Starving (or Fattening) the Golden Goose?: Generic Entry and the Incentives for Early-Stage Pharmaceutical Innovation[†]

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Version: 10 December 2012

[†]**Acknowledgements:** We thank Tamer Abdelgawad, Iain Cockburn, Darren Filson, Carolin Haeussler, Bart Hamilton, Dietmar Harhoff, Sherry Knowles, Margaret Kyle, Joseph Mahoney, Alex Oettl, Ivan Png, Jerry Thursby, and Brian Wright as well as seminar participants at: University of Illinois, University of Passau, University of California Berkeley, Carnegie Mellon University, Ludwig Maxmilians University Munich, National University of Singapore, India Statistical Institute (Delhi), Georgia Institute of Technology and conference participants at USPTO Conference on Patents, Entrepreneurship and Innovation (Washington, DC), for valuable comments and discussions. Programming and research assistance by Jeremy Watson, Winston Yang and Suvojyoty Sahais gratefully acknowledged. We also thank IMS Health Incorporated for their generous support and access to their data. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities. The statements, findings, conclusions, views, and opinions contained and expressed in this article are based in part on data obtained under license from the following IMS Health Incorporated or affiliate information service(s): IMS Midas™, IMS Lifecycle™, IMS National Disease and Therapeutic Index™, IMS National Prescription Audit™, June 1997 to December 2008, IMS Health Incorporated or its affiliates. All Rights Reserved. Portions of this paper were completed while Branstetter was on leave serving on the Council of Economic Advisors. The statements, findings, conclusions contained and expressed herein are not necessarily those of the Council of Economic Advisors or any of its affiliated or subsidiary entities. Higgins acknowledges funding from The Imlay Professorship. Chatterjee acknowledges IIM Bangalore for supporting his extended research visit to Georgia Tech/Carnegie Mellon and for the Young Faculty Research Chair. Higgins and Branstetter acknowledge funding from NSF SCISIP Grant #1064122. Authors are listed alphabetically and the usual disclaimers apply.

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ABSTRACT

Over the last decade, generic penetration in the U.S. pharmaceutical market has increased substantially, providing significant consumer surplus gains. But is generic entry reducing the flow of early stage pharmaceutical innovation and therefore future availability of new medicines? We explore this question using novel data sources and an empirical framework that models the flow of early-stage pharmaceutical innovations as a function of generic penetration, scientific opportunity and challenges, firm innovative capability, and additional controls. Our estimates suggest a sizable, robust, negative relationship between generic entry and early-stage pharmaceutical research activity. A 10% increase in generic penetration *decreases* early-stage innovations in the same market by 7.3%. This effect is weaker in top therapeutic markets where an increase in generic penetration by 10% decreases the flow of early-stage innovations by 2.2%. However, in those top markets, a 10% increase in the stock of Paragraph IV challenges decreases the flow of early-stage innovation by 3.9%. Our estimated effects appear to vary across therapeutic classes in sensible ways, reflecting the differing degrees of substitution between generics and branded drugs in treating different diseases. Finally, we are able to document that with increasing generic penetration, firms in our sample are shifting their R&D activity to more biologic-based (large-molecule) products rather than chemicals-based (small-molecule) products as evidenced in their early-stage pipelines. We conclude by discussing the potential implications of our results for long-run consumer welfare, policy, and innovation.

1 Introduction

In his provocative paper, "The Health of Nations," Yale University economist William Nordhaus (1999) argues that the advances in human welfare generated by better medical science over the past half century have been equal in value to all of the consumption increases from all other sources put together. Nordhaus's claim is backed up by evidence documenting the extensive gains in longevity and other dimensions of human health over the period; multiplying these gains by even conservative estimates of the value of a "statistical life" result in very large numbers (*e.g.*, Murphy and Topel, 2006). Celebrated experts in the economics of health care, such as Victor Fuchs, have suggested that most of the real improvement in human health generated over this period stems from modern medicine's expanding arsenal of pharmaceutical products. While documenting these claims in a way that meets modern evidentiary standards is challenging, the work of scholars such as Frank Lichtenberg (2001, 2004, 2007) has provided evidence suggesting the gains from pharmaceutical innovation have been very large. In the long run, global investments in pharmaceutical research have proven to be very good ones.

These benefits, however, have not come without significant costs; pharmaceutical innovation is highly risky and expensive. These costs are passed on to consumers in the form of higher prices. Currently, prescription drug spending in the U.S. exceeds $300 billion, an increase of $135 billion since 2001, comprising approximately 12 percent of total health care spending (GAO, 2012). Over this time period, generic products continue to account for an ever increasing share of these prescriptions drug expenditures, saving consumers an estimated $1 trillion (GAO, 2012). Current regulation attempts to balance the trade-off between access to lower cost generics while at the same time continuing to incentivize innovation. And while the presence of generics has been shown to be welfare enhancing in the short-run (Branstetter *et al*., 2011), others have argued that this balance has 'tipped' in favor of access (Higgins and Graham, 2009; Knowles, 2010). Still unanswered, however, is whether this increase in generic entry has harmed long term innovation. Our study attempts to address this question and quantify, for the first time, the impact of generic entry on early-stage pharmaceutical innovation.

We start by constructing a novel and unique dataset which allows us to analyze this issue at a narrow therapeutic level. Instead of relying on patents as measures of innovation we instead focus on actual early-stage pipeline products. While patenting is certainly important in the pharmaceutical industry, it can occur anytime throughout the drug development process. Our focus, on the other hand, allows us to analyze what is happening specifically to the early-stage inputs of the clinical development process. Current regulation provides the mechanisms by which generics are allowed to enter the U.S. market. As such, if we find a relationship between generics and early-stage innovation, our findings should add to a

rich historical literature dealing with regulation and innovation (*e.g.*, Schumpeter, 1934; Arrow, 1962; Temin, 1979;Dasgupta and Stiglitz, 1980;Jaffe and Lerner, 2006).

Our empirical framework starts by modeling the flow of early-stage pharmaceutical innovations as a function of generic entry and penetration, as well as scientific opportunity and challenges, firm innovative capability and a vector of additional controls. In doing so, we make several contributions to the literature. Firstly, we document a negative and significant relationship between generic entry (penetration) and early-stage innovation. The elasticity from our specification implies that a 10% increase in generic penetration in a particular market will *decrease* early-stage innovations, in that same market, by 7.3%.

Second, we isolate the top therapeutic markets and while our baseline result remain robust we also find that early generic Paragraph IV challenges are associated with declines in early-stage innovation, a finding consistent with the theoretical predictions of Hughes *et al* (2002). Third, Branstetter *et al.* (2011) document the extent of cross-molecular substitution (CMS) in the hypertension market. We focus on one such sub-market, anti-epileptics, where we expect CMS to be low for medical and scientific reasons. Interestingly, in this sub-market, we find no evidence that the growing presence of generics is slowing the flow of early-stage innovation in anti-epileptics. This finding suggests a possible differential effect of generics across sub-markets depending on the extent of CMS.

Finally, if the *flow* of innovation in a particular market is slowing, the natural question arises as to where pharmaceutical innovation is taking place? We consider the possibility that a *rotation* is occurring out of chemical-based (small molecule) products into biologic-based (large molecule) products. Current regulation does not extend to biologics and there is no pathway for 'biosimilars' to enter the U.S. market. Exploiting this regulatory difference between chemical and biologic-based innovations we indeed find a positive relationship between generic entry and a *rotation* towards biologic-based products. As conjectured by Golec *et al*. (2010), such a rotation suggests that the nature of innovation taking place in the pharmaceutical industry is changing.

Our results should be viewed in a nuanced manner. On one hand, we demonstrate that the advent of generics is related to a declining flow of early-stage innovation. If the flow of early-stage innovation slows it is rational to expect the flow of late-stage products to also decline. On the other hand, one could argue that regulation is in fact 'pushing' innovation away to therapeutic markets for which viable generics do not exist. As a result, R&D efforts and expenditures could potentially be flowing to other therapeutic areas which may be more underserved. While conducting a more micro analysis of which therapeutic categories might have gained, it is beyond the scope of this paper. That said we do document that a broad rotation is occurring from chemical-based to biologic-based products. This change in the type of innovation may have significant implications for the future, especially since biologics tend to be more

expensive, on average, than chemical-based products and until current regulatory challenges are resolved, these higher prices will persist for longer periods of time.

The paper proceeds as follows. Section 2 offers a brief discussion of the regulatory environment around generic competition in which pharmaceutical firms operate. Section 3 discusses related literature. Our empirical specification and data are outlined in Section 4. Results are presented in Section 5 and we conclude in Section 6.

2 Regulatory environment and generic entry

The current regulatory environment faced by pharmaceutical companies in the United States can be traced to the passage of the Drug Price Competition and Patent Term Restoration Act in 1984, informally known as "Hatch-Waxman". One of the hallmarks of the legislation is its purported trade-off: it allows expedited Food and Drug Administration (FDA) approval for generic entry while extending the life of pharmaceutical patents in order to compensate innovators who lost time on their "patent clocks" waiting for FDA approval (Grabowski, 2007). This balance was deemed necessary to equalize two conflicting policy objectives: giving pharmaceutical firms incentives to conduct drug research while simultaneously improving consumer welfare by enabling generic firms to quickly bring copies to market (Federal Trade Commission (FTC), 2002).

When a pharmaceutical company submits a New Drug Application (NDA) to the FDA for approval they are required, by law, to identify all relevant patented technologies necessary to create the drug; these patents are subsequently listed in the FDA Orange Book. Upon approval of a drug, the FDA will restore patent term to the pharmaceutical firm for time used by the FDA in the approval process (Grabowski, 2007).[1] In addition, the FDA will also grant each new approved product regulatory protection lasting for five years ("data exclusivity") which runs concurrently with patent protection.[2] During this data exclusivity period, regardless of the status of the underlying patent(s), no generic entry may occur. At the conclusion of data exclusivity branded products are protected only by their patents; this period running from the cessation of data exclusivity to the expiration of the patent(s) is commonly referred to as "market exclusivity" (Figure 1).

