Strategically Timing New Drug Introductions: Regulatory Constraints and the Role of Complementary Assets

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Abstract

We demonstrate the role regulatory constraints have on competition in the pharmaceutical industry. We develop theory and evidence on the strategic response of incumbent pharmaceutical firms to a change in their competitive environment—the increasing use by generic entrants of regulatory provisions in the Hatch-Waxman Act. Noting that generic firms are using the Paragraph IV certification to challenge branded products in the period between the loss of exclusivity and patent expiration, we theorize that a compression is occurring in incumbent firm payback periods, thus causing significant revenue losses in the pharmaceutical industry. By analyze pharmaceutical firms' responses to these challenges, our findings suggest that some firms have been able to strategically time the introduction of new products in order to protect revenue streams. Using a novel set of product level data we explore the determinants of firm performance at new product timing, including the importance that downstream complementary assets, internal research capabilities and patent strategy play in mounting a well-timed response. Because our data also allows us to determine the types of new products that are being strategically introduced, we find a higher dependence on reformulations and next-generation products both of which require underlying novel products, thus further emphasizing the importance of novel drug development.

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1.0 Introduction

How well are pharmaceutical firms able to manage new product introductions given a complex innovation environment and long time horizons? Our paper explores this question by using novel pharmaceutical-firm data, using a combination of actual new product introductions, their associated product sales data, and information about the firms' research pipelines and patents, including therapeutic classes. We add to these data information about the product market into which new products are being introduced. Our analysis demonstrates that pharmaceutical firms appear quite adept at timing their new product introductions to substitute for their loss of regulatory protection on other of the firm's products selling in the marketplace.

Our explanation for this behavior recognizes the strong incentives firms have to effectively manage complementary assets. Downstream complementary assets have been shown to be a significant factor in determining incumbent firms' success at bringing new products to market (Teece, 1986), no less so in the pharmaceutical industry. Several studies of firm innovation have shown that possessing these assets is advantageous, but previous research has tended to examine changes in the character of technology inputs, focusing on derivative measures of innovative success such as market share or overall firm profitability (Tripsas, 1997; Rothaermel, 2001). We, conversely, remain agnostic about the technology inputs into the process, and how firms manage their access to new technologies. Instead, our paper focuses upon firms' performance at timing their new product introductions.

Mismanaging the timing of new product introductions increases "adjustment costs" associated with the relevant complementary assets (Chan *et al*., 2007), while managing their timing may be particularly difficult given the technological complexity of pharmaceutical development, the cumbersome regulatory environment, and the long innovation lags. For example, new products take an average of ten to fifteen years to develop from initial discovery to final FDA approval (DiMasi, 2001). The downstream assets needed to bring products to market are costly to create and maintain, particularly when those assets are specific to the innovation (Williamson, 1985). Firms face strong incentives to ensure access to these complementary assets. Conversely, holding unproductive assets is costly, particularly if these

downstream assets tend to atrophy when not employed. Accordingly, the effective management of such assets, we suggest, has implications for firm performance in the innovating company.

Our analysis in this paper demonstrates that the timing of pharmaceutical firms' new product introduction is substantially explained by the loss of FDA-sanctioned market exclusivity on a current product, providing evidence that firms are effectively managing long and complex innovation processes. We demonstrate that the importance of this loss of exclusivity in these incumbent firms' strategic reaction is primarily due to two factors: the increased use Paragraph IV challenges under the Hatch-Waxman Act by generic entrants, and the resulting compression of product life cycles for the incumbent firms. To test the implications of these findings, we also analyze the determinants of firms' demonstrated ability to hit these targets, and find evidence that minimizing the "adjustment costs" of mismatched specialized complementary assets plays a primary role.

The pharmaceutical industry faces many challenges. For example, the industry is confronting pricing pressures, drug re-importation and public policy issues surrounding escalating health care costs. Generic competition has also increased (Saha *et al*., 2006) at the same time internal productivity has declined in terms of replacing existing branded products with new ones (Higgins and Rodriguez, 2006). Unlike other research-intensive industries, the pharmaceutical industry faces a dynamic regulatory environment. This is not surprising given the important public health implications of its products. However, regulation has created an environment that has facilitated the rise and expansion of the generic industry. This growth and expansion in the generic industry has created lower prices for consumers but it has also had an impact on the pharmaceutical industry. These impacts (and responses) are the focus of this paper.[1]

2.0 Regulation, patent challenges and firm strategy

2.1 Regulatory environment

[1] There are different aspects to the regulatory environment in which the pharmaceutical industry operates. Our focus is on the expansion of the generic industry as a result of Hatch-Waxman. Other research has focused on the role the regulatory environment has played on prices (Danzon and Chao, 2000a, 2000b), price controls (Kyle, 2007; Danzon *et al*., 2005; Lanjouw, 2005) and entry costs (Djankov *et al*., 2002).

The current regulatory environment can be traced to the passage of the Drug Price Competition and Patent Term Restoration Act, informally known as the "Hatch-Waxman Act," (Hatch-Waxman), in 1984. One of the hallmarks of Hatch-Waxman is its purported trade-off, both allowing expedited Food and Drug Administration (FDA) approval for generic entry while at the same time restoring to the incumbent its patent term for time used to obtain FDA approval (Grabowski, 2007).[2] This balance was deemed necessary to equalize two conflicting policy objectives: inducing pharmaceutical companies to continue novel drug research while simultaneously enabling generic firms to bring copies of these drugs to market quickly (Federal Trade Commission (FTC), 2002).

Introductions of generic drugs have risen dramatically since the passage of Hatch Waxman, especially since 1990 (Saha *et al*, 2006). This rise can be attributed to the use of the "bioequivalence" provisions within Hatch-Waxman.[3] Generic entrants are permitted to rely on previous FDA findings of efficacy and safety for an incumbent's brand-named drug, thereby by-passing costly clinical trials (FTC, 2002). Reiffen and Ward (2005) find that the cost of obtaining an Abbreviated New Drug Application (ANDA) had fallen to approximately one million dollars by the early 1990s. Moreover, the Congressional Budget Office (CBO) found that between 1989 and 1993 the average time to market after patent expiration was only one to three weeks, as compared against approximately three years prior to Hatch-Waxman (CBO, 1998).[4]

Important for our study are two provisions of Hatch-Waxman affecting the incumbent firm's ability to stave-off competition. The first is a requirement that a firm disclose for each new drug application (NDA) all of its patented technologies necessary to create the drug, by listing these in the FDA's Orange Book. The second is that, regardless of the strength of the firm's patents, every successful

[2] In a 1998 study the United States Congressional Budget Office (CBO) estimated for a sample of drugs a present value loss of 12 percent due to increased generic competition. This resulting loss exceeded the gain from the patent extensions (Grabowski, 2007).

[3] 21 U.S.C. § 355(j)(2)(A)(iv). Bioequivalence means that the rate and extent of absorption of the generic drug is not significantly different from the rate and extent of absorption of the listed drug when administered at the same dosage.

[4] This view focuses on the supply-side of the generic industry. There has also been a dramatic increase in demand due to the growth of managed care (PhRMA, 2001; Berndt, 2002).

NDA is given "market exclusivity" for a period of five years during which no generic firm may enter the market.[5] Hatch-Waxman created a floor of exclusivity to allow the incumbent to recoup some of its R&D costs, but this period is in general insufficiently long to recoup all these costs (Grabowski, 2007). After exclusivity ends, however, there is still a window of protection that lasts so long as the patents attached to the branded product are valid and can be used to prevent any entrant firm from infringing (by producing or selling). Because the U.S. patent term is now twenty-years from the date of filing, patent protection can protect the incumbent from generic entry substantially beyond Hatch-Waxman's exclusivity period.

We focus in this project on the loss of exclusivity protection by incumbents, and on the provisions of Hatch-Waxman that permit entrants to challenge them when such exclusivity ends but while patent protection still exists. Upon expiration of exclusivity, a generic entrant can seek to compete with the incumbent's branded product by filing an Abbreviated New Drug Application (ANDA) for approval of its generic drug. This ANDA must contain one of four "certifications" challenging each patent listed by the incumbent in the original NDA.[6] For purposes of this research project we will focus on the fourth allowable certification, the Paragraph IV or "Cert-IV" challenge. Using this challenge the generic entrant claims either that (1) the patent listed in the FDA Orange Book is invalid or (2) the ANDA does not infringe on the patent. A Paragraph IV challenge sets off a series of regulatory and legal actions starting with a 45 day clock in which the patent holder has an option to sue the generic applicant. Such a suit will trigger the grant of an automatic 30-month extension to exclusivity by the FDA. Absent a suit, the FDA may move to approve the ANDA immediately.

While the law and legal strategies associated with Paragraph IV challenges have been described in the literature (FTC, 2002; Bulow, 2004; Berndt *et al*, 2007a), our study is not focused on the legal

[5] There are additions to this time period for orphan (7 years) and pediatric drugs (6 months). Reformulations receive 3 years.

