/30/2012.

Weber, J. Curing Warner Lambert Before It Gets Sick. *Business Week* (8 December 1991). Accessed at <http://www.businessweek.com/stories/1991-12-08/curing-warner-lambert-before-it-gets-sick> on July 15, 2012.

Warner Lambert Company. 1994. Annual report 1993. Retrieved from EDGAR Online database: <http://www.sec.gov/edgar.shtml>.

Warner Lambert Company. 1998. Annual report 1997. Retrieved from EDGAR Online database: <http://www.sec.gov/edgar.shtml>.

Warner Lambert Company. 2001. Annual report 2000. Retrieved from EDGAR Online database: <http://www.sec.gov/edgar.shtml>.

Welch Jr., W.M., Harbert, C.A., Koe, K., and Kraska, A.R. 1985. U.S. Patent 4,536,518. Washington, DC: U.S. Patent and Trademark Office.

Yamamoto, M., Okada, H., Ogawa, Y., and Miyagawa, T. 1988. U.S. Patent 4,728,721. Washington, DC: U.S. Patent and Trademark Office.

Appendix

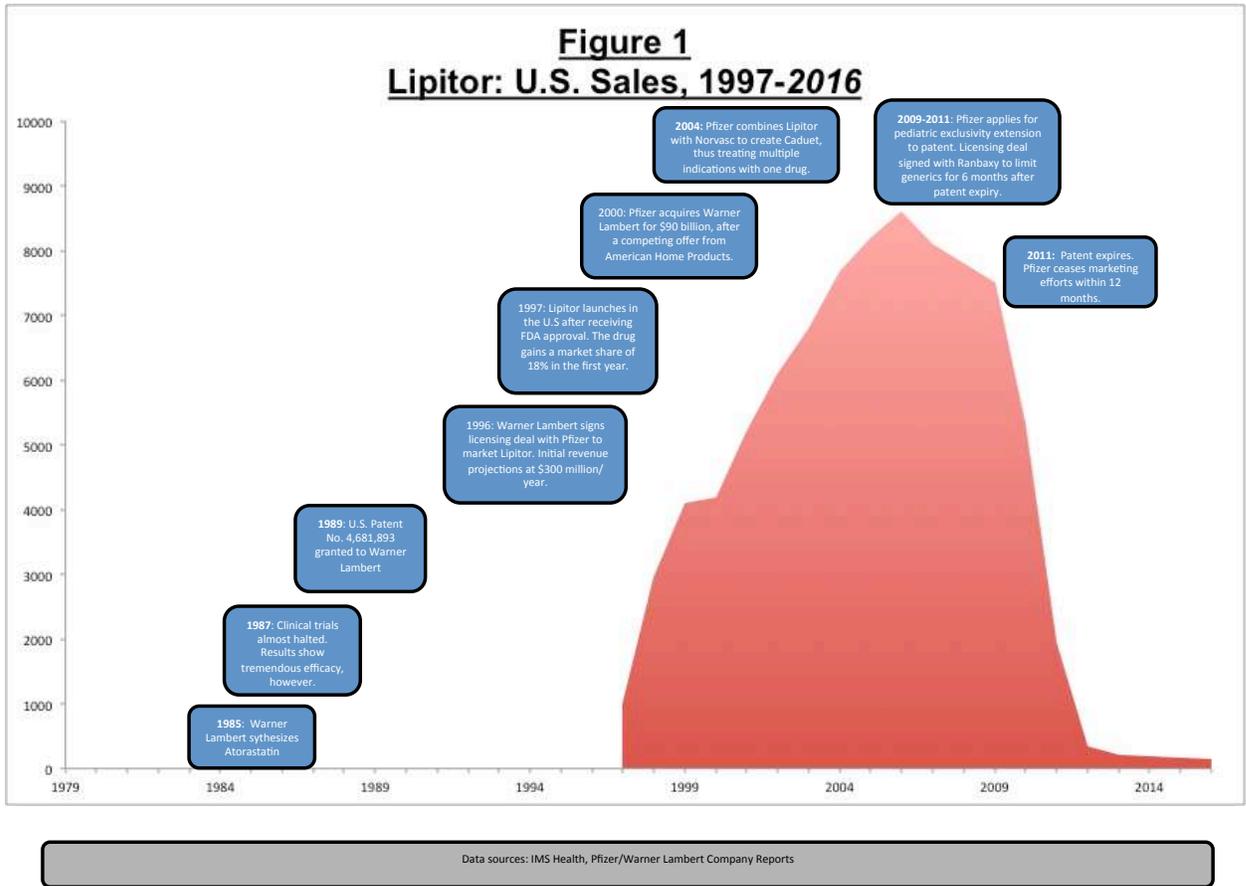
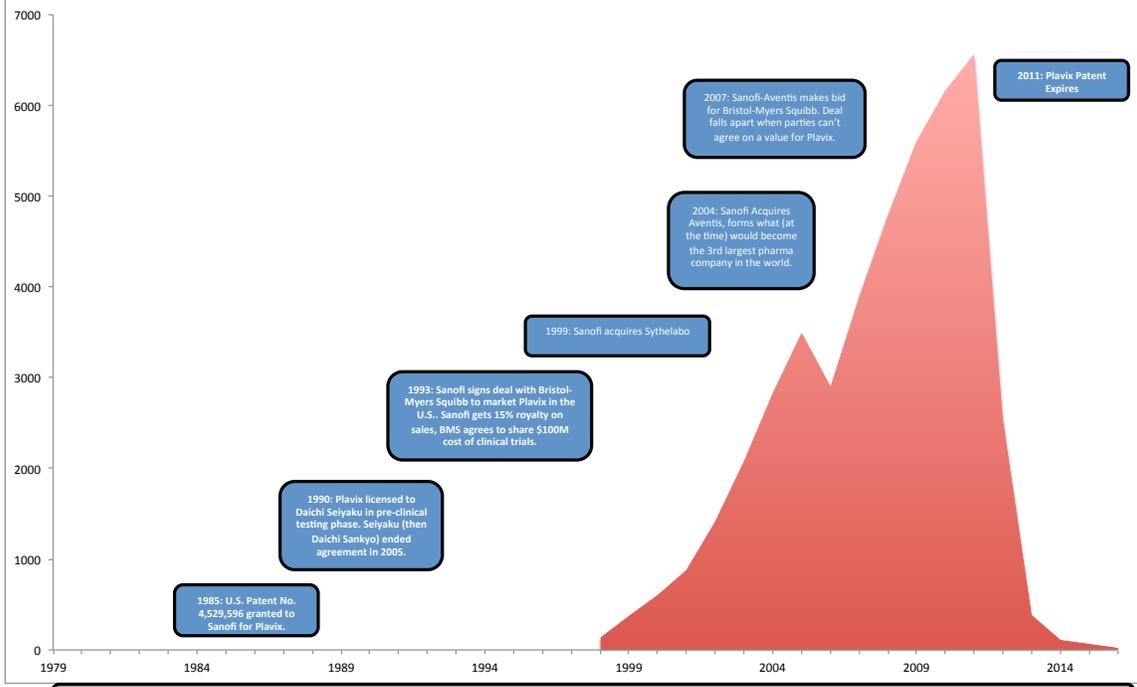