Prior to the passage of Hatch-Waxman, generic manufacturers seeking to sell their products in the U.S. market had to demonstrate the safety and efficacy of their products by putting them through clinical trials. While the outcome of these trials lacked the uncertainty involved in the trials of an innovative new

[1] There are limits to this. Pharmaceutical firms cannot receive a patent extension of more than five years, nor are they entitled to patent extensions that give them effective patent life (post approval) of greater than 14 years.
[2] Orphan drugs receive 7 years of data exclusivity; reformulations receive 3 years of data exclusivity and pediatric indications receive an additional 6 months of data exclusivity.

drug, the time and expense involved were a significant disincentive for generics manufacturers to put products on the market, since they could not charge a premium price to offset the costs of clinical trials. Before Hatch-Waxman, it is estimated that more than 150 products existed without any patent protection and without any generic entry (Mossinghoff, 1999). While Hatch-Waxman did not lessen the burden of the clinical trials process for branded pharmaceutical companies seeking approval for new drugs, it essentially eliminated the requirement for separate clinical trials for generic manufacturers. This was made possible since generic manufacturers could simply demonstrate "bioequivalence" with branded products by showing that the active ingredient in their product diffused into the human bloodstream in a manner similar to the original product.

Hatch-Waxman provides four pathways (or "Paragraphs") a generic firm may follow in order to gain entry into a market (Figure 2).The process starts with the filing of an Abbreviated New Drug Application (ANDA) by a generic manufacturer with one of the four Paragraph certifications. A Paragraph I certification is one for which the originator firm has not filed patent information for its branded product. Paragraph II certification relates to when the branded product's patent has already expired (*i.e*., the end of market exclusivity), and Paragraph III certification relates to cases when the generic manufacturer notes that the patent on the branded product *will* expire on a certain date and that it seeks to enter only after patent expiry or end of market exclusivity. The fourth certification, Paragraph IV, argues that the generic manufacturer does not infringe on a branded product's patents or that those patents are invalid. More importantly, however, a Paragraph IV certification can be acted on by the FDA after the conclusion of *data exclusivity* anytime during the market exclusivity window.[3]This suggests that, if successful, these challenges can significantly decrease the effective patent life of branded products bringing generics to the market earlier than otherwise would be the case (Higgins and Graham, 2009; Grabowski and Kyle, 2007). By the end of the 2000s ANDA applications with Paragraph IV certifications accounted for more than 40% of all generic filings (Higgins and Graham, 2009; Berndt *et al*., 2007).

3 Related literature

This paper draws upon the economics of innovation literature, which has a rich history dating back to Schumpeter (1934, 1942). Schumpeter argued that large monopoly firms could become the focus of innovation. This led to systematic investigations of market structure and firm size on innovation (*e.g.*, Mason, 1951; Mansfield, 1981; Prusa and Schmitz, 1991; Henderson, 1993; Cohen and Klepper, 1996a,

[3] Generic manufacturers may file a Paragraph IV certification up to one year prior to the end of data exclusivity but the FDA may not act on it until the conclusion of data exclusivity.

1996b). Subsequent work in this stream has considered other determinants behind a firm's innovative capacity: for example, firm characteristics (Henderson and Cockburn, 1994, 1996; Ahuja*et al*., 2009), firm capabilities (Trajtenberg, 1989; Cohen and Levinthal, 1989), R&D expenditures (Griliches, 1979); the degree of interaction between R&D and other functions of the firm (Teece, 1986; Mowery and Rosenberg, 1989), and a firm's ability to tap external technology markets (Arora, 2011).

Across industries, appropriability considerations have also been shown to play an important role in shaping incentives for innovation (Cohen, 2010). Intellectual property has been an important lever in understanding the role government plays in creating or destroying incentives for innovation (Rocket, 2010). More broadly, Jaffe and Lerner (2006) point out that over time, U.S. patent policies have changed from being the "fuel for the engine to the sand in the gears." This can be especially troubling for industries that depend on patents since there is evidence that stronger intellectual property laws positively enhance incentives for innovation and social welfare (*e.g.*, Cassiman and Veugelers, 2002; Schotchmer, 2004; Bloom *et.al.*, 2007).

Empirical evidence demonstrating the benefits of intellectual property has been mixed. For example, Hall (2007) suggests that a strengthened patent system results in more use, it is less clear if it has an effect on aggregate innovative activity. This finding is supported by Sakakibara and Branstetter (2001) and Qian (2007) in different settings. This question continues to evoke interest among scholars, especially those interested in the pharmaceutical industry, since herein lies a natural experiment to explore how variation in intellectual property policies and accompanying regulatory pathways could potentially drive or reduce innovation, which has significant implications for social welfare in the long run (Hopenhayn and Mitchell, 2001; Hopenhayn*et.al.*, 2006; Higgins and Graham, 2009).

3.1 Regulation and innovation

The debate over the relationship between regulation and innovation has a long history. Classical economic theory argues that regulation imposes a cost burden on firms causing them to reallocate their innovation expenditure towards circumventing or complying with regulatory frameworks. As a result, a trade-off is created wherein societies have to grapple with their development trajectory while at the same time trying to enhance social welfare. The 'Porter Hypothesis' has been particularly influential in this context, arguing that environmental, health and safety regulations may regularly induce innovation and could possibly even enhance competition in more regulated industries. Moreover, Porter argues that early regulation that spurs innovation in compliance can create a type of first mover advantage for firms (Porter, 1991; Porter and van der Linde, 1995; Ashford and Hall, 2011).

An empirical snapshot across industries provides mixed results in studying the relationship between regulation and innovation. In manufacturing, Jaffe and Palmer (1997) find that while environmental compliance costs seem not to influence patent counts of U.S. manufacturers, there is a significant relationship between R&D expenditures and compliance. Further, Pickman (1998) finds that regulation can cause firms to change the direction of innovation from market to social innovation. Similar effects of regulation on enhanced social but decreased market innovation are documented in the nuclear power industry (Cohen, 1979; Marcus, 1988) and in healthcare organization (Walshe and Shortell, 2004). Mixed results have been seen in telecommunications (Prieger, 2007; Kahn *et al*., 1999) while positive effects have been documented in in the financial sector (Baer and Pavel, 1988; Silber 1983), fisheries (Aerni, 2004) and autos (Atkinson and Garner, 1987; Goldberg, 1998). Finally, in the pulp and paper industry Norberg-Bohm and Rossi (1998) find that regulation potentially enhances innovation but the innovation might be more incremental in nature.

Despite these extensive studies a fundamental question in the economics of innovation remains unsettled, with direct impact on this discussion. Ambiguity still remains on the optimal market structure required for enhancing innovation (Farrell and Shapiro, 2008) and the accompanying regulatory environment required herein. As a result policy makers have found it difficult to align social and private benefits from innovation simply by increasing or decreasing innovation incentives through regulatory policies, intellectual property or otherwise. For example, Segal and Whinston (2007) discuss how competition policies that protect new entrants from exclusionary behavior by incumbents can raise entrant profits, thereby encouraging entrant innovation. However, lower possible future profits from incumbency can eventually slow the rate of innovation.

3.2 Regulation and incentives to innovate in the pharmaceutical industry

The pharmaceutical industry offers a 'fascinating laboratory' to investigate what we know and do not know about the economics of innovation (Scherer, 2010). Historically, regulation has played a key role in this industry (Wiggins, 1981; Danzon *et al*., 2003; Danzon and Keuffel, 2007) especially with the social planner trying to achieve the right balance between private and social benefits from innovation (Grabowski *et al*., 1978; Higgins and Graham, 2009; Munos, 2009).Moreover, current patent policy appears to have bifurcated competition within the industry into two categories (Lichtenberg and Philipson, 2002; Philipson and Dai, 2003). The first is “within-patent competition” or direct competition from generic manufacturers producing the same product as a pharmaceutical company. The second,

"between-patent competition", results from similar products other pharmaceutical companies might be producing.

Studying various aspects of regulation on pharmaceutical innovation, researchers have come to differing conclusions. One on hand, some have found regulation harmful for innovation. For example, Hauptman and Roberts (1987) found a temporary reduction in innovation due to increased stringency of regulation on young biotechnology firms. Grabowski and Vernon (1977) argued that increased stringency and compliance uncertainty due to regulatory delay resulted in decreased innovation. Grabowski *et al* (1978) arrived at similar conclusions in analyzing the impacts of the 1962 Kefauever-Harris Amendments, which increased the rigor of drug screening. Using the UK as a baseline for regulatory stringency, Thomas (1990) argued that gradual increases in regulatory stringency harmed innovation in smaller pharmaceutical firms. In contrast, studies by Katz (2007) and Eisenberg (2007) found that regulation promoted more clarity and complete information in the market thereby stimulating innovation. More specifically, Katz argued that stringent regulation acted as an "anti-lemons" device. This increased the value of drugs making it to market which, in turn, incentivized innovation. This view is supported by Munos (2009). While these studies have focused on the flows of innovation, Golec *et al* (2010) argues that the flow might not change but rather the nature of the innovation.

The overarching role of regulation for innovation in the industry is further complicated by the nature of drug discovery. Getting a new drug to market is a highly probabilistic event that is long and requires significant R&D commitments (DiMasi *et al*., 1991, 2003; Pisano 2006). While there were quite a number of new drugs launched in the mid-1990s, the number of new chemical entities introduced since then have stagnated or declined. This raises a fundamental question about the productivity of pharmaceutical R&D (Cockburn, 2006). These declines are taking place in an era of increasing R&D expenditures, a robust supply of basic science coming from university research, and a healthy market for ideas and technology.

Apart from the nature of drug discovery, generic entry and competition have been important determinants in innovation incentives in the pharmaceutical industry (Grabowski and Vernon, 1990; Comanor and Scherer, 2011). Regulation, namely Hatch-Waxman, provides the mechanism for all modes of generic entry. Prior research has analyzed the entry decision by generic manufacturers after branded patent expiration (*e.g.*, Scott Morton, 2000; Reiffen and Ward, 2005) as well as the early entry decisions via Paragraph IV challenges (Berndt *et al*.,2007; Higgins and Graham, 2009; Hemphill and Sampat, 2011). While recent work has explored the impacts of these early generic challenges on welfare (Branstetter *et al*., 2011; Mulcahy, 2011), firm value (Panattoni, 2011) and alliance formation (Filson and

Oweis, 2010), less attention has been paid to demonstrating the effects, if any, of generic entry on innovation.