[6] Paragraph I certifications claim that the required patent information has not been filed; Paragraph II certifications claim the patent has expired; Paragraph III certifications claim the patent has not expired but will expire on a particular date; and, Paragraph IV certifications claim the patent is invalid or non-infringement by the generic entrant. Note, traditionally generic entrants have waited until patent expiration (versus loss of exclusivity) to file an ANDA with a Paragraph II or III certification. In contrast, a Paragraph IV certification challenges the incumbent's patents *prior* to their expiration.

maneuvering of firms. We instead take a different approach and focus on the affect these Paragraph IV challenges have on incumbent firms' management of their new product introductions. As we describe below, managing the R&D pipeline has been significantly altered by the advent of Paragraph IV challenges, a fact that is exacerbated by a sharp growth in the incidents of these challenges (Berndt *et al*, 2007a; Grabowski, 2007). By the year 2000, twenty percent of ANDA filings contained a Paragraph IV challenge compared to twelve percent during the 1990s overall (FTC, 2002).

Once the incumbent's 5-year exclusivity period has ended, generic firms are increasingly filing ANDA applications with Paragraph IV certifications.[7] More importantly, Grabowski (2004) and Scherer (2001) find that these challenges are beginning to take place earlier in the product life cycle, especially when the branded product is a "blockbuster" drug (Saha *et al*., 2006). A successful challenge frees the FDA to approve the generic drug notwithstanding some remaining term on the patents attached to the branded product. Hatch-Waxman provides a further incentive for generic firms to engage in such challenges because, if successful, the generic entrant enjoys a 180-day period as the exclusive generic provider (Siegel, 2004).

Recent evidence shows that Paragraph IV challenges have important economic impacts. Studying the outcomes of the 104 ANDA applications with Paragraph IV certifications, the FTC found that 75 of these applications had resulted in litigation (FTC, 2002). Of the 53 cases that had been resolved by the 2002 publishing of the study, 22 were resolved in the generic firm's favor, thus leading to the introduction of a generic product prior to the expiration of the incumbent's underlying patent protection.[8]

The economic impact to an incumbent firm of losing a Paragraph IV challenge may be significant. An example can be found in Merck's branded product Fosamax®, one of its products that were subject to a Paragraph IV challenge by the generic manufacturer Teva. Fosamax® had sales of $3

[7] Technically, they can file with the FDA up to one year *before* the end of market exclusivity.

[8] 20 of the cases that were litigated were settled out of court. Bulow (2004), Berndt *et al.* (2007a), Berndt *et al* (2007b) and the FTC (2002) have focused their attentions on these settlements and the strategic use of authorized generics by pharmaceutical companies.

billion in 2007 and was one of only five products exceeding one billion dollars in sales Merck reported in their 2007 Annual Report.[9] Teva was successful in its challenge and was allowed in February 2008 to market a generic form, approximately 10 years before three of Merck's underlying patents were due to expire.[10] It is reported that sales of Fosamax™ will plunge to around $1 billion in 2008 (WSJ, 2008).

So long as the practice of Paragraph IV challenges is profitable, it is likely that generic firms will continue conducting them. In their 2007 annual report, the generic producer Teva Pharameuticals reported that as of February 2007 they had 160 product registrations (ANDAs) pending before the FDA.[11] The branded products specified in these 160 ANDAs had sales in excess of $100 billion in 2007. In what may be a broadening of this practice by would-be entrants, many of the branded drugs being challenged have market sizes below $100 million, suggesting that "blockbuster" drugs are no longer the primary focus (Grabowski and Kyle, 2007; Grabowski, 2007). More importantly, 92 of Teva's 160 product registrations (57.5 percent) contained Paragraph IV challenges. They note in their report "As part of its strategy, Teva actively reviews pharmaceutical patents and seeks opportunities to challenge patents that it believes are either invalid or are not infringed by its generic version. In addition to financial benefits to Teva associated with marketing exclusivity, Teva believes that its patent challenges "..improve healthcare by allowing consumers earlier access to more affordable, high quality medications" (Teva annual report, page 16). Teva is only one of several generic manufacturers active in this space: Dr. Reddy's of India, for example, reported 33 ANDA filings in the U.S. in 2007 with 7 (21 percent) of these containing a Paragraph IV challenge.[12]

2.2 Responding to the challenge: new product introductions and complementary assets

[9] The five billion-dollar drugs reported by Merck were: Singulair® ($4.2 billion), Cozaar/Hyzaar® ($3.3 billion), Fosamax® ($3.0 billion), Gardasil® ($1.4 billion) and Pro-Quad/M-M-R II/Varivax® ($1.3 billion). The also received $1.7 billion from their relationship with Astra-Zeneca for Nexium® and Prilosec®.

[10] A court determined that Merck's patent claims were invalid. Fosamax™ has 5 patents attached to its original FDA filing (#021575). Three of the patents expire in 2018, one expires in 2014 and one expired in late 2007.

[11] U.S. Securities and Exchange Commission Form 20-F, Teva Pharmaceutical Industries Limited, December 31, 2007 (http://www.tevapharm.com/pdf/teva20f2007.pdf).

[12] Dr. Reddy's 2007 Annual Report (http://www.drreddys.com/investors/pdf/annualreport2007.pdf).

Incumbent pharmaceutical firms have not remained idle while these changes and growing challenges have occurred in their external environment, but they have responded in several ways. First, they have confronted these challenges through litigation. Second, some firms pre-empt the first-to-file ANDA by teaming up with another generic firm and authorizing a generic product (Berndt *et al*., 2007a). While this strategy moves a branded product into generic production, the firm can capture some of the rents while diminishing the entry incentive to generic firms by stripping from them the possibility of a 180-day exclusivity period. Finally, firms can protect their revenue stream by strategically introducing new products that cannot be threatened by generics for a period of time because they will be protected by Hatch-Waxman's initial market exclusivity.[13] These new introductions can either be novel products (aided by a robust research pipeline), product substitutes or reformulations.[14]

Firms following this third strategy—new product introduction—would have the advantage of enjoying unencumbered revenues during the five years of preliminary market exclusivity. This certainty over firm income stands in contrast to the uncertainty faced by an incumbent once its five-year exclusivity period expires. Firm income from a product supported only by patents, which are by their nature probabilistic property rights (Lemley and Shapiro, 2007), has become increasingly uncertain as generic entrants have become more active in pursuing Paragraph-IV challenges. Given the demand of Wall Street and revenue smoothing, a positive (and increasing) probability of losing virtually all the revenues from branded products post-exclusivity is likely to trigger a strong firm response.

A strong firm response is conditioned upon both the strength of its technological research and also the complementary assets necessary for development and commercialization. Complementary assets are important to an innovating firm because they may not be able to appropriate rents from innovation if complementary assets necessary for commercialization are not in place (Teece, 1986; Rothaermel, 2001). A firm that expends financial resources to develop a new product without building the necessary

[13] Pharmaceutical firms can side-step these issues all together by focusing on biologics as they are not currently subject to Hatch-Waxman. We thank Brian Wright for making this observation.
[14] An example of a substitute product would be Nexium® which came on the market to replace Prilosec®. An example of a reformulation would be Claritin-D® which replaced Claritin®.

downstream assets for commercialization, such as distribution channels, marketing capabilities, and manufacturing and production capabilities, must outsource these activities at a significant cost to the firm (Higgins, 2007 and Adegbesan and Higgins, 2007). Integration of these functions is therefore critical for pharmaceutical firms to avoid disgorging the profits necessary to recoup the tremendous cost of a new product development (DiMasi, 2001; DiMasi *et al*., 2003), especially given the threat from functionally similar "me-too" drugs (Grabowski and Vernon, 1992). In the face of discontinuous technological change, complementary assets held by incumbent firms have been shown to offer shelter from the winds of creative destruction (Tripsas, 1997) and to be positively related to firm financial performance (Rothaermel, 2001).

As an effective firm response to the loss of exclusivity on an existing drug, new product introduction is supported by extensive research. There is a large body of literature on new product introductions spanning multiple disciplines, e.g., Ulrich *et al.* (2004), Krishnan and Ulrich (2001), Griffin and Hauser (1996), Brown and Eisenhardt (1995) and Cusumano and Nobeoka (1992). Relevant to the pharmaceutical industry is the theoretical work that focuses on entry in the face of fixed costs, with some predicting too little entry (Spence, 1976; Dixit and Stiglitz, 1997) and others predicting the opposite (von Weizecker, 1980; Perry, 1984), all complimented by industry-specific studies (e.g., Kyle, 2006; Caves *et al*., 1991; Grabowski and Vernon, 1992; Lanjouw, 2005; Kyle, 2007; Danzon *et al*., 2005; Scott Morton, 1999). Simple economics suggests that the profit-maximizing firm's rational choice, ceterus paribus, is to commercialize its new products sooner rather than later, and research has demonstrated a boost to firm performance from following such a strategy (Sharma and Lacey, 2004; Bayes *et* al, 2003; Koku *et* al, 1997; Chaney *et al*., 1991; Wooldridge and Snow, 1990).[15] But managing the timing of new product introduction is constrained by the possession of the necessary firm resources in commercialization.