Figure 2: Plavix U.S. Sales, 1998-2016



Data sources: IMS Health, Bristol Myers Squibb/Sanofi Company Reports

Figure 3: Actos U.S. Sales, 1999-2016

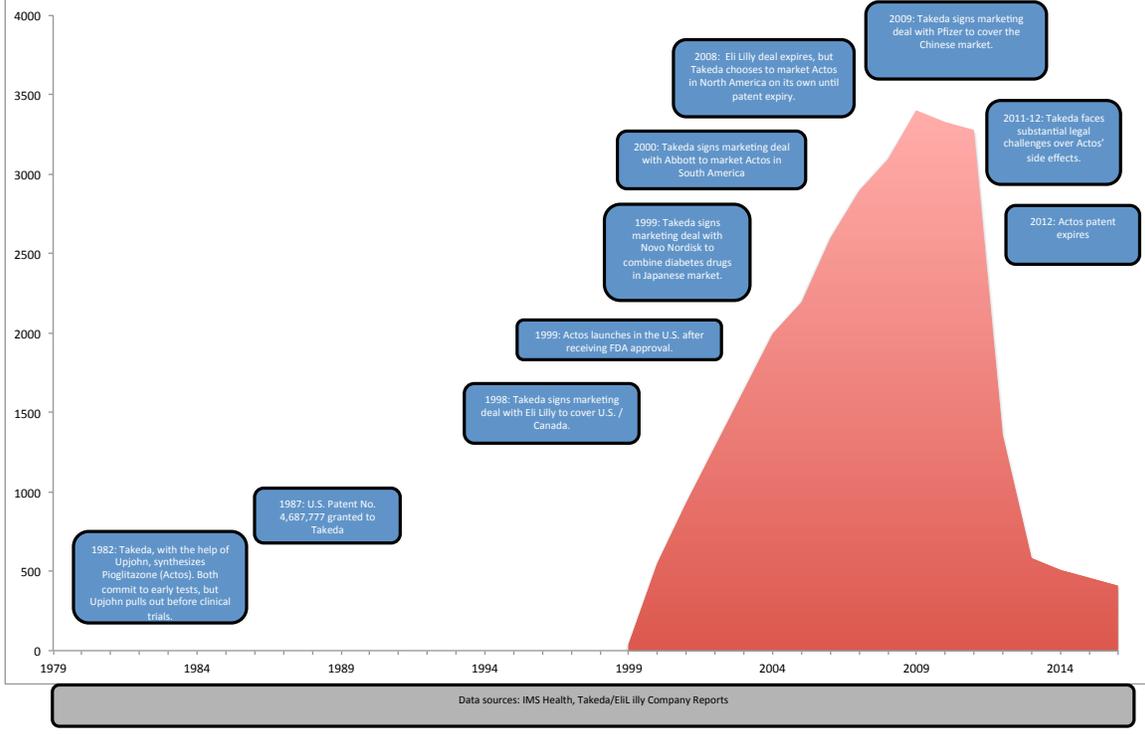


Table 1: Summary Statistics	
Total Number of Blockbuster Drugs	121
% of all blockbuster drugs marketed by a major firm	87.6%
% of all blockbuster drugs originated by a non-major that were licensed to a major	24.7%
% of all blockbuster drugs originated by a non-major that were acquired/merged into a major	37.1%
% of all blockbuster drugs originated by an academic institution/research center that were licensed to a major	4.1%
% of out-licensed drugs that were licensed prior to, or after launch	43.3%
% of out-licensed drugs that were licensed in early development	56.7%
Average late stage revenue for drugs marketed by a major	\$2,385 million
Average late stage revenue for drugs marketed by a non-major	\$1,973 million

Table 2: Blockbuster Drugs and Major Pharmaceutical Firms					
Firm	Years With Major Status Within Sample Period	Total Number of Blockbuster Drugs Marketed	Blockbuster Drugs Marketed via Merger/Acquisition	Blockbuster Drugs Marketed via Licensing	Blockbuster Drugs Marketed via Internal Development
Pfizer (incl. Wyeth)	1980-2012	17	11	3	3
Merck	1980-2012	15	3	4	9
GlaxoSmithKline	1995-2012	11	11		
Eli Lilly	1980-2012	11	2	3	6
Bristol-Myers Squibb	1989-2012	10	3	7	
AstraZeneca	1999-2012	9	7		2
Johnson & Johnson	1980-2012	8		4	4
Sanofi	2004-2012	7	4	3	
Novartis	1996-2012	6	6		
Abbott Laboratories	1980-2012	6		4	2
Roche	1980-2012	5	2	1	2
Bayer AG	1987-1994	1			1