Hughes *et al* (2002) theoretically predicts a decrease in the flow of new drugs and other authors have hypothesized about the impact (Grabowski and Kyle, 2007; Higgins and Graham, 2009; Branstetter *et al*., 2011). One exception is a study by Filson and Oweis (2010). They find a negative relationship between early generic challenges and alliance formation. Within the biopharmaceutical context prior research has linked alliance formation with innovation and new product development (Rothaermel and Deeds, 2004; Hoang and Rothaermel, 2005), thereby providing an indirect link between early generic entry and diminished innovation.

4 Empirical specifications and data

Previous research in this area has struggled with data limitations. We are fortunate to have access to a range of unique and comprehensive data sets that provide us with powerful leverage over some of the econometric challenges we confront. First, data from Pharmaprojects is used to construct our innovation measure as well as provide information on late-stage and current products. This data was also used to obtain information on pipeline suspensions and discontinuations as well as product withdrawals. Sales (branded and generic) and promotions data for all drugs sold in the U.S. for our sample firms was obtained from IMS MIDAS™. Data from Parry Ashford Publications (www.paragraphfour.com) allows us to identify each Paragraph IV certification dating back to 2003.[4] This data provides full drug level information about the challenge and outcome which we can link to our other data resources. For data prior to 2003 we filed a Freedom of Information Act (FOIA) request with the FDA. Publications data was obtained from PubMed with relevant citations gathered from SCOPUS. Finally, data from IMS NDTI™ and IMS MIDAS™ were combined in order to create a concordance between ICD-9 and ATC.[5]

Due to data constraints our final sample covers 1998 to 2010. Firms are included in our sample if they had at least one approved product and at least one early-stage innovation, limiting our focus to larger firms. This limitation excludes smaller, research-intensive firms. Clearly these smaller firms are important to the industry however our focus is on how generic competition an incumbent pharmaceutical firm faces within a product market influences their early stage innovation decision. Thus, our unit of

[4] Paragraph IV certification data only became publicly available in 2003. In order to supplement the data prior to 2003 we filed a FOIA request with the FDA. Other researchers (Berndt *et al*., 2007) have used survey data in order to capture pre-2003 activity. In a recent study, Panattoni (2011) collected data from District Court decisions.

[5] The 9th revision of the International Disease Codes (ICD) is maintained jointly by the National Center for Health Statistics and Centers for Medicare and Medicaid Services. Anatomical Therapeutic Codes (ATC) are controlled by the World Health Organization Collaborating Centre for Drug Statistics (WHOCC).

observation is at the firm, therapeutic class, and year level. Since not all firms innovate in all every therapeutic category in every year of our sample, the panel is unbalanced. All financial variables are converted to constant 2005 dollars.

4.1 Empirical specifications

The regulatory structure imposed on the pharmaceutical industry makes early-stage product development relatively easy to track. Before obtaining approval to market a new drug, pharmaceutical firms must bring each prospective new product through a series of clinical trials, each one more comprehensive than the previous one. Because the introduction of new drugs is so important for the financial health of drug companies, the progress of new candidate drugs through the development "pipeline" is closely tracked, and commercial databases contain rich data on these candidates. Not only is there nearly universal coverage of all candidate drugs being tested for eventual sale in the U.S. market, but we also know the chemical composition of the drug, the prospective disease targets, and the development history (some drugs are initially developed to fight one disease but then are discovered to have positive effects against others). The richness of the data allows us to pose the following question: has the rising intensity of generic entry caused a slowdown in the early-stage introduction of new compounds?

Attempts to assess this relationship confront a major challenge. At the same time that generic entry has been rising, the pharmaceutical industry has encountered a widely publicized "productivity crisis" (Cockburn, 2006). R&D expenditures rose throughout the 1990s and early-to-mid 2000s, but new drug approvals peaked in the mid-1990s and have been stagnant or falling ever since. Many inside and outside the industry speak of an exhaustion of research opportunities; the easy-to-discover drugs have already been introduced; and, the diseases that are now the focus of research effort are extremely complex and difficult to treat. To the extent that there really is a decline in research productivity, this could lead firms to ratchet back R&D expenditure, even in the absence of a growing generic threat to profitability. Our empirical challenge will be assess the impact of increased generic entry on new innovation while controlling for contemporaneous changes in research opportunities.

We propose to do this using a regression specification that models introductions of new compounds into early stage clinical development as a function of scientific opportunity and challenges, firm innovative capability, downstream co-specialized assets, and generic entry, with a vector of additional controls.

$$I_{ijt} = \alpha_0 + \beta_1 GP_{ijt} + \beta_2 G_{ijt} + \beta_3 O_{jt-1} + \beta_4 Z_{ijt-1} + \beta_5 D_{ijt-1} + \beta_6 P_{ijt-1} + \beta_7 SA_{ijt} + \beta_8 S_{it} + \varepsilon_{ijt} \qquad (1)$$

where I_{ijt}, measures early-stage pipeline innovations by firm *i* in ATC 2-digit market *j* in time *t*. Because the outcome variable is a count variable, the statistical model employed in our regression should be one designed to handle count data. We use the fixed effects Poisson and negative binomial estimators developed by Hausman *et al*. (1984), with the standard errors for the Poisson model adjusted as recommended by Woolridge (1999). Given that not all firms innovate in each therapeutic category in each year, it is possible that the data may contain zeros. The negative binomial has the advantage of dealing with this in a natural way. The specification includes fixed effects for year (α_t), firm (α_i), and therapeutic (ATC) category (α_j). It is possible that we are not capturing all the dynamic, unobserved nature of technological opportunities arising in product markets. Therefore, we also include a paired fixed effect, interacting therapeutic market dummies with year dummies, (α_j*α_t).[6]

With the passage of Hatch-Waxman generic drugs have been able to enter the market more easily and quickly (Congressional Budget Office, 1998; Saha *et al.,* 2006). As such, we attempt to capture the influence of generic penetration (GP_{ijt}) and incidence of attempted early generic entry (G_{ijt}) facing firm *i* in market *j* and time *t*. If our goal is to isolate the possible generic effects on innovation, then we need to control for underlying scientific opportunities (O_{jt-1}) and challenges (Z_{ijt-1}) within a specific therapeutic market (*j*) and time (*t-1*).

Pharmaceutical firms differ in their research and development capabilities which they have built over time. A given firm is more likely to introduce a new compound in a therapeutic category in which it already has substantial research expertise. We control for this expertise by constructing a three-year moving average of past product introductions (D_{ijt-1}) for firm *i* in therapeutic market *j* lagged one period, *t-1*. In addition to past introductions we capture products in later-stage development (P_{ijt-1}) for firm *i*, in therapeutic market *j* lagged one period, *t-1*.Prior research has also documented a strong connection between a firm's downstream co-specialized assets and their R&D decision (Teece, 1986; Chan *et al*., 2007). We measure a pharmaceutical firm's, *i*, downstream investment by a ratio of their promotions

[6] Technological opportunities maybe unobserved at the product market level and evolve over time as a function of the nature of the innovation process as well as the market's response to the launch of a new innovation (Schmookler, 1962); this is a characteristic not uncommon to pharmaceuticals. Statin drugs, which today are one of the largest selling therapeutics, had a difficult beginning in 1978 with the unsuccessful launch of Mevacor®. Over time, however, these difficulties subsided as new technological opportunities led to the five types of statin-molecules currently sold in the U.S.

expenditures and sales in particular therapeutic market, *j*, and time, *t*. Finally, we use sales by firm *i* in year *t* to control for firm size.[7]

Current regulation provides an alternative for estimating the impact of generics on innovation. Chemistry-based pharmaceutical products become susceptible to Paragraph III generic entry after patent expiration. However, they also become susceptible to early generic entry via Paragraph IV challenges after only five years after approval (Figure 1). The same legal frameworks do not (yet) provide the same pathway for biosimilar entry after biologic patent expiration or the equivalent of a Paragraph IV challenge. Furthermore, biotechnology-based products are explicitly guaranteed 12 years of data exclusivity so even if and when Paragraph IV challenges of biologic drugs become feasible, they will occur much later in the product life cycle. Clearly, this difference in regulation creates an incentive for pharmaceutical companies to favor biologic-based ("large molecule") therapies over chemistry-based ("small molecule") therapies, even if the latter may be more effective in a purely therapeutic sense. This suggests an alternative specification:

$$CI_{ijt} - BI_{ijt} = \alpha_0 + \beta_1 GP_{ijt} + \beta_2 G_{ijt} + \beta_3 O_{jt-1} + \beta_4 Z_{ijt-1} + \beta_5 (CD_{ijt-1} - BD_{ijt-1}) + \beta_6 P_{ijt-1} + \beta_7 (CSA_{ijt} - BSA_{ijt}) + \beta_8 S_{it} + \varepsilon_{ijt} \quad (2)$$

Here, the dependent variable measures the difference between chemistry-based innovations and biologic-based innovations. Likewise, our controls for firm-specific development capability and market presence are redefined to reflect relative capability in chemistry-based versus biologic-based development. Given these controls, we would not expect generic penetration (GP_{ijt}) or early generic entry (G_{ijt}) to have an impact on the choice of technology – unless firms' research choices are being affected by the prospect of generic competition.

4.2 Dependent Variables

4.2.1 Early-stage innovation (I_{ijt})

Innovation in the pharmaceutical industry has been measured a number of different ways, for example, by patents or new products. Unlike patents which can be obtained for a drug candidate at any stage of development, given our current interest, we want to ensure that we are consistently observing activity at any early reported stage of development. If firms are responding to exogenous factors, such as generic penetration, early generic entry or changes in scientific opportunity, this is the area in the pipeline

[7] Optimally we would like to measure a firm's R&D expenses at the therapeutic category level. Unfortunately, this data is not publicly reported. Since R&D expenses are only available at the firm, year level, we exclude them and sweep that effect into our firm size variable, S_{it}, and firm fixed effect, α_i.

we would expect to observe the impact. Moreover, when viewed in its entirety, this portion of the research pipeline has the lowest opportunity costs in terms of switching, altering or abandoning a project. As such, using data from Pharmaprojects we define (I_{ijt}) as a count of pre-clinical and Phase I products for firm *i*, in therapeutic market *j* at time *t*.