An effective timing strategy will thus depend not only on a robust research program, but also on the availability of complementary assets that are costly to create, to purchase, and to maintain. Firm

[15] While we are focused on actual new product introduction this is an extensive companion literature dealing with the "vaporware" or the practice of announcing new products well in advance of actual market availability. This strategy can be used by dominant firms to attempt to deter entry (Bayus *et al*., 2001).

capabilities in distribution, manufacturing, and marketing are relevant to the successful merchandizing of new products, and the effective management of these assets can increase the likelihood that the firm will possess them when needed. Avoiding undersupply is beneficial to the firm because these capabilities often require substantial resources and time to create, and thus an undersupply would leave the firm either lacking them (and thus unable to commercialize) or, if the assets are specialized, subject to hold-up in small-numbers bargaining if forced to acquire them from external sources (Williamson, 1985).

There is a flip-side to this logic: while the firm does not want to be undersupplied in these downstream assets it also wants to avoid be oversupplied in them. Maintaining unproductive downstream assets is costly. If the assets are specialized to a particular technology, the firm will generally be unable to direct the assets to alternative uses internally. Moreover, attrition may also have its costs: underutilization of such downstream assets may lead to their erosion, thus forcing upon the firm the costs associated with undersupply of the assets when the firm needs to commercialize a relevant product in the future.

No one firm specializes in every therapeutic category and there exists evidence of firm heterogeneity in research productivity (Henderson and Cockburn, 1996). As a result, firms build an expertise in a few selected research programs or therapeutic categories. This expertise is built along research lines, but also in the complementary assets required to support that research. This matching of research to resources drives firms to enter markets that are similar to those in which they already compete (Kyle, 2006).

However, there is a potential downside to creating a full value chain from research to distribution and marketing. Firms in effect "lock" themselves into specific therapeutic categories. This "lock in" requires the firm to continually find similar drug candidates to keep their research pipelines robust (Chan *et al*., 2007). If a firm's internal research is not sufficient to replenish its pipeline, the firm may be required to outsource its R&D through either alliances or acquisitions (Higgins and Rodriguez, 2006; Chan *et al*., 2007). While recent research (Ceccagnoli and Higgins, 2008) has shown that this approach can be an effective strategy for improving research productivity, Chan et al. (2007) demonstrate that

mismanaging the introduction of new products is likely to increase "adjustment costs" associated with the relevant complementary assets.

Complicating the delicate balance between over-supply and under-supply of complementary assets is the mix of new products a firm develops. On one hand, new products require increased advertising (Bly, 1993). On the other, Angell (2000) argues that in the context of pharmaceuticals "the less important the drug, the more marketing it takes to sell it. Important new drugs do not need much promotion. Me-too drugs do" (p. 1903). As a result, the demand for downstream specialized assets will fluctuate with the new product mix being brought to market. Thus a firm's ability to strategically time its introduction of new products is related to the firm's ability to manage the fluctuations in costs related to its downstream assets.

2.3 Managing the timing of new product introductions

We offer a simple schematic of the management of the complementary assets necessary for new product introduction in Figure 1. Bauer and Fischer (2000) and Higgins and Rodriguez (2006) demonstrate that pharmaceutical product sales over time take on something approximating an "inverted U" shape, and Figure 1 illustrates stylized representations of new products being introduced by a firm. For simplicity, we show the firm maintaining a constant level of complementary assets over time as a dashed line "CA." We note that at the apex of product sales, complementary assets are fully utilized and the region representing complementary assets unmatched to current product (denoted by "Z") is minimized.

Panel (A) depicts a situation with little threat of generic entry or early challenge, in which the firm introduces new drugs at periods t1 and t3.[16] The revenue stream for a drug expands and dissipates more slowly if the firm is not pressured to replace the drug. A drug will lose its 5-year market exclusivity, but will continue its strong market position with patents that last as long as 20 years. With long product cycles, the area Z is relatively small.

[16] These are just representative time periods and are not reflective of years. Their purpose is demonstrative only.

This simple schematic captures a valuable insight. Firms have strong incentives to maximize the utilization of those complementary assets necessary to commercialize new products. Our logic is equivalent to the observation in Chan *et al*. (2007) that pharmaceutical firms seek to minimize the "adjustment costs" associated with failing to effectively manage their product pipelines. While Chan *et al.* (2007) used a simulation approach to examine how firms choose between projects in their pharmaceutical pipelines we employ actual pharmaceutical-industry data to empirically test firms' abilities to effectively manage their innovation processes.

But firm management of these assets does not occur in an institutional vacuum. We represent in Panel (B) the effect on the firm, ceterus paribus, of a rise in generic entry and the increase in Paragraph IV challenges. Their effect is to compress the product revenue cycles associated with branded drugs (in Panel (B) product life cycles are relatively short, depicted with a compressed inverted "U" compared to the lower and flatter ones depicted in Panel (A)). We note that such a compression expands the area of unproductive assets Z (shaded for emphasis). As generic industry pressure has grown and Paragraph IV challenges have increased, marketing length has decreased (Grabowski and Kyle, 2007) and the revenue streams for branded products have become more compressed. At the same time sales tend to fall off more sharply as generics capture market share (Grabowski and Vernon, 1996). Evidence that such a compression is occurring can also be found in the increased reliance by firms on marketing and advertising early in the life of the branded drug to sharply increase sales. The firm in Panel (B), still launching new products at times t1 and t3, will suffer increased costs of maintaining complementary assets unmatched to revenues.

Panel (C) of Figure 1 represents a particular firm response to the Paragraph-IV challenge—earlier new product introduction. Note that the firm faces strong incentives, given its level of complementary assets and the compression of revenues associated with branded products, to introduce new products sooner in time. Panel (C) illustrates this firm response with product introductions at times t1, t2, and t3. Note that such an approach tends to reduce the area of unproductive assets (Z). Thus, as incumbent firms have become more reliant on the certainty of profits during short 5-year exclusivity windows, it is

increasingly important for them to strategically time the introduction of new products, a difficult proposition in an industry already suffering from research productivity declines (Higgins and Rodriguez, 2006).

The pharmaceutical industry offers us some advantages in testing whether firms are effective at managing the timing of their new product introductions. It is well understood that downstream assets such as distribution channels, marketing, and manufacturing capabilities are crucial to success in pharmaceuticals (Pisano, 1991; Macher and Boerner, 2006). Furthermore, as we discussed in Section 2.1, product life cycles are limited by legal and regulatory conditions. In fact, we are able to calculate, using our data, the precise dates when new drugs were approved for sale by the FDA as well as the dates on which companies lost their exclusivity protection on currently marketed products. These latter dates are well known to the firms *ex ante*, and thus allow managers to predict when sales will potentially begin to erode due to competition from generic producers. As such, firms may be able to forecast the approximate point in Figure 1 when an existing product's sales will slow, thus offering managers a readily available target for introducing a new product if, as we hypothesize, the objective is to minimize adjustment costs and smooth revenues.[17]

3.0 Empirical methodology and data

3.1 Empirical methodology

Our research questions focus on two strategic responses taken by an incumbent firm: First, does the firm introduce a new drug and, contingent upon such an introduction, is the firm able to strategically target a specific window associated with a regulatory-mandated event? Our framing of these research questions emphasizes the binary nature of these two decisions, and the likelihood of interdependence between these decisions warrants the use of a Heckman probit selection model. The Heckman probit selection model has two components – a regression equation and a selection equation. The dependent

[17] There are general sources of uncertainty that firms face. For example, upon approval the firm knows when exclusivity will end. Starting with the end of exclusivity until patent expiration there is some positive probability a Paragraph IV challenge will occur ($p \rightarrow 1$ for "block-buster" drugs.)

variable in the regression equation will be observed if the selection equation is greater than zero (Greene, 2000).

Our regression equation is $y_{i,t} = (\mathbf{x}_{i,t}\beta + \mu_{i,t} > 0)$ where $y_{i,t}$ equals one if a firm introduces a new drug in a given year and is zero otherwise. The measure $\mathbf{x}_{i,t}$ is a vector of independent variables we believe affect the probability that a firm will introduce a new product onto the market. These variables are grouped into several broad categories that will be discussed more fully in following sections, including complementary assets, internal capabilities, patent strategy and controls. The dependent variable, however, is not observed in every year: it takes the form $y_{i,t}^* = (\mathbf{z}_{i,t}\gamma + \varepsilon_{i,t} > 0)$, where z is a vector of variables thought to determine whether a firm will strategically introduce a drug in a given year.[18] The Heckman probit model assumes that μ and ε are distributed (0,1) with a correlation between them defined as ρ.[19] We also include year dummies in all specifications and cluster standard errors by firm in order to control for any possible intra-group correlation.