4.2.2 Difference in early-stage innovation ($CI_{ijt} - BI_{ijt}$)

If current regulation is in fact causing biologic-based innovation to be preferred to chemical-based innovation then we need to modify our innovation measure in order to capture this change. Using the *Origin of Material* field within Pharmaprojects we are able to sort early-stage innovation (I_{ijt}) into either a biologic-based (BI_{ijt}) or chemical-based (CI_{ijt}) innovation. In operationalizing Equation (2), the dependent variable is the difference between these two types of innovation, $CI_{ijt} - BI_{ijt}$. A negative coefficient on a right-hand side (RHS) variable (GP_{ijt} or G_{ijt}) would imply that as that variable increased the difference ($CI_{ijt} - BI_{ijt}$) would decline. In other words, BI_{ijt} is greater than CI_{ijt} or the flow of biologic-based innovations exceeds the flow of chemical-based innovations.

It is possible for firm *i*, in therapeutic market *j* in time *t* to have more biologic-based than chemical-based innovations. In this case, our difference variable ($CI_{ijt} - BI_{ijt}$) will become negative, negating the use of count variable models. As such, we create a new variable, $dum(CI_{ijt} - BI_{ijt})$, that equals 1, 2 and 3 if ($CI_{ijt} - BI_{ijt}$) is negative, zero or positive, respectively. This reclassification will permit us to use an ordered logit specification (Hausman*et al.*, 1992).[8] Again, a negative coefficient on a RHS variable would imply that as that variable increased $dum(CI_{ijt} - BI_{ijt})$ will decline. In this case the difference, ($CI_{ijt} - BI_{ijt}$), will become negative and the interpretation is the same as above.

4.3 Independent Variables

4.3.1 Generic penetration (GP_{ijt})

Hatch-Waxman laid out the modes by which generic manufacturers can enter chemical-based therapeutic markets. This entry eventually leads to rapid deterioration in branded market sales (Saha*et al*, 2006). The pharmaceutical industry has engaged in a variety of tactics to delay this loss, such as authorized generics, however these efforts are at best temporary. Using product level data from IMS MIDAS™ we are able to determine the extent of generic penetration that firm *i* faces in therapeutic *j* in time *t*. We define generic penetration (GP_{ijt}) as the sum of generic sales in therapeutic *j* at time *t* divided

[8] We thank Jerry Thursby for this suggestion.

by the sum of generic and firm *i* sales in therapeutic *j* at time *t*. A negative coefficient on GP_{ijt} implies that as generic penetration in a therapeutic market increases, the flow of innovations decrease.

4.3.2 Paragraph IV challenges (G_{ijt})

Early generic entry via Paragraph IV challenges have steadily increased since early 2000. Successful challenges permit early entry of generic products prior to the expiration of branded product patents, effectively compressing patent lives (Grabowski and Kyle, 2007) leading to producer loss (Branstetter *et al*, 2011). We use data from Perry Ashford Publications (www.paragraphfour.com) and FDA in order to track these product challenges. For each firm *i* we generate a stock of challenges, G_{ijt}, in therapeutic market *j* at time *t*. A negative coefficient on G_{ijt} implies that as early generic challenges increase in a therapeutic market, the flow of innovations decrease. This is consistent with the theoretical prediction of Hughes *et al.* (2002).

4.4 Controls

4.4.1 Scientific opportunities (O_{jt-1})

Our interest is in capturing potential changes in early stage innovations. Equation 1 captures both the change in flows in innovations within therapeutic market *j* while Equation 2 captures the potential rotation between chemical-based and biologic-based innovations. A major concern will be effectively capturing and controlling for underlying scientific opportunities within each therapeutic market *j* at time *t*. Sufficiently capturing scientific and technological opportunities has been a grand challenge in the economics of innovation literature dating back to Griliches' (1979) seminal work. Similar to Furman *et al*. (2006), we construct a novel bibliographic measure that captures publicly available academic research in the life sciences. Prior research has demonstrated the link between academic research and inputs into the innovation process (Mansfield, 1995; Gittelman and Kogut, 2003).

We start by merging data from IMS MIDAS™ and IMS NDTI™ in order to create a concordance between ICD-9 codes and ATC4. Created within this concordance is a list of standardized keywords from ICD-9. These keywords are searched within the National Library of Medicine's PUBMED database which we then assign to the matching ATC4. This search identified a unique sample of 6.5 million journal articles between 1950 and 2010. Journal articles can be applicable to multiple ATC4 categories thus creating a raw article count of over 20.9 million. Next, the SCOPUS database was used in order to gather forward citations from the year of publication to the end of 2010. Our sample of 20.9 million articles generated over 345 million forward citations. Finally, since our unit of observation in a therapeutic market is at the two-digit ATC level, we aggregate this data from ATC4 to ATC2. Thus our variable O_{jt-1},

we argue, captures scientific opportunities available in therapeutic market *j* at time *t-1*. A natural log transformation was applied to this variable.

4.4.2 Scientific challenges (Z_{ijt-1})

In contrast to scientific opportunities that may potentially "pull" firms *towards* a specific therapeutic market, we control for scientific challenges that may "push" firms *away* from a specific therapeutic market. Utilizing data from Pharmaprojects we identify all suspended, discontinued and withdrawn products across the entire research pipeline from pre-clinical candidates to approved products. Development can be ended and products pulled for a multitude of reasons many of which, at their most fundamental level, are due to some type of scientific challenge. For example, Merck pulled Vioxx® from the market due to negative side-effects while the Alzheimer disease drug candidate semagacestat was discontinued by Eli Lilly in Phase III clinical trials after disappointing results. We define Z_{ijt-1}as the number of scientific challenges faced by firm *i*, in therapeutic market *j* at time *t-1*.

4.4.3 Other controls

Clearly, pharmaceutical companies differ in their drug development capabilities they have built over time. A given firm is more likely to introduce a new compound in a therapeutic category in which it already has substantial research expertise. In order to control for this persistence we use data from Pharmaprojects to create a three-year moving average of past drug introductions, D_{ijt-1}, by firm *i* in the same therapeutic market *j*. This three-year moving average is then lagged one period,(*t-1*). Finally, for our specification in Equation 2 we decompose this variable into chemical-based (CD_{ijt-1}) and biologic-based (BD_{ijt-1}) products.

In addition to controlling for past products, we also control for late-stage innovations within the product pipeline. Using data from Pharmaprojects we define P_{ijt-1}as the number of Phase II and Phase III innovations in firm *i*'s pipeline in therapeutic market *j* in time *t-1*.

Prior research has also documented the connection between downstream co-specialized assets and a strong commitment to research efforts within a particular therapeutic class (Chan *et al*, 2007). The presence of these assets can create a 'lock-in' effect, suggesting a positive relationship with early-stage innovation. Similar to Ceccagnoli *et al* (2010) we proxy a firm's downstream co-specialized assets by a ratio of promotions to product sales, SA_{ijt}, for firm *i* within therapeutic market *j* at time *t*. Promotions and product sales are collected from IMS MIDAS™ and promotions consists of detailing, journal advertising and direct-mail. Detailing is the direct promotion of products by pharmaceutical representatives to physicians. As with our prior controls, for the specification in Equation 2, we decompose this ratio into a

firm's chemical-based (CSA_{ijt}) and biologic-based (BSA_{ijt}) commitments. Finally, firm size can impact innovation rates. As a result, we control for firm size with pharmaceutical sales by firm *i* in year *t*, S_{it}. Sales data was gathered from IMS MIDAS™ and natural logs were taken.

5 Empirical Results

5.1 Descriptive statistics

Descriptive statistics for our variables are presented in Table 1 and a correlation matrix is presented in Table 2. Our dependent variable, I_{ijt}, captures early-stage innovation and varies between 0 and 36 for firm *i*, in therapeutic market *j*, at time *t*. While our firms had, on average, 0.78 early-stage innovations within a therapeutic market at time *t*, if should be remembered that not every firm has an early-stage innovation, in every therapeutic market in each year. If we focus solely on therapeutic categories with activity, then the average increases to 2.12 early-stage innovations. Firms in the top quartile of firm size had, on average, 3.07 innovations within a therapeutic market *j* at time *t*, as compared to 1.45 innovations for the smallest quartile firms. ATC N, focusing on the nervous system, had the largest number of innovations, while ATC P, which focuses on anti-parasitic products, had the lowest number of innovations. The relative contribution to total innovations of each broad therapeutic category (ATC1) over our sample period is displayed in Figure 3.

Generic penetration, GP_{ijt}, was about 54% at the mean and just over 80% at the median. Generic penetration was greatest in ATC S (sensory organs) and lowest in ATC J (anti-infectives). Over our sample period, generic penetration ranged from 53% to 57% with the last two years seeing an increase to 56% and 57%, respectively. Further, on average, the stock of Paragraph IV challenge (G_{ijt}) that firm *i*, faced in a therapeutic category *j*, in year *t*, was 0.01 with a maximum of 3 faced by Pfizer in 2010 within urological drugs (ATC G4). If we focus on those categories where challenges occur, the average number of drugs being challenged increases to 1.10. Consistent with prior findings (Higgins and Graham, 2009), the number of Paragraph IV challenges are increasing over our sample period.

Our measure of technological opportunity, O_{jt-1}, measured by the logarithm of stock of citation weighted articles in year *t-1* for therapeutic market *j*, varied between 0 and 17.9, with an average of 8.09. This average translates into an absolute value of approximately 4.35 million citations for each therapeutic market *j* in each year *t-1*. Over our sample period the greatest technological opportunity existed in ATC categories N5 (psycholeptics) and N6 (psychoanaleptics). ATC N5 includes antipsychotics, anxiolytics, and hypnotics and sedatives. ATC N6 includes antidepressants, psychostimulants, combined psycholeptics and pschoanaleptics, and anti-dementia. This measure of technological opportunity is

negatively correlated with our measure of technological challenges, Z_{ijt-1}. On average our firms faced 0.05 challenges in therapeutic market *j* at time *t-1*. The number of challenges varied between 0.26 and 6 with the greatest technical challenges experienced in ATC T2, which includes various recombinant-based products, such as interferon.

On average, our firms had a lagged three-year moving average of 0.24 products and 0.09 late-stage products in therapeutic market *j* at time *t-1*. Our control for downstream co-specialized assets, the ratio of promotions to sales for firm *i* in therapeutic market *j* at time *t*, averaged 45%. This suggests firms are making significant downstream investments in therapeutic areas in which they operate (and plan to operate). Finally, it is essential to control for firm size, which we do by the logarithm of total pharmaceutical sales for firm *i* in year *t*, which, on average, is 12.64.