3.2 Data

We collect financial data from Compustat, stock market data from CRSP, proprietary pharmaceutical sales data from IMS Health, research pipeline data from NDA Projects and Pharmaprojects, new product data from the FDA Orange Book and patent data from IMS Patent Focus and the USPTO. All financial variables are presented in constant 2000 dollars. When the original source is in a foreign currency, we convert into U.S. dollars using the average of the 12 monthly foreign/U.S. exchange rates over the relevant year. Table 1 presents descriptive statistics and correlations.

We limit our sample to firms having at least one approved product during the period 1985 to 2001. Making this limitation leaves us with a more homogenous overall sample and tends to concentrate our analysis on commercially successful firms and, more importantly, on those firms that have demonstrated the characteristic on which our analysis is focused—the introduction of new products in the

[18] Prior to analyzing the Heckman probit selection model we pull out the selection equation and study it independently in Table 2. We do so in order to explore, independently, the question of *whether* a firm introduces a product in a given year and to also test the robustness of our results with a logit model, which they are.

[19] When $\rho \neq 0$ we know that standard regression techniques applied to the regression equation will yield biased results.

marketplace.[20] Unique firms are identified from the FDA Orange Book. For each firm we are then able to identify its portfolio of FDA-approved products. Subsidiaries are identified using the LexisNexis Corporate Affiliations database.

In examining new product introductions, we focus exclusively on new products introducing in the US market by both domestic and foreign firms. This limitation is appropriate because we are concerned here with the impact that a specific US law, namely the Hatch-Waxman Act, has had on the pharmaceutical industry. While this law may have effects on firm behavior in other jurisdictions, such questions are beyond the scope of this paper. We exclude biologic compounds since they do not fall under the jurisdiction of Hatch-Waxman. As a result, biotechnology firms are included in the sample only if (1) they have introduced a product during our time frame and (2) it is a non-biologic compound.

3.2.1 Dependent variable

We follow Jensen (1987) and use new FDA approved drugs for our dependent variable.[21] This choice is appropriate because new products are a main driver of pharmaceutical firm revenue and our interest is how firms respond to the introduction of a positive probability of losing these revenue streams. Moreover, drug product launches and losses are significant corporate events (Sharma and Lacey, 2004). Data from the FDA Orange Book allows us to define *Newdrugs* as an indicator equaling one if a company introduces a new FDA approved product in a given year and zero otherwise.

While the introduction by the focal firm of a new drug in a given year is of interest to us, we are also interested in discovering the determinants of how the firm performs in timing its new drug introductions relative to another significant event—the loss of Hatch-Waxman exclusivity protection five years after a brand product's initial launch. Accordingly, we generate a dummy variable *Drugwindow* that equals one if a firm introduces a new product within the three-year window surrounding the loss of exclusivity of an existing product in a firm's branded-drug portfolio of products, and zero otherwise. This

[20] 1985 is the first year of the Hatch-Waxman regulatory regime. We are further limited to the time frame 1990 to 2001 due to data limitations on our proprietary product level sales data obtained from IMS Health.

[21] In fact, Graham and Higgins (2007) raise concerns over the relationship between patenting and new product introductions in the pharmaceutical industry.

three year window is defined as years *t-1, t,* and *t+1* where *t* is the year that exclusivity protection expires on the brand product.

3.2.2 Independent variables

Loss of exclusivity. Prior research has shown that generic firms are challenging branded products earlier in the product's life-cycle (Berndt *et al*., 2007a). Because we are interested in the incumbent firms' response to Paragraph IV challenges, we focus on a window surrounding the first opportunity at which generic firms may issue such a challenge. We define a dummy, *Drugloss(t)*, that equals one if a firm has at least one existing branded product that loses its exclusivity protection in a given year, and zero otherwise. We also consider two lags, one backward, *Drugloss(t-1)*, and one forward, *Drugloss(t+1)*. The highest correlation between any of these three variables is 0.19. We include the backward lag because, technically, generic firms are allowed to file an ANDA citing a Paragraph IV challenge during the year before exclusivity on a branded product expires. Since our firm and year variables are constructed using calendar, and not relative, years, we also include the forward lag to capture the responses by incumbent firms for products that may lose exclusivity protection late in a calendar year. We also aggregate these three variables into one dummy, *Lossdrug*, which equals one if a firm has an approved product that loses exclusivity in this three year window. We collected exclusivity data from FDA reporting for each approved new product.

Paragraph IV challenges. Extensive data on Paragraph IV challenges is not readily available to researchers. The FDA itself only reports Paragraph IV challenges dating back to 2003. There exits two other sources that we employed to build a database of pre-2003 challenges: A Federal Trade Commission study (FTC, 2002) and Berndt *et al* (2007a). In its study "Generic Entry Prior to Patent Expiration," the FTC reported some limited information that it obtained from the FDA. Berndt *et al* (2007a) reports pre-2003 data obtained in a survey sponsored by an industry trade group. Using these data we are able to define *CumIV* as cumulative index of Paragraph IV challenges from these two data sources starting in 1990. This cumulative index provides us with a measure which proxies for the increasing relevance of Paragraph IV challenges to the pharmaceutical industry, year on year.

Given data limitations, we cannot determine the number of Paragraph IV challenges in specific therapeutic categories in any given year. We can, however, determine the number of generic products being sold in the market in a particular therapeutic category during a given year. We create a variable, *Generics*, that represents this count in the therapeutic class of the incumbent firm's drug losing exclusivity. Building the variable in this manner will allow us to explore the relationship between Paragraph IV challenges and the existence of generic products in the market in which a branded drug is losing its Hatch-Waxman exclusivity protection.

Research pipeline profiles. Firms need robust research pipelines in order to facilitate a continuous flow of internally-generated new products. In an effort to determine which products are in development we use data from Pharmaprojects and extract the number of firm products in some stage of clinical testing during any given year. Recognizing that projects vary on many dimensions, we attempt to account for some of this heterogeneity. We follow a method described in Higgins and Rodriguez (2006) and create a variable *Pipelinescore* which is a weighted measure of a firm's research pipeline based on derived clinical probabilities that products will reach the market. A firm showing a relatively high value in *Pipelinescore* indicates a more robust research pipeline, with products in later stages of clinical trials. This measure compares favorably with a simple count variable in which a higher value indicates nothing about the likelihood of reaching the market *per se* (e.g., such a score could reflect a larger number of earlier stage products). For our analytical purposes, later stage products are more important because they are critical inputs to a firm's strategy of timing new product introductions.

Co-specialized assets. Downstream co-specialized assets are important in the pharmaceutical industry (Chan *et al*, 2007). Unfortunately, we do not have direct, firm-level data relating to sales forces, manufacturing capabilities and marketing expenditures at the therapeutic level.[22] We can, however, create a reasonable proxy that provides information with respect to the downstream assets a firm may possess. Using proprietary product-level sales data obtained from IMS Health, we are able to generate a

[22] We are not aware of any sources for therapeutic level sales force data or manufacturing capabilities. IMS Health has product level marketing data available but we do not yet have access to it.

count of the prior number of drugs introduced by a firm in any given year. For all incumbent firms introducing a new drug, we define *ATCExp* as this count, but because we are interested in assets specific to the technology being currently launched by the firm, we restricting the count to only those prior drugs within the same therapeutic category as the new drug being introduced by the incumbent firm.

These proprietary data also allow us to define *ATCWindow* as a dummy that equals one if the therapeutic category for the approved drug is the same as the therapeutic category for any drug that losses exclusivity protection in the year before, the year of, or the year after approval (*t-1, t, t+1*). Examples of these drugs include reformulations[23] or next-generation drugs.[24] We employ data from IMS Health, identifying drugs by trade-name and sorting them into the appropriate therapeutic categories (up to 4-digit). These trade-names are then matched into the FDA Orange Book to identify the drug's approval date. Finally, we define *ATCcount* as the count of the total number of prior FDA-approved products for each firm, regardless of therapeutic category.

Market conditions. We generate several variables that control for the overall market conditions a firm faces at the time it introduces a new drug. Using data from IMS Health we define *CompetitorATC* as a dummy that equals one if a competing drug existed in the market, within the same therapeutic category, at the time of FDA approval. This provides us with a notion of whether a firm has a first-mover advantage or it is a "Me-Too" drug. Next, we define *ATCSize* as the ratio of product level sales by primary ATC code divided by total pharmaceutical sales. This ratio provides us with the relative size of a particular market. Many firms have consumer product divisions and other non-pharmaceutical revenues which often mask the lumpiness generated by the volatility in pharmaceutical sales. Our measures based on the aggregation of actual product level sales (as opposed to overall firm sales from sources such as Compustat) unmask these other influences. Finally, we define *BrandSales* as the product level sales in the year prior to loss of exclusivity.