5.2 Results

5.2.1 Impact of generic entry on the flow of innovation

We start by considering the possible effects on the flow of early-stage innovation due to overall generic penetration and early generic challenge. We first test Equation 1 with a Poisson specification (Table 3). However, given the Poisson's well know problem of assuming that the mean of the distribution is equal to the variance, we also present results using a fixed-effect negative binomial specification (Table 4). The dependent variable, in all specifications is I_{ijt} or the count of firm *i* innovations in therapeutic market *j* at time *t*. Model 1 in both tables (Table 3 and Table 4) presents a baseline regression with firm controls and firm, year and therapeutic market fixed effects; Model 2 in each table adds controls for scientific opportunity (O_{jt-1}) and scientific challenges (Z_{ijt-1}); finally, in Models 3, 4, and 5 again for each table, we include our complete specification with differing sets of fixed effects. Model 3 includes just firm and year fixed effects, Model 4 adds therapeutic fixed effects while Model 5 includes an interaction between the year and therapeutic market fixed effects. This interaction, we argue, controls for unobserved changes in a particular therapeutic market in a specific year. Standard errors in Table 3are adjusted according to Wooldridge (1999).

Across all specifications and models we find a negative and significant coefficient estimate on GP_{ijt}. This negative relationship suggests that increases in generic penetration are related to decreases in the flow of early stage innovation. Taking the coefficient from our complete specification (Model 5, Table 4) we calculate an elasticity equal to -0.73. In other words, a 10% increase in generic penetration is related to a 7.3% decrease in early-stage innovation. To our knowledge this is the first empirical evidence that documents the effect of generic penetration on early-stage pharmaceutical innovation in the U.S.

Since the pathway for generic entry is provided for under Hatch-Waxman, we can attribute this potential loss in innovation coming from regulation. If fewer candidates are entering a therapeutic pipeline then fewer drugs will eventually come out.

For much of the last decade the pharmaceutical industry has been experiencing a productivity decline (*e.g.*, Moses *et al*., 2005; Cockburn, 2006; Munos, 2009; Pammolli, *et al*., 2011); for markets that have experienced significant generic penetration our results provide one possible explanation for this decline. Unlike other types of markets, once a generic becomes available, uptake increases significantly due to their lower cost and utilization by drug insurance plans. Over our sample period, the total generic share of the prescription market in the U.S. increased from 51% to 67%.[9]As such, in many markets generics have come to dominate.

Generic penetration into a market is clearly harmful for branded producers; though, from a social welfare perspective the interpretation is more nuanced. If viable generics are present in a market, our results indicate that innovation will decrease *in that market.*[10]Notwithstanding this decrease, it is reasonable to expect those research expenditures to be deployed to other therapeutic markets. Indeed Pammolli *et al*. (2011) argues that one of the reasons R&D productivity has declined has been a shift into areas with unmet therapeutic needs, which also have higher risks of failure. Our results support this view and provide one possible explanation for why this shift may be occurring. In essence regulation, namely Hatch-Waxman, by providing mechanisms of entry for generics create conditions under which the pharmaceutical industry redirects R&D efforts to markets less (or not) served by generics.

If such a rotation from one therapeutic market to the next is occurring, this can possibly have significant future consequences. First and foremost, if the therapeutic category that is seeing research expenditures leave has a different transition probability than the therapeutic category where expenditures are flowing, this could have consequences on the net flow of innovation (either increasing or decreasing). Second, if the rotation is causing a shift from chemical-based (small molecule) products to biologic-based

[9] Based on author's calculations using data from IMS MIDAS™ accessed 12 March 2012.

[10]In theory, generics should be perfect substitutes for branded drugs since they are bioequivalent. Cleanthous (2002) shows that the data do not support this relationship and suggests this is the result of 'spurious product differentiation', which he defines as arising "…when consumers perceive physically identical products to differ in quality." Recent evidence, however, may suggest that consumer perceptions have merit and while drugs may be bioequivalent, they may indeed differ in quality. Several articles appeared in the April 17, 2007 edition of the prestigious journal *Neurology* discussing the high incidence of break-through seizures with generic anti-epileptics. Insurance companies such as Blue Cross Blue Shield of Georgia allow pediatric customers to stay on branded anti-epileptic medications even though generics are available. Differences across generics for the same brand have also been reported. We are not suggesting all generics have problems but it appears in some instances where the therapeutic window is very narrow these perceptions may have some merit.

(large molecule) products (we consider this possibility below) then this could have severe consequences for the nations' future prescription drug bill as large molecule drugs are often orders of magnitude more expensive than small molecule drugs. Currently Hatch-Waxman does not extend to biologic-based products. They also have longer data exclusivity (12 years versus 5 years) and there is currently no regulatory path for "biosimilars" to actually enter the market. In sum, the current regulatory environment has created an economic incentive to pursue biologic-based products over chemical-based ones.

For chemical-based products Hatch-Waxman provides a mechanism for possible early entry via the Paragraph-IV challenge. Prior work has demonstrated the welfare effects (Branstetter *et al.*, 2011) and impacts on alliances (Filson and Oweis, 2010) of early generic entry via these challenges. In our models we consider whether these early challenges appear to have any influence on the early-stage innovation decision. For our overall sample, across all specifications we find no significant effect of Paragraph-IV challenges, G_{ijt}, on early-stage innovation. These challenges are probabilistic events and while they have been relatively successful (Higgins and Graham, 2009) generic entry is not guaranteed. These combined results seem to suggest that, for our overall sample, the impact on innovation does not start until actual entry.

Turning to our controls for scientific opportunity (O_{jt-1}) and scientific challenges (Z_{ijt-1}) we find that both positively and significantly influence the flow of early-stage innovation. Using a similar approach in the creation of their scientific opportunity variable, Furman *et al.* (2005) find a positive relationship with patenting. Our results take this one step further and document a relationship with actual early-stage pipeline innovation. Much of the basic science research that is captured in our variable takes place in academic settings; as such this finding is broadly consistent with past work documenting the role of academic research in industrial innovation (*e.g.*, Mansfield, 1995; Cohen *et al*., 2002). Interestingly, while our findings are consistent with our *a priori* beliefs with respect to scientific opportunity, the same cannot be said with respect to scientific challenges. Our initial beliefs were that opportunity might serve as a mechanism to 'pull' innovation while challenges might serve as a mechanism to 'push' innovation away from a particular field. It appears, however, that firms do not shy away from scientific challenges but rather appear to respond by probing harder into these particular therapeutic markets. As others have suggested, failures can serve as a learning mechanism for future endeavors (Chiou *et al.*, 2012). Statin drugs, which today are one of the largest selling therapeutics, had a difficult beginning in 1978 with the unsuccessful launch of Mevacor®. Over time, however, the industry worked through these difficulties as new technologies led to the five types of statin-molecules currently sold in U.S.

Finally, we control for firms' research capabilities by their innovative output in a particular therapeutic market, as measured by lagged late-stage pipeline products,P_{ijt-1}, and lagged product introductions, D_{ijt-1}. Expectantly, both are positively and significantly related to the flow of early-stage innovations. The only variable that was inconsistent across the two specifications (Table 3 and Table 4) is our measure for firm size, S_{it}. Focusing on the negative coefficient on our fixed-effect negative binomial model in Table 4 seems to suggest that larger firms are laggards in terms of early-stage innovation; a relationship documented elsewhere in the literature (*e.g.*, Graves and Langowitz, 1993; Rothaermel and Hess, 2007).

5.2.1.1 Isolation of the top therapeutic categories

While other factors certainly matter, we know from prior research that market size will attract generic competition (Kyle and Grabowski, 2007; Hemphill and Sampat, 2011). In an effort to understand whether innovation decisions in the largest markets are different than our overall sample, we isolate the top seven therapeutic markets in terms of sales as of 2010 (Table 5).[11] In general, results for these top markets are similar to our overall sample with two exceptions. First, the implied elasticity associated with generic penetration, GP_{ijt}, decreases to -.22. In other words, as generic penetration increases by 10%, the flow of early-stage innovations decreases by 2.2%. Second, the coefficient on G_{ijt}, which captures the stock of Paragraph IV challenges faced by firm *i* in market *j* at time *t*, is now negative and significant. The implied elasticity from the coefficient in Model 4 (Table 5) is -0.39. In other words, a 10% increase in the stock of Paragraph IV challenges decreases the flow early-stage innovation by 3.9% within market *j* for firm *i* at time *t*.

It appears that in the largest markets, pharmaceutical firms are not waiting until actual entry occurs to make early innovation decisions. We conjecture that this might be a result of the sheer volume of challengers that attack a larger market drug. Recent work documents a positive relationship between the number of generic manufacturers involved in a Paragraph IV challenge and the likelihood that early entry will occur (Palermo *et al*, 2012). As such, in these larger markets, it appears that firms may be making the innovation decision *before* generic entry actually occurs. Furthermore, the findings in Table 5 provide empirical support for the theoretical prediction of Hughes *et al*. (2002). Paragraph IV challenges and subsequent early entry have led to a compression in effective patent lives (Grabowski and Kyle,

[11]The seven markets include: ATC A2 (stomach acid-related disorders), C10 (statins for diabetes and hypertension), G3 (sex hormones and modulators of the genital system), J1 (anti-bacterial drugs for systemic use), L1 (anti-neoplastic agents or cancer drugs), N5 (anti-epileptics), N6 (anti-depressants), and R3 (obstructive airway diseases). Results are robust when we consider only the top five markets.

2007); Hughes *et al*. hypothesized that this decrease would lead to a decline in the flow of innovation, which is what we observe with our results in Table 5.

5.2.1.2 Case study: Anti-epileptics (ATC N5)

Most prescription health plans in the U.S. allow for the use of branded products until generics become available. In most cases patients will be given the generic by retail pharmacies unless the prescription is written "Dispense as Written" or if the patient explicitly asks for a branded drug (in which case there is usually a much higher co-payment). More recently, however, insurance firms have begun to engage in "cross-molecular" substitution. For example, let's assume there are 3 branded products in a particular market, *Drug A*, *Drug B* and *Drug C*, sold by three different pharmaceutical firms and that a generic for *Drug B* just entered the market. Cross-molecular substitution exists when insurance companies attempt to encourage patients taking *Drug A* or *Drug C* to switch to *Generic B*. While insurance firms cannot force patients to move they can entice them with lower (or no) copayments for *Generic B*.