[23] For example, Sanofi-Aventis' Ambien® was followed by its earlier product Ambien CR®.
[24] For example, AstraZeneca introduced Nexium® following its earlier product Prilosec®.

Patent and continuation profiles. We use patents issued in the U.S. by the United States Patent and Trademark Office (USPTO) and define *Patent* as the total number of patents filed by a firm in a given year. Following Graham and Higgins (2007) we lag *Patent* five years.[25] For robustness purposes we also consider citation-weighted patents and define *Citations* as the total citations, including self cites thru 2004, for our patent sample. We make one more correction to the patent data. It is common for researchers to use the "application date" disclosed on the front page of the U.S. patent document to represent the approximate date on which an invention was created, or entered the formal patent system. As described in Graham (2006), this practice fails to account for the string of "continuations" in the application history of the patent. Thus, we define *Continuepatent* as the number of continuations by filing firm for each year divided by *Patent*. This variable, consistent with *Patent* is lagged five years.

Patent continuations are particularly important in the pharmaceutical industry. Consistent with Graham (2006), there is strategic advantage to firms using this procedure, especially in the era of Paragraph IV challenges. Because the continuation allows both for the patent applicant to control the timing of the issue of a patent or the continuation "child" of a previously-prosecuted "parent" patent, the procedure has particular relevance to incumbent firms that face a probability with value less than one that a Paragraph IV challenge will be successful. If the challenge is not successful, the value of an attached patent of long life is substantial. The revenues of branded drugs that survive beyond the loss of exclusivity protection would be undiminished by generic competition.

In addition to this timing characteristic of the continuation process, there is another important dimension—the claims dimension. Claims are the text in the patent document that describe the patentable elements of the technology, and define its breadth and scope. The continuation process also allows patent applicants to amend claims, giving the applicant an opportunity to "bulletproof" a patent application as it observes, over time, the development of the technology and markets (Graham, 2006). Accordingly, the

[25] Graham and Higgins (2007) empirically investigate the relationship between patent filing and FDA approval. Over their sample period they found a mean lag between patent filing (for the patents attached to NDAs in the FDA Orange Book) and FDA approval was 59.6 months while the median lag was 61 months. This lag is longer than the three-year lag empirically derived by Comanor and Scherer (1969).

patent continuation allows the incumbent firm to rewrite its original patent application to make it stronger for a possible future fight with generic firms over the patent's validity during a Paragraph IV challenge.

Other controls. Studies that have considered firm-size in the context of patenting and firm performance have come to inconsistent conclusions about the role that *firm size* plays. On one hand, Jensen (1987) employs actual new products as a dependent variable and reports that firm size has no effect when introduced as an independent variable. On the other hand, studies that have proxied for new products have shown firm effects to be significant (e.g., Rothaermel and Hess, 2007; Shan *et al*., 1994). Given this inconsistency we use the number of employees (*Employees*) to control for any possible size effect. In order to control for investment in a firm's knowledge base and to possibly control for some type information not embedded in our pipeline or patent measures we define *R&D* as the natural log of research and development expenditures.

4.0 Empirical findings

4.1 Determinants of new product introductions

Table 2 presents probit estimates for our data regressing *Newdrugs* on a series of independent variables expected to affect the introduction of a new FDA approved product. *Newdrugs* equals one if a new product was introduced by a firm in a given year. Marginal effects are reported next to the corresponding model for statistically significant variables. Model 1 and Model 2 include mainly controls with and without year dummies in order to generate a baseline. Standard errors are clustered by firm.

We add *Drugloss* with its forward and backward lag in Models 3 - 5. The loss of exclusivity in time *t* is the single largest predictor of new product introductions. The backward lag, *Drugloss(t-1)* and forward lag, *Drugloss(t+1)*, are also both significant predictors of product introductions.[26] Combined marginal probabilities for these three variables range from 19.62 percent to 25.34 percent. Recall that in the pharmaceutical industry there are two types of protections available to a product – exclusivity and patent protection. At the end of exclusivity is a window of patent protection which usually runs for a number of years. Generic entry is expected at the end of patent protection and these entrants normally

[26] For robustness, we tested both *Drugloss(t-2)* and *Drugloss(t+2)*. Neither is significant at conventional levels.

take market share quickly (Grabowski and Vernon, 1992). This view is reflective of Panel A in Figure 1 in which firms have much longer payback periods. However, if this view told the whole story we would not expect to see such an emphasis placed on this earlier event – loss of exclusivity.

Paragraph IV challenges explain why a firm would be concerned with the loss of exclusivity and attempt to target new product introductions around that time frame. Under Hatch-Waxman, generic firms are able to submit ANDA applications with Paragraph IV or "Cert-IV" claims in an attempt to introduce a product before the branded product's patents have expired. Indeed, the number of Paragraph IV claims has increased significantly (Berndt *et al*, 2007; Grabowski, 2007). Our findings support this view. In Models 6 to Model 8, we interact *Lossdrug* with *CumIV*; results are positive and significant at the 1 percent level. Since *CumIV* represents the cumulative stock of Paragraph IV challenges over our time frame, we interpret this interaction effect to suggest that the loss of exclusivity has become even *more* important with time.

Several factors explain why this intensification may be taking place. First, the generic industry has grown in size and resources such that pursuing litigation is a viable strategy. Indeed, discussions with an industry representative put the cost at pursuing and litigating a Paragraph IV challenge at around $5 to $10 million; a relatively low cost given the potential payoff. Second, in 2000 the FDA began allowing generics to enter the market and start their 180-exclusvity period upon the first favorable court decision.[27] Third, there has been a general decline in the overall IP environment due to a series of cases and legislation (Graham and Higgins, 2008).

Research pipelines, *PipelineScore*, and patent portfolios, *Patents*, are both positive and significant predictors of new products introductions. These are the only two controls that were significant, across all models, and both variables speak to a firm's internal capabilities. Neither of these results is unexpected because both are a necessary condition to the firm generating a flow of new products. As a robustness check, we replace *Pipelinescore* with *Pipelinecount* which is a simple un-weighted measure of pipeline

[27] Although, this is a calculated risk in that if subsequent rulings overturned the favorable ruling the generic firm could be liable for damages as a result of lost revenues to the branded product.

products. Interestingly, *Pipelinecount* is not significant across any specification. Since *Pipelinescore*, by construction, weights later-stage products more heavily than early-stage products, the difference between these two variables points to the *type* of research pipeline products that matter for new product introductions. While the result is not surprising that late-stage projects matter more, it does draw attention to these differences for future research purposes.

It should be no surprise that pharmaceutical firms attempt to manage product introductions so as to smooth revenues, especially given the increased pressure from generic firms. What is more surprising is that firms appear to be successful in managing that process, especially given the long lags involved in new product development. The loss of exclusivity on an existing drug is an important and economically meaningful event to the firm.[28] As such, we take it that firms are aware of which revenue streams they have that are threatened, and have strong incentives to act strategically. In an effort to illustrate this point, we combine proprietary sales data from IMS Health with FDA drug approvals from 1990 to 2001. Consistent with Higgins and Rodriguez (2006), we find that approximately 74 percent of sales occur during this five-year exclusivity protection period after FDA approval, while approximately 15 percent of sales are realized in the three years following the loss of exclusivity.

Finally, we measure firm size by *Employees*. Contrary to other work (which proxies new product development with patenting) that has found some effect, either positive or negative, between firm size and innovative performance; we find no correlation between firm size and new product introductions. Our findings, which are consistent with Jensen (1987), coupled with our findings in Graham and Higgins (2007) suggests that these previous firm-size findings are related in some way to patenting and not new product introductions. Our findings, in contrast to Jensen (1987), might also be a function of our sample selection process. Since we are focusing on firms that have at least one FDA approved product we are sampling larger firms.

[28] A successful challenge by a generic firm would open the path for generic introduction prior to patent expiration. Merck's Fosamax® is an example of a product that was challenged after the loss of exclusivity but prior to the expiration of the underlying patents. The courts have upheld the generic firm's claims of non-infringement thereby allowing the generic to produce effective February 2008. According to Merck's annual report, Fosamax® revenues exceed $1 billion.