The extent of these impacts will vary across therapeutic categories as some drugs are more easily substitutable. For example, we would expect higher substitutability in markets such as hypertension and allergy and lower substitutability in markets such as depression and epilepsy. Moreover, the "quality" of generic drugs has been questioned in some therapeutic markets. Multiple articles in the April 17, 2007 edition of the prestigious journal *Neurology* discussed the high incidence of break-through seizures with generic anti-epileptics. These concerns and the associated costs of break through seizures led some insurance companies, such as BlueCross Blue Shield of Georgia, to allow pediatric customers to stay on branded anti-epileptic medications even though a generic was available (Branstetter *et al*., 2011).

Economic intuition suggests that if a class of drugs was less susceptible to cross-molecular substitution and patients were more sensitive to (permitted) differences with generics, then we might expect to see a differential innovation response in that particular sub-market. Focusing on the sub-market that includes anti-epileptics (ATC N5) we indeed see this in our results (Table 6). More specifically, neither increases in generic penetration, GP_{ijt}, nor Paragraph IV challenges, G_{ijt}, appear to have any significant effect on early-stage innovation in anti-epileptics. This suggests that there are sub-markets for which direct substitution to a generic may be problematic, cross-molecular substitution is low and as a result the effect on early-stage innovation is less of a concern.

5.2.2 Are generics enhancing the switch to biologics?

Andrew Witty, CEO GlaxoSmithKline, has been a vocal proponent of generics publicly noting that the industry is moving away from 'white pill, Western markets' due to increased generic competition.[12] Others have conjectured that declining revenues associated with small molecule (chemical-based) products are increasingly motivating firms to switch to large-molecule (biologic-based) products (Wong, 2009). This suggests that generic entry may well "change the nature of technological change" in the pharmaceutical industry (Arora and Gambardella, 1994; Golec *et al*, 2010).

As we discussed above, such a rotation could have mixed consequences for future drug development. On the one hand, if the rotation is also to an underserved therapeutic market, then society may benefit from needed drugs. On the other hand, if this rotation is to a therapeutic market with a lower transition probability, then the overall flow of new drugs available to society may decline. Ultimately, fewer new drugs will also limit the potential future supply of generics. Such a rotation from chemical-based to biologic-based products, regardless of whether it is occurring in the same or different therapeutic market may also have an impact on future drug expenditures. Biologics are more expensive than chemical-based products, on average (Aitken *et al*., 2009; Trusheim *et al*., 2010). If uptake between the two types of products over their entire product lifecycle remains similar then, all else equal, the percent of overall health care expenditures spent on pharmaceuticals will increase.

In order to consider whether a rotation to biologic-based products may be occurring, we empirically test our specification in Equation 2. The dependent variable in this specification is the difference between early-stage chemical-based innovations and early-stage biologic-based innovations. As constructed this variable can now take on negative values, which negates the use of count models. As such we create a variable, $dum(CI_{ijt}\text{-}BI_{ijt})$, that equals 1, 2 and 3 if the difference ($CI_{ijt} - BI_{ijt}$) is negative, zero, or positive, respectively.[13]

Given the construction of our dependent variable, $dum(CI_{ijt}–BI_{ijt})$, we test Equation 2 with an ordered logit model (Table 7). For comparative purposes we also report results from OLS regressions (Table 8); results are qualitatively robust. Across all specifications our measure of generic penetration is negatively and significantly related to the difference in types of early-stage innovations. This suggests that as generic penetration increases, our dependent variable, $dum(CI_{ijt}\text{-}BI_{ijt})$, declines which, in turn, implies that the difference, ($CI_{ijt} - BI_{ijt}$) is decreasing. In other words as generic penetration increases the

[12] http://www.fiercepharma.com/story/glaxo-grows-out-white-pills-and-western-markets/2009-10-28-0

[13] The distribution of $dum(CI_{ijt}\text{-}BI_{ijt})$ has around 60% of the observations tightly centered around 0 but the rest equally spread between being positive and negative.

flow of biologic-based innovations is greater than the flow of chemical-based innovations for firm *i*, in market *j*, at time *t*. It appears that pharmaceutical firms are responding to generic competition by rotating to biologics where they do not face similar competitive constraints.

Consistent with our overall findings, early generic Paragraph IV challenges, G_{ijt} have no impact on the difference in early-stage innovations. Interestingly, however, the positive and significant coefficient on O_{jt-1}suggests that as scientific opportunity increases the difference between these two types of early-stage innovations decreases. In other words, the flow of chemical-based (small molecule) innovations exceeds the flow of biologic-based (large molecule) innovations. This seems somewhat counter-intuitive given the explosion of basic science research in the biologic-based sciences over the past decade. That said, the construction of O_{jt-1}starts in 1950 -- so it includes decades of research before the introduction of biologics.

Finally, our controls for firm capabilities offer mixed results. The difference in chemical-based and biologic-based approved products, ($CD_{ijt-1} - BD_{ijt-1}$), is positive and significant, as expected. In other words, if a firm has more chemical-based products (approved) relative to biologic-based products then the flow of chemical-based early-stage innovations relative to biologic-based innovations is greater. Not only do pharmaceutical firms continue to develop products within the same therapeutic category but they also appear to continue to develop products of the same type.

6 Conclusion

For many years, scholars have been interested in the effect that regulation may have on innovation. In the pharmaceutical industry current regulation provides the mechanism by which generic products are able to enter the market. We are able to exploit this framework in order to estimate the effects of generics on early-stage pharmaceutical innovation. For the first time we quantify the loss in innovation due to the presence of generics. More specifically, as generic penetration increases by 10% we observe a decrease of 7.3% in early-stage innovation. While we do not observe any relationship between early generic Paragraph IV challenges and the flow of innovation for our overall sample, when we focus specifically on the top therapeutic markets we find a slightly negative relationship. For that sample, a 10% increase in Paragraph IV challenges relates to a 3.9% decrease in the flow of early-stage innovation. For the overall sample, it appears that the firms are waiting until actual entry before making early-stage innovation decisions. However, in the largest markets it appears that firms begin to make those innovation decisions earlier when existing products are being challenged.

We observe in Branstetter *et al*. (2011) the importance of cross-molecular substitution. This suggests that there are potential submarkets where the presence of generics may have less of an impact. This is indeed what we observe in one such submarket, ATC N5, which covers anti-epileptics. In this market, we observe no effect of generics on the early-stage innovation decision. In this particular submarket, and other similar markets with low CMS, switching to another medicine, even a generic, can potentially be medically problematic. While we just analyze one particular sub-market, our analysis does suggest that there are potentially important differences across therapeutic categories. This could have policy implications in terms of how regulation related to competition can be designed such that there is a differential incidence of its intensity across various therapeutic markets.

If the flow of early-stage innovations in a particular market declines; a natural question becomes whether we observe an increase in other markets. We address this question by exploiting the differential economic incentives created by regulation between chemical-based and biologic-based products. Currently, data exclusivity is longer for biologic-based products and there exists no pathway to market for biosimilars. We conjecture that as chemical-based products are pressured by generics pharmaceutical firms will begin to change the nature of their innovation by rotating to biologics. This is indeed what we observe. Increases in generic penetration in market *j* are related to a decrease in the difference between innovation types. In other words, the flow of early-stage biologic-based innovations exceeds the flow of chemical-based innovations in the same market, *j*. Firms do not appear to be abandoning market *j* but rather changing the nature of the innovation taking place. This is intuitive especially if a firm has significant investments in downstream co-specialized assets, for example, in marketing, manufacturing and distribution.

The interpretation of our results is more nuanced than we originally anticipated when we undertook our investigations. On the one hand, it appears that generics are having an effect on the flow of early-stage pharmaceutical innovation. If the flow of early-stage innovation slows, the flow of new products will most likely also slow thereby hurting innovator firm revenues. On the other hand, one could argue that regulation is performing a social welfare enhancing role. That is, if viable generics are available in a market, their presence pushes the pharmaceutical industry to redeploy their resources to other, possibly more underserved, therapeutic markets. While analyzing the rotation *between* therapeutic markets is beyond the scope of this paper, what we do observe is that as the thumb of market competition is pressed down on a particular market, firms appear to be changing the nature of their innovation. That is we see a rotation *within* a market from chemical-based to biologic-based innovation. This rotation will have long term consequences in terms of overall societal welfare and on future medical expenditures

since these drugs are, on average, more expensive and they enjoy a market devoid of direct generic competition.

No paper is without caveats and limitations; ours is no exception. While we believe we make a significant contribution to the literature, more work needs to be done. While we capture the effects of what is taking place within a particular therapeutic market, future work needs to understand the dynamics between markets. However, such a task would require a far more nuanced understanding of the scientific relationship between therapeutic markets. Future research should also supplement our results with a careful assessment of the overall welfare effects coming from generics. Many are interested in the 'access vs. innovation' debate surrounding the passage of Hatch-Waxman. Prior research has demonstrated short term consumer (producer) gains (losses) but the question remained whether a trade-off was being made against future innovation (Branstetter *et al*., 2011). Our results seem to suggest that indeed there is a decline in the flow of innovation allowing us to get one step closer to being able to answer the access vs. innovation question in a more holistic manner. As is usually the case in economic research, much more remains to be done.

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Figure 1.Exclusivities and innovation in pharmaceuticals. This figure demonstrates the two types of protection conferred on new drugs. When a new drug is approved by the FDA the first five year period (seven years for orphan drugs and 5 ½ years for pediatric drugs) carries with it a regulatory protection called 'data exclusivity' that runs concurrent with underlying patent protection. Data exclusivity protects the underlying clinical data. At the conclusion of data exclusivity a drug is protected only by its patents until they expire, a period termed 'market exclusivity'. Para-IV challenges occur only during the market exclusivity period. Note that patents are generally applied for and granted well before a drug is approved by the FDA.