4.2 Strategic introduction of new products and the role of complementary assets

We move beyond our analysis of the determinants of new product introductions and explore whether firms are able to strategically time these releases. The ability to strategically introduce products is critical to the firm due to the compression on payback periods for branded products (as demonstrated in Figure 1, Panel B), the desire to smooth revenues, and the growing importance of the loss of exclusivity on branded products. As discussed above, we use a Heckman probit model to explore this research question. The dependent variable for the selection equation focuses on *whether* a new product is introduced while the dependent variable for the regression equation, conditional on introduction, focuses on *when* the product release is strategically timed. For the first three models in Table 3 we use Model 5 (Table 2) for the selection equation. For robustness purposes we use Model 8 (Table 2) as the selection equation for Models 4 and 5 in Table 3. Across all specifications presented in Table 3 the Wald test statistics reject the null, $\rho = 0$, justifying the use of the Heckman selection equation with these data.[29]

The dependent variable in the regression is *Drugwindow* which is a dummy that equals 1 if a firm introduces a new product within the three-year window surrounding the loss of exclusivity. Our interest is in what drives a firm's ability to strategically launch these products. Our theory relies on the importance of complementary assets coupled with internal capabilities. Essentially, firms that have these downstream specific assets in place for a particular therapeutic category will be able to move quickly to bring a product to market. Internal capabilities, as we will discuss below, are necessary but not sufficient. For example, if a firm has a productive pipeline but not the downstream assets then launch could be significantly delayed harming the financial performance of the firm (Hendricks and Singhal, 2008). At the same time, these specific assets have a downside—they tend to lock the firm into specific technology classes and markets.

We use several variables to try to proxy for the presence of downstream assets since firm level data (and more fine grain data at the therapeutic level) are not available. The focus of our proxies is on

[29] Where ρ is the correlation between the error terms in the selection and regression equations. When $\rho \neq 0$, standard regression techniques applied to the regression equation will yield results that are biased.

the presence of other drugs being introduced *within* the same therapeutic class. Across all specifications presented our specific-asset proxies have the largest marginal effect on the probability that a firm is able to strategically introduce. In Model 1 our proxy is *ATCWindow* is a dummy that equals one if the therapeutic category of the new product is exactly the same as the therapeutic category of the drug that is losing exclusivity. Coefficients are positive and significant and marginal effects exceed 17 percent. Drugs that fit this description fall into several categories: They can be reformulations of an existing product, next generation drugs (for example, Nexium® replaced Prilosec®) or they can be unrelated but within the same therapeutic category. We will delay further discussion of the exact product mix until Section 4.3 (the discussion on Model 3 and Model 4, Table 3 will also be delayed).

In Model 2 we use a broader proxy, *ATCExp*, which is the total count of prior approved products a firm has within the same therapeutic category as the drug being approved. We repeat the same specification in Model 5 but with a different selection equation. Across both models the coefficients on *ATCExp* are positive and significant with marginal effects ranging between 15 and 18 percent. We interpret this result as suggest that, as a firm's commitment to a particular therapeutic category increases, it is more likely to protect a revenue stream with follow-on products. Likewise, as a firm builds a research competency in a particular therapeutic category it also builds a companion set of downstream specialized assets which allow the firm to better manage their introductions. Our findings on *Generics* and *BrandSales* support this view. Both variables are positive and significant. As the number of generic products already in the market in a particular therapeutic category increases, or if the sales for the product losing exclusivity protection are relatively large, then a firm is more likely to introduce a new product. It appears to us that firms are more likely to attempt to smooth and protect their revenue stream. Next to our proxies for complementary assets, the size of the revenue stream being threatened has the largest marginal effect, ranging from 10.25 to 11 percent.

Just as was the case in analyzing *whether* a firm introduced a new product, patents and research pipelines remain important in determining *when* a firm introduces. Across all specifications, *Patents* and *Pipelinescore* are positive and significant. Marginal effects are smaller but appear important nonetheless.

These two variables speak to a firm's internal capability and are necessary conditions for pharmaceutical firms to engage in time-targeted introductions. Research pipelines can be built in many ways; they can be internally developed, built by acquisitions (Higgins and Rodriguez, 2006) and/or alliances (Rothaermel and Deeds, 2004). The combinations of these activities can even change over time. For example, in December 2004, Merck had 42 products in either Phase I, II or III clinical testing with six of these being the result of license, alliance or acquisition. By August 2007, Merck had 47 products in either Phase I, II or III clinical testing with 12 the result of license, alliance or acquisition. We remain agnostic on how firms *build* their research pipelines: What is important in the current context is the sheer size of firms' later-stage pipeline.[30]

"Continuation" application practices permitted in the U.S. patent system allow firms to manage the timing of their patent grants. Because patent applicants may choose to "continue" an application at will, even in the face of a positive grant decision by the patent examiner, the patentee is able to have significant control over the ultimate grant-date of the issued patent.[31] Discussions with patent attorneys, and empirical evidence in Graham (2006), support the notion that pharmaceutical firms use continuation applications to map the grant-date of important patents to the approval of drugs in the FDA-endorsement process. The continuation is an important strategic option available to firms (Hegde, et al. 2007), and its extensive use proxies, we contend, for a firm-specific strategic capability in using patents. Our empirical findings support this view; across all specifications, *Continuepatent* or the number of continuations per patent is positive and significant at the 1 percent level. Interestingly, patent strategy, in terms of the use of continuations, was not important in determining *if* a firm introduced (*Continuepatent* was not significant in Table 2) but rather in *when* they introduce. Taken together, the results in Table 3 appear to

[30] Similar to our robustness check in Table 2, we replace *Pipelinescore* with *Pipelinecount*. Again, the coefficients on *Pipelinecount* are not significant. Our interpretation remains the same – *Pipelinecount* tends to bias earlier stage projects while *Pipelinescore* tends to bias later stage projects. Within our context, it is important for firms to have a healthy supply of later-stage projects.

[31] This practice promised greater reward for the pharmaceutical firms prior to 1995 when the patent term was 17 years from date of issue. In the current regime, the patent term is 20 years from date of first application, and thus the firm suffers one day of lost patent term for each additional day of continuation application it chooses. See Graham (2006).

demonstrate that three different capabilities are needed in order for firms to be able to strategically introduce: complementary assets; internal research capabilities; and, an effective patent (continuation) strategy.

Finally, the presence of a competitor's drug in the same therapeutic class being currently marketed, *CompetitorATC*, has no effect on whether a firm strategically introduces a new product. Unlike the "thickness" of the generic market (measured by the positive result on *Generics*) this lack of a relationship suggests that firms introducing "me-too" drugs are not affected by the presence of competition in the market.[32]

4.3 Composition of strategically introduced new products

In Table 3 we analyzed whether firms were able to strategically introduce new products. Our results suggest that firms are successful in this type of strategic behavior. The question now becomes what *types* of products are firms strategically introducing?[33] By analyzing the therapeutic classification of approved products we identify three broad categories of new drugs: (1) reformulations of existing drugs, (2) substitute drugs, and (3) novel, unique drugs. Reformulations of existing drugs require that additional clinical data be provided and, as a result, a period of new exclusivity protection is granted by the FDA. Common reformulations are drugs that move from being taken twice-a-day to once-a-day, for example, Claritin® and Claritin-D®. Substitutes are new drugs that replace older drugs for the same indication. For example, AtraZeneca's antacid Nexium® replaced its Prilosec®. Novel drugs are those for which the firm had no prior approved drugs for a specific therapeutic indication.

For products that are introduced within the three-year window surrounding the loss of exclusivity protection we find the following shares: novel (41.5 percent), reformulations (30.5 percent) and substitutes or next-generation (28 percent). In our entire sample of approved drugs, we find the following: novel (68.5 percent), reformulations (18.6 percent) and substitutes or next-generation (12.9

[32] "Me-too" drugs are those that are structurally similar to those products currently on the market.
[33] We thank Brian Wright for drawing our attention to this point.

percent).[34] These figures suggest that over 50 percent of drugs introduced within a 3-year window of exclusivity-loss rely on a firms' past research experience and thus are comparatively more likely to be products for which specialized downstream assets are necessary.

We return to Models 3 and 4 in Table 3 to further analyze the issue of reformulations. We define *Reform* as a dummy that equals 1 if the strategically-introduced product is a reformulation of the product losing exclusivity protection.[35] In Model 3 the coefficient on *Reform* is both positive and significant. In Model 4 we interact *Reform* with *ATCExp* and the resulting coefficient is positive and significant. Taken together these results suggest that reformulations are important in a firm's ability to strategically introduce.

The significant differences between the types of products that are strategically introduced around the loss of exclusivity of another portfolio drug and the overall population of introduced drugs implies that as overall productivity in the industry has fallen (Higgins and Rodriguez, 2006), in terms of novel products, firms have been able to use reformulations and substitutes or next-generation products as a method to protect revenue streams and minimize the costs associated with under-utilized specialized assets, or the possible loss of those valuable and hard-won assets due to attrition when un-used. Given that this strategy hinges on the underlying availability of novel products in which to reformulate, it is still necessary that firms (and the industry) work to improve novel product development.