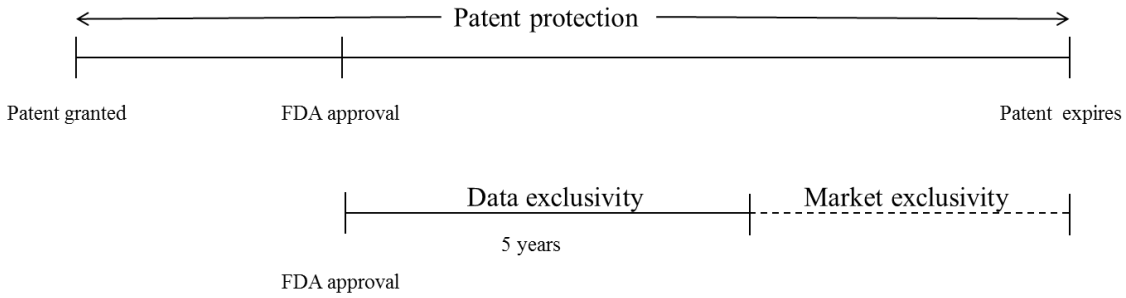

Figure 2. ANDA patent certification options for generic manufacturers. The regulatory pathway for generic entry in the U.S. can occur in one of four ways. Paragraph I, Paragraph II, and Paragraph III are used by generic manufacturers for drugs whose patents are either not listed in the FDA Orange Book or for those patents that have expired (or will expire). Paragraph IV is the only pathway that facilitates generic entry before expiry of patents or the conclusion of market exclusivity. Source: FTC (2002).

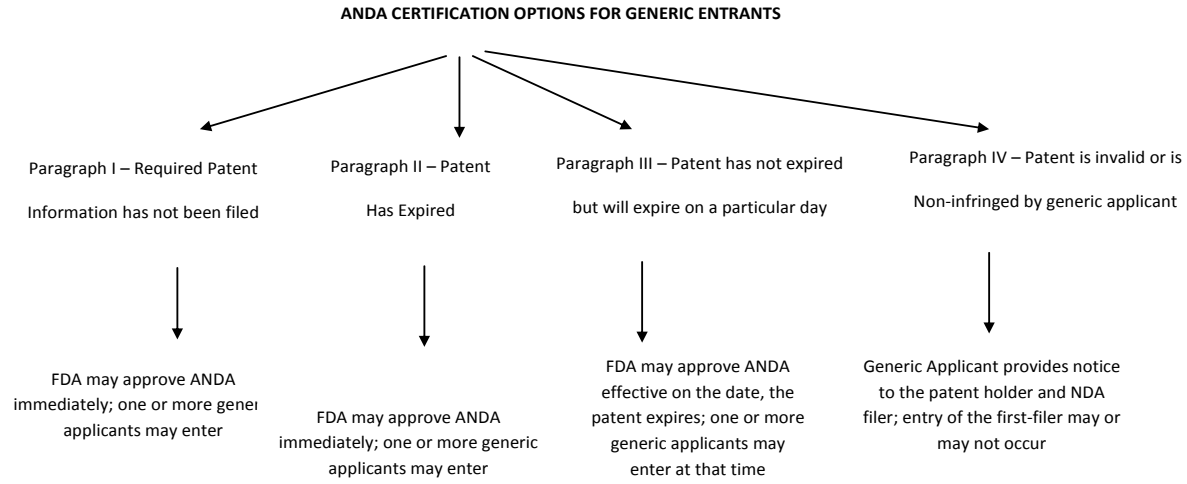

FIGURE 3.RELATIVE CONTRIBUTION TO TOTAL INNOVATIONS ACROSS THERAPEUTIC CATEGORIES

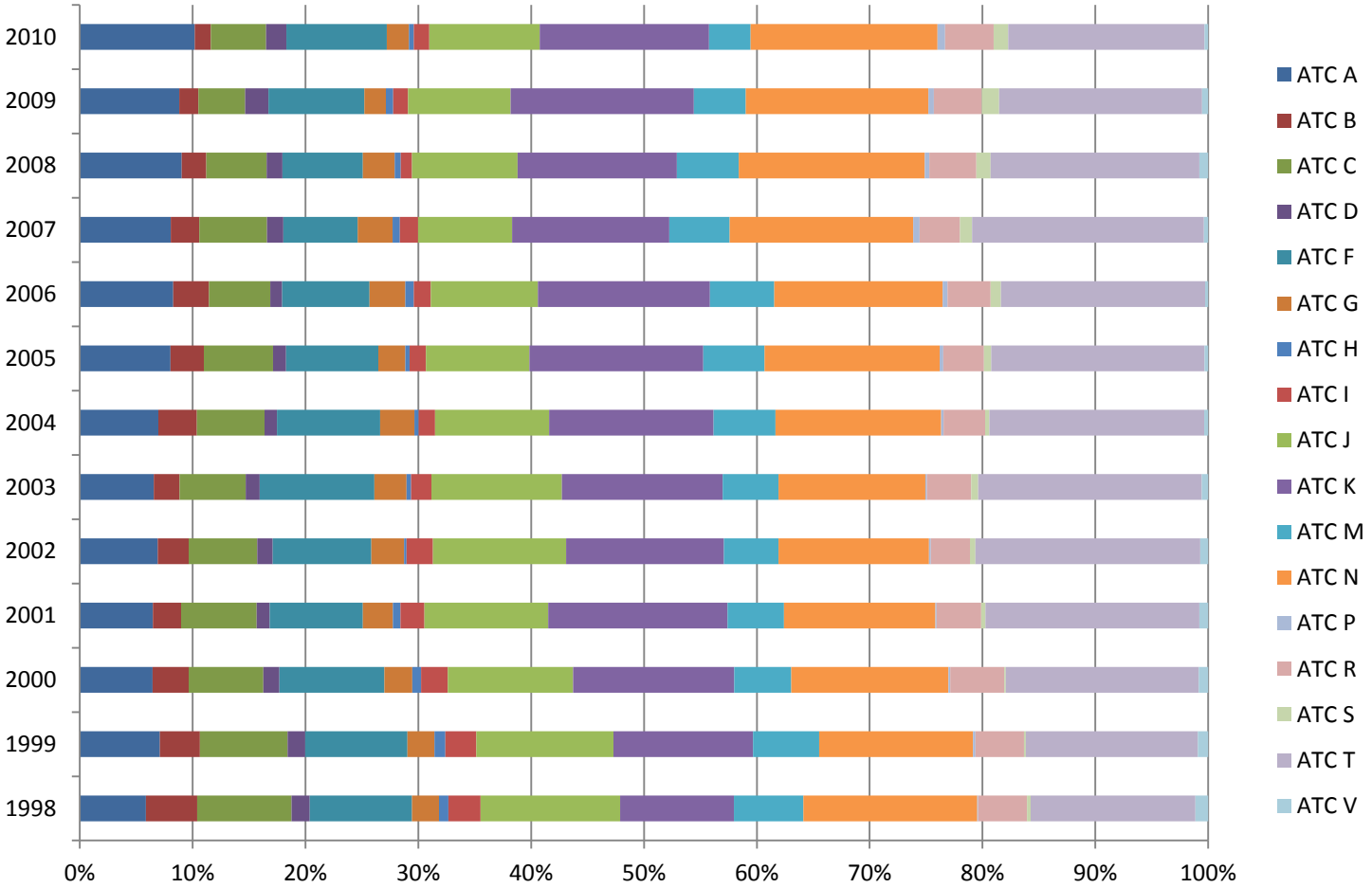

TABLE 1. VARIABLE DEFINITION AND DESCRIPTIVE STATISTICS

VARIABLES	DEFINITION	SOURCE	OBS	MEAN	S. DEV.	MIN	MAX
I_{ijt}	Early stage innovations: Count of early stage pipeline (Pre-clinical + Phase 1) at *i, j, t* level.	Pharmaprojects	31970	0.78	1.81	0	36
GP_{ijt}	Generic penetration: Ratio of generic sales to sum of focal firm and generic sales at *i, j, t* level.	IMS MIDAS	31970	0.54	.46	0	1
G_{ijt}	Paragraph IV challenges: Stock of Paragraph IV challenges faced by firm at *i, j, t* level.	Paragraphfour.com and USFDA	31970	0.01	0.01	0	3
O_{jt-1}	Technological opportunity: Logarithm of stock of citation-weighted articles in year *t-1* for *jth* therapeutic market.	IMS NDTI & MIDAS, PubMed and SCOPUS	31970	8.09	7.30	0	17.9
Z_{ijt-1}	Technological challenges: Counts of suspended or discontinued pipeline projects and withdrawn approved products at *i, j, t-1* level.	Pharmaprojects	31970	0.05	0.26	0	6
D_{ijt-1}	Firm innovative capability: Moving average of product introductions in *t-1, t-2, t-3* at the *i, j, t-1* level.	Pharmaprojects	31970	0.24	1.01	0	25.67
P_{ijt-1}	Firm innovative capability: Count of Phase II and Phase III products at the *i, j, t-1* level.	Pharmaprojects	31970	0.09	0.35	0	6
SA_{ijt}	Downstream co-specialized assets: Ratio of promotions at the *i,j, t* level and total pharmaceutical sales at the *i, j, t* level.	IMS MIDAS	31970	0.45	19.36	0	2225
S_{it}	Firm size: Logarithm of total pharmaceutical sales at the *i, t* level.	IMS MIDAS	31970	12.64	4.45	0	17.23

TABLE 2. CORRELATION MATRIX

VARIABLES	I_{ijt}	GP_{ijt}	G_{ijt}	O_{jt-1}	Z_{ijt-1}	D_{ijt-1}	P_{ijt-1}	SA_{ijt}	S_{it}
I_{ijt}	1.000								
GP_{ijt}	-0.358	1.000							
G_{ijt}	0.030	-0.016	1.000						
O_{jt-1}	-0.143	0.447	0.069	1.000					
Z_{ijt-1}	0.361	-0.139	0.027	-0.036	1.000				
D_{ijt-1}	0.357	-0.180	0.053	-0.083	0.152	1.000			
P_{ijt-1}	0.334	-0.225	0.008	-0.127	0.198	0.357	1.000		
SA_{ijt}	-0.007	0.018	-0.002	-0.001	-0.004	-0.005	-0.005	1.000	
S_{it}	0.068	0.101	0.053	0.027	0.041	0.104	0.036	0.008	1.000