5.0 Conclusions

Our foregoing analysis provides strong evidence that pharmaceutical firms are both effectively managing the timing of their new product introductions, and that reducing adjustment costs associated with mismatched downstream specialized assets are driving this strategic choice. This paper thus supports previous research that has found the possession of downstream complementary assets to be critical to innovative success (Teece, 1986; Tripsas, 1997; Rothaermel, 2001). We are furthermore able to extend this research by bringing the first empirical evidence of which we are aware on the performance

[34] Differences between results are significantly different from zero at the 1 percent level.
[35] We are able to make a mapping between proprietary product level data from IMS and the FDA Orange Book.

of firms at managing the timing of new product introductions, and the extent to which specialized complementary assets play a role in the necessity of managing that timing effectively. This evidence allows us to both validate empirically and to contribute meaningfully to the simulation findings in Chan *et al* (2007).

These finding have implications for our understanding of the role of specialized downstream assets in the innovation process. While Williamson (1985) gives us a framework to understand the importance of maintaining specialized assets inside the firm, he also reminds us that, by integrating all these functions within one organization, the firm suffers the costs of low-powered incentives and increased bureaucracy. The pharmaceutical firms in our study appear to be able to manage these complex assets within the firm, even in the face of these costs that would seem to militate against such successful management of timing. Our study thus raises questions about the "costliness" of these downsides to hierarchy, at least in the modern pharmaceutical firm, and how the players in this industry have seemingly been able to mitigate the harshness of these attributes.

We make multiple contributions to the literature. First, we demonstrate that the most important predictor of the introduction of a new drug is the *loss of exclusivity protection* on a current product. This supports our contention that regulation, and specifically Paragraph IV challenges launched by generic entrants, are an extremely critical and deeply underappreciated characteristic of competition in the pharmaceutical market.

Second, our evidence suggests that pharmaceutical firms are acting strategically, targeting the three-year window around the loss of exclusivity to introduce new products. This finding has implications both for our understanding of firm innovation strategy, and also upon the availability of new pharmaceutical products to consumers. In terms of innovation strategy, the apparent ability of pharmaceutical firms, in general, to smooth firm revenues by targeting introductions appears to us impressive given the long development periods they face. In terms of the consumer market, the role of generic entry under Hatch-Waxman in terms of incumbent firms' ability to recoup R&D, prompting new

product introductions, and inducing particular *types* of product introductions (such as reformulations and substitutes) has to this point been underappreciated.

In a third contribution, we explore the notion of strategic product market timing in more depth. Our findings suggest that three main factors predict whether a pharmaceutical firm is able to engage in strategic market timing: the weighted measure of a firm's research pipeline, their specialized investments and experience in a particular therapeutic category, and their use of the continuation process.

Fourth, unlike the extant empirical literature, we explicitly control for each pharmaceutical firm's underlying research portfolio. Across all specifications tested we find a positive and significant impact on new product introductions. This finding confirms prior research that shows the importance for firms to maintain healthy research pipelines (Higgins and Rodriguez, 2006).

Finally, we find no relationship between firm size and new product introductions. Other work that uses patenting as a proxy for new product development has found a relationship between these two variables, either positive or negative (Rothaermel and Hess, 2007; Shan *et al*., 1994; and, Acs and Audretsch, 1989). In contrast, our findings are consistent with prior work that uses actual new product introductions as a dependent variable and introduces firm size as an independent variable, and finds the size effect is not significantly different from zero (Jensen, 1987).[36]

[36] While consistent with Jensen (1987) our result may be a function of our sample selection.

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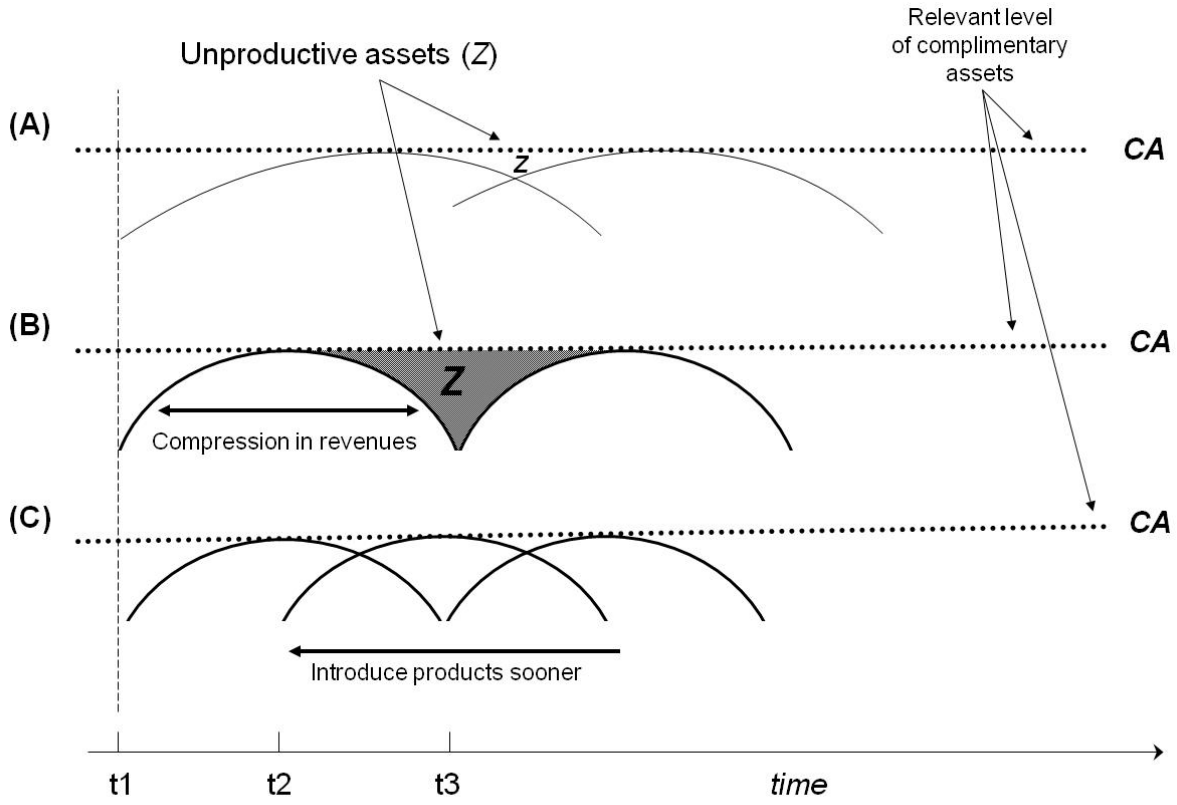

Fig. 1. Impact increases in patent challenges have on revenues and new product introductions in the pharmaceutical industry. *Z* represents the size of unproductive downstream complementary assets. Note, *t* (our measure of time) is a general time measure not reflecting years, per se.

Table 1: Descriptive statistics and correlation matrix

	Variable	Mean	σ	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	Newdrugs	0.26	1.17	1.0000														
2	Drugwindow	0.17	0.38	0.4484	1.0000													
3	Drugloss	0.10	0.67	0.1407	0.1749	1.0000												
4	Log CumIV	3.86	1.25	0.1574	0.1268	0.2434	1.0000											
5	Generics	4.90	0.44	0.0774	0.0620	0.0984	0.3765	1.0000										
6	Log Pipelinescore	1.65	1.71	0.2039	0.1334	0.1711	0.1772	-0.1544	1.0000									
7	ATCExp	0.59	0.98	0.2101	0.2206	0.1395	0.1096	0.0480	0.1113	1.0000								
8	ATCWindow	0.32	0.44	0.2724	0.2676	0.1516	0.0875	0.0466	0.0679	0.1541	1.0000							
9	CompetitorATC	0.37	0.64	0.0447	0.0617	0.0922	0.0991	0.0412	0.0891	0.1795	0.1516	1.0000						
10	ATCSize	0.11	0.38	0.1073	0.1010	0.1354	0.1352	0.0478	0.1873	0.1555	0.1390	0.1564	1.0000					
11	Log BrandSales ($m)	8.35	2.01	0.0566	0.0161	0.0826	0.1618	0.0310	0.0536	0.0405	0.0220	0.0348	0.0165	1.0000				
12	Patent	13.83	27.45	0.2562	0.3087	0.1902	0.0051	0.0043	0.1974	0.1997	0.1576	0.1369	0.1192	-0.0190	1.0000			
13	Citations	31.39	91.15	0.2075	0.2314	0.1325	-0.0712	-0.0455	0.1447	0.1375	0.1173	0.0916	0.1664	-0.0348	0.8548	1.0000		
14	Continuepatent	0.54	0.98	0.1112	0.0410	0.0402	0.0373	-0.0195	0.1313	0.0410	0.0218	0.0500	0.0565	0.0008	0.1598	0.1637	1.0000	
15	Employee (000s)	47.46	53.33	0.0384	0.0219	0.0708	0.0609	0.0298	0.0085	0.0376	0.0279	0.0363	0.0036	0.3374	-0.0231	-0.0241	-0.0236	1.0000

*** All financial figures in 2000 constant dollars.

Table 2: Probability a pharmaceutical firm introduces a new product

	Model 1	∂Φ/∂x	Model 2	∂Φ/∂x	Model 3	∂Φ/∂x	Model 4	∂Φ/∂x	Model 5	∂Φ/∂x	Model 6	∂Φ/∂x	Model 7	∂Φ/∂x	Model 8	∂Φ/∂x
z_1: *Drugloss(t-1)*					0.2982 (0.1171)[a]	0.0633	0.2374 (0.1133)[b]	0.0521	0.1628 (0.0813)[b]	0.0517						
z_2: *Drugloss(t)*					0.3417 (0.1015)[a]	0.1073	0.3262 (0.1062)[a]	0.0943	0.2628 (0.1030)[a]	0.0804						
z_3: *Drugloss(t+1)*					0.3772 (0.0981)[a]	0.0828	0.0252 (0.0951)[a]	0.0790	0.2332 (0.0980)[a]	0.0641						
z_4: *Lossdrug*											0.7140 (0.2030)[a]	0.2323	0.6879 (0.1824)[a]	0.2175	0.6822 (0.1929)[a]	0.2073
z_5: *CumIV*					0.0016 (0.0078)		0.0030 (0.0059)		0.0021 (0.0057)		0.0020 (0.0060)		0.0034 (0.0052)		0.0027 (0.0063)	
z_6: *Lossdrug x CumIV*											0.4119 (0.1006)[a]	0.0913	0.4059 (0.1182)[a]	0.0846	0.3814 (0.1278)[a]	0.0761
z_7: *Pipelinescore*	0.1325 (0.2364)[a]	0.0225	0.1469 (0.0230)[a]	0.0256	0.1407 (0.0243)[a]	0.0254			0.1246 (0.0225)[a]	0.0211	0.1424 (0.0239)[a]	0.0256			0.0971 (0.0227)[a]	0.0161
z_8: *R&D*	0.0479 (0.0519)		0.0520 (0.0385)				0.0326 (0.0199)		0.0462 (0.0375)				0.0325 (0.0212)		0.0230 (0.0151)	
z_9: *Patent*	0.2330 (0.0270)[a]	0.0396	0.2231 (0.0263)[a]	0.0388			0.2504 (0.0247)[a]	0.0422	0.2484 (0.0280)[a]	0.0409			0.2568 (0.0234)[a]	0.0431	0.2340 (0.0247)[a]	0.0387
z_{10}: *Continuepatent*	0.0443 (0.0365)		0.0573 (0.0355)				0.0495 (0.0371)		0.0407 (0.0263)				0.0715 (0.0382)		0.0673 (0.0317)	
z_{11}: *ATCSize*	0.0015 (0.0322)		0.0036 (0.0218)		0.0012 (0.0011)				0.0014 (0.0008)						0.0009 (0.0011)	
z_{12}: *Employees*	-0.0064 (0.0167)		-0.0140 (0.0159)		0.0260 (0.0213)				0.0226 (0.0176)		0.0258 (0.0391)				0.0137 (0.0163)	
Constant:	Y		Y		Y		Y		Y		Y		Y		Y	
Time dummy:	Y		N		Y		Y		Y		Y		Y		Y	
Cluster S.E.:	Y		Y		Y		Y		Y		Y		Y		Y	
Observations:	4060		4060		4060		4060		4060		4060		4060		4060	
χ^2:	321.61		280.23		374.28		288.79		351.14		336.04		372.63		394.00	

[a], [b], [c]: significant at the 1, 5 and 10 percent levls, respectively

∂Φ/∂x: marginal effects are reported only for statistically significant variables

Standard errors are clustered by firm

Table 3: Strategic introduction of new products by pharmaceutical firms

	Model 1	∂Φ/∂x	Model 2	∂Φ/∂x	Model 3	∂Φ/∂x	Model 4	∂Φ/∂x	Model 5	∂Φ/∂x
x_1: *ATCWindow*	4.7343 (0.0874)[a]	0.1704								
x_2: *ATCExp*			0.5633 (0.1788)[a]	0.1502			0.6581 (0.1976)[a]	0.1924	0.6423 (0.1677)[a]	0.1873
x_3: *Reform*					0.1486 (0.0630)[a]	0.0729	0.0766 (0.0369)[b]	0.0326		
x_4: *ATCExp x Reform*							0.1305 (0.0672)[b]	0.0286		
x_5: *Generics*	0.2072 (0.1118)[c]	0.0400	0.1972 (0.1173)[c]	0.0395	0.2064 (0.1235)[c]	0.0399	0.1978 (0.1177)[c]	0.0396	0.2021 (0.1188)[c]	0.0399
x_6: *BrandSales*	0.6821 (0.3427)[b]	0.1086	0.7010 (0.3200)[b]	0.1102	0.6982 (0.2958)[b]	0.1098	0.6808 (0.3196)[b]	0.1025	0.6833 (0.3178)[b]	0.1033
x_7: *CompetitorATC*	0.1121 (0.1139)		0.0891 (0.1892)		0.1059 (0.1535)		0.0908 (0.1472)		0.0821 (0.1973)	
x_8: *Pipelinescore*	0.1089 (0.0197)[a]	0.0205	0.1123 (0.0195)[a]	0.0237	0.1132 (0.0199)[a]	0.0231	0.1154 (0.0203)[a]	0.0261	0.1108 (0.0210)[a]	0.0210
x_9: *R&D*	-0.0455 (0.0382)		-0.0431 (0.0401)		-0.0433 (0.0419)		-0.0469 (0.0395)		-0.0452 (0.0397)	
x_{10}: *Patent*	0.1110 (0.0330)[a]	0.0209	0.0950 (0.0273)[a]	0.0200	0.0946 (0.0295)[a]	0.0193	0.1076 (0.0280)[a]	0.0231	0.0827 (0.0276)[a]	0.0187
x_{11}: *Continuepatent*	0.0746 (0.0284)[a]	0.0140	0.0809 (0.0302)[a]	0.0171	0.0870 (0.0295)[a]	0.0178	0.0675 (0.0225)	0.0095	0.1051 (0.0392)[a]	0.0238
x_{12}: *Employee*	0.0040 (0.0166)		0.0047 (0.0169)		0.0079 (0.0164)		0.0142 (0.0182)		0.0065 (0.0177)	
z_1: *Drugloss(t-1)*	0.2617 (0.0675)[a]		0.3273 (0.0845)[a]		0.3626 (0.0816)[a]					
z_2: *Drugloss(t)*	0.3793 (0.0675)[a]		0.4096 (0.0676)[a]		0.4118 (0.0664)[a]					
z_3: *Drugloss(t+1)*	0.4080 (0.0688)[a]		0.4269 (0.0680)[a]		0.4455 (0.0694)[a]					
z_4: *Lossdrug*							0.8534 (0.1248)[a]		0.8684 (0.1286)[a]	
z_5: *CumIV*	0.0010 (0.0009)		0.0012 (0.0008)		0.0011 (0.0008)		0.0017 (0.0010)		0.0017 (0.0011)	
z_6: *Lossdrug x CumIV*							0.2305 (0.0416)[a]		0.2367 (0.0379)[a]	
z_7: *Pipelinescore*	0.1113 (0.0188)[a]		0.1065 (0.0183)[a]		0.1060 (0.0181)[a]		0.1138 (0.0210)[a]		0.1070 (0.0189)[a]	
z_8: *R&D*	0.0391 (0.0279)		0.0373 (0.0281)		0.0376 (0.0283)		0.0368 (0.0287)		0.0323 (0.0284)	
z_9: *Patents*	0.1920 (0.0199)[a]		0.1856 (0.0195)[a]		0.1818 (0.0192)[a]		0.1870 (0.0194)[a]		0.1899 (0.0201)[a]	
z_{10}: *Continuepatent*	0.0257 (0.0282)		0.0373 (0.0265)		0.0323 (0.0264)		0.0284 (0.0259)		0.0379 (0.0301)	
z_{11}: *ATCSize*	0.0022 (0.0016)		0.0020 (0.0018)		0.0020 (0.0017)		0.0020 (0.0018)		0.0022 (0.017)	
z_{12}: *Employees*	-0.0066 (0.0139)		-0.0053 (0.0135)		-0.0061 (0.0134)		-0.0048 (0.0136)		-0.0023 (0.0136)	
Constants	Y		Y		Y		Y		Y	
Cluster S.E.	Y		Y		Y		Y		Y	
Observations	4060		4060		4060		4060		4060	
Censored Obs.	3537		3537		3537		3537		3537	
Uncensored	523		523		523		523		523	
χ^2 *(Wald test, ρ =0)*	87.46		116.73		96.76		131.53		167.86	

[a], [b], [c]: significant at the 1, 5 and 10 percent levls, respectively

∂Φ/∂x: marginal effects are reported only for statistically significant variables

Standard errors are clustered by firm