TABLE 3.FLOW OF INNOVATION: POISSON REGRESSION

VARIABLES	MODEL 1	MODEL 2	MODEL 3	MODEL 4	MODEL 5
	I_{ijt}	I_{ijt}	I_{ijt}	I_{ijt}	I_{ijt}
	COEFF STD. ERROR	COEFF STD. ERROR	COEFF STD. ERROR	COEFF STD. ERROR	COEFF STD. ERROR
GP_{ijt}			-1.606*** (0.023)	-1.353*** (0.024)	-1.338*** (0.024)
G_{ijt}			0.045 (0.051)	0.034 (0.051)	0.067 (0.051)
O_{jt-1}		0.012*** (0.001)	0.008*** (0.001)	0.035*** (0.001)	0.034*** (0.001)
Z_{ijt-1}		0.402*** (0.001)	0.456*** (0.010)	0.373*** (0.001)	0.374*** (0.010)
D_{iit-1}	0.106*** (0.003)	0.113*** (0.003)	0.091*** (0.003)	0.101*** (0.003)	0.105*** (0.003)
P_{ijt-1}	0.246*** (0.010)	0.139*** (0.010)	0.237*** (0.010)	0.132*** (0.010)	0.141*** (0.010)
SA_{iit}	-0.003* (0.002)	-0.003* (0.002)	-0.001 (0.001)	-0.001 (0.001)	-0.001 (0.001)
S_{it}	0.010*** (0.003)	0.011*** (0.003)	0.018*** (0.003)	0.019*** (0.003)	0.019*** (0.003)
Constant	0.371 (1.004)	0.234 (1.004)	-0.101 (1.001)	-0.378 (1.004)	-0.047 (1.084)
Firm Fixed Effect	Y	Y	Y	Y	Y
Year Fixed Effect	Y	Y	Y	Y	Y
Therapeutic Fixed Effect	Y	Y	N	Y	Y
Year*Therapeutic Fixed Effect	N	N	N	N	Y
Pseudo R^2	0.35	0.37	0.34	0.40	0.41
N	31,970	31,970	31,970	31,970	31,970

Adjusted standard errors (Woolridge 1999) in parentheses

*** p<0.01, ** p<0.05, * p<0.1

TABLE 4. FLOW OF INNOVATION: FIXED EFFECT NEGATIVE BINOMIAL REGRESSION

VARIABLES	MODEL 1	MODEL 2	MODEL 3	MODEL 4	MODEL 5
	I_{ijt}	I_{ijt}	I_{ijt}	I_{ijt}	I_{ijt}
	COEFF STD. ERROR	COEFF STD. ERROR	COEFF STD. ERROR	COEFF STD. ERROR	COEFF STD. ERROR
GP_{ijt}			-1.932*** (0.030)	-1.691*** (0.031)	-1.678*** (0.031)
G_{ijt}			0.037 (0.075)	0.024 (0.070)	0.048 (0.070)
O_{it-1}		0.003** (0.002)	0.009*** (0.001)	0.029*** (0.002)	0.029*** (0.002)
Z_{ijt-1}		0.448*** (0.013)	0.469*** (0.014)	0.398*** (0.013)	0.399*** (0.013)
D_{ijt-1}	0.103*** (0.004)	0.106*** (0.004)	0.090*** (0.004)	0.094*** (0.004)	0.098*** (0.004)
P_{ijt-1}	0.142*** (0.016)	0.036** (0.015)	0.074*** (0.016)	0.028* (0.015)	0.037*** (0.015)
SA_{ijt}	-0.010 (0.006)	-0.008 (0.006)	-0.005 (0.004)	-0.001 (0.002)	-0.001 (0.002)
S_{it}	-0.043*** (0.003)	-0.040*** (0.003)	-0.043*** (0.003)	-0.028*** (0.003)	-0.027*** (0.003)
Constant	0.457*** (0.060)	0.431*** (0.060)	1.000*** (0.052)	0.553*** (0.061)	0.488*** (0.117)
Firm Fixed Effects	Y	Y	Y	Y	Y
Year Fixed Effects	Y	Y	Y	Y	Y
Therapeutic Fixed Effects	Y	Y	N	Y	Y
Year*Therapeutic Fixed Effects	N	N	N	N	Y
Log Likelihood	-28950.64	-28545.61	-28280.31	-26833.91	-26732.74
N	31,970	31,970	31,970	31,970	31,970

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

TABLE 5. EFFECTS OF GENERIC ENTRY IN TOP THERAPEUTIC MARKETS

VARIABLES	NBREG FIXED EFFECTS	NBREG FIXED EFFECTS	NBREG FIXED EFFECTS	NBREG FIXED EFFECTS
	MODEL 1	MODEL 2	MODEL 3	MODEL 4
	I_{ijt}	I_{ijt}	I_{ijt}	I_{ijt}
	COEFF STD. ERROR	COEFF STD. ERROR	COEFF STD. ERROR	COEFF STD. ERROR
GP_{iit}			-0.794*** (0.082)	-0.333*** (0.082)
G_{iit}			-0.139 (0.117)	-0.229** (0.102)
O_{jt-1}		0.874*** (0.176)	0.239*** (0.017)	0.840*** (0.179)
Z_{iit-1}		0.220*** (0.032)	0.256*** (0.039)	0.221*** (0.033)
D_{iit-1}	0.143*** (0.015)	0.149*** (0.015)	0.168*** (0.016)	0.135*** (0.016)
P_{iit-1}	0.093* (0.051)	0.111** (0.050)	0.096 (0.063)	0.097* (0.051)
SA_{iit}	-0.006 (0.030)	-0.005 (0.028)	0.004 (0.018)	-0.000 (0.023)
S_{it}	-0.004 (0.011)	0.008 (0.011)	-0.005 (0.010)	0.016 (0.011)
Constant	0.884*** (0.301)	-10.457*** (2.371)	-2.304*** (0.319)	-10.144*** (2.411)
Firm Fixed Effects	Y	Y	Y	Y
Year Fixed Effects	Y	Y	Y	Y
Therapeutic Market Fixed	Y	Y	N	Y
Log Likelihood	-2242.11	-2210.90	-2565.95	-2200.67
N	3,919	3,919	3,919	3,919

Standard errors in parentheses (Adjusted standard errors for Model 1 (Woolridge 1999)).
*** p<0.01, ** p<0.05, * p<0.1

TABLE 6.CASE STUDY OF ANTI-EPILEPTIC DRUGS (ATC N5)

VARIABLES	NBREG	NBREG	NBREG	NBREG
	MODEL 1	MODEL 2	MODEL 3	MODEL 4
	I_{ijt}	I_{ijt}	I_{ijt}	I_{ijt}
	COEFF STD. ERROR	COEFF STD. ERROR	COEFF STD. ERROR	COEFF STD. ERROR
GP_{iit}			-1.630*** (0.167)	0.156 (0.330)
G_{iit}			0.442 (0.587)	-0.023 (0.366)
O_{jt-1}		-0.238 (0.269)	-0.230 (0.250)	-0.188 (0.171)
Z_{iit-1}		0.423*** (0.135)	0.290** (0.117)	0.141** (0.062)
D_{iit-1}	0.137*** (0.034)	0.445*** (0.045)	0.288*** (0.039)	0.116*** (0.037)
P_{iit-1}	-0.036 (0.100)	0.464*** (0.156)	0.561*** (0.144)	-0.084 (0.104)
SA_{iit}	-0.335 (0.533)	0.214 (0.714)	0.922 (0.652)	-0.398 (0.623)
S_{it}	0.021 (0.016)	0.062*** (0.014)	0.115*** (0.015)	0.026 (0.020)
Constant	-14.68 (454.7)	2.508 (4.558)	2.958 (4.237)	4.129 (2.858)
Year Fixed Effects	Y	Y	Y	Y
Firm Fixed Effects	Y	N	N	Y
Log Likelihood	-426.29	-719.46	-669.94	-423.74
N	620	620	620	620

Standard errors in parentheses (Adjusted standard errors for Model 1 (Woolridge 1999)).
*** p<0.01, ** p<0.05, * p<0.1

TABLE 7.CHANGE IN THE NATURE OF INNOVATION: ORDERED LOGIT

VARIABLES	MODEL 1	MODEL 2	MODEL 3
	$dum(CI_{ijt}\text{-}BI_{ijt})$	$dum(CI_{ijt}\text{-}BI_{ijt})$	$dum(CI_{ijt}\text{-}BI_{ijt})$
	COEFF STD. ERROR	COEFF STD. ERROR	COEFF STD. ERROR
GP_{ijt}		-2.062*** (0.044)	-2.070*** (0.045)
G_{ijt}		-0.082 (0.146)	-0.063 (0.147)
O_{jt-1}	0.006** (0.002)	0.030*** (0.002)	0.030*** (0.002)
Z_{ijt-1}	3.111*** (0.169)	3.065*** (0.188)	3.095*** (0.191)
D_{ijt-1}	1.161*** (0.058)	1.164*** (0.058)	1.162*** (0.058)
P_{ijt-1}	-0.754*** (0.072)	-0.974*** (0.073)	-0.963*** (0.073)
$diffSA_{ijt}$	-0.001*** (0.000)	-0.001*** (0.000)	-0.001*** (0.000)
S_{it}	0.018* (0.010)	0.018* (0.010)	0.021** (0.010)
Constant	-17.520 (174.700)	-15.870 (71.480)	-15.11 (49.53)
Firm Fixed Effects	Y	Y	Y
Year Fixed Effects	Y	Y	Y
Therapeutic Fixed Effects	Y	Y	Y
Year*Therapeutic Fixed Effects	-	-	Y
N	31,970	31,970	31,970
Log pseudolikelihood	-18083.096	-16896.315	-16817.51
Pseudo R^2	0.320	0.364	0.367

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

TABLE 8. CHANGE IN THE NATURE OF INNOVATION: OLS

VARIABLES	MODEL 1	MODEL 2	MODEL 3
	$dum(CI_{ijt}\text{-}BI_{ijt})$	$dum(CI_{ijt}\text{-}BI_{ijt})$	$dum(CI_{ijt}\text{-}BI_{ijt})$
	COEFF STD. ERROR	COEFF STD. ERROR	COEFF STD. ERROR
GP_{ijt}		-0.373*** (0.008)	-0.374*** (0.008)
G_{ijt}		0.006 (0.025)	0.010 (0.025)
O_{jt-1}	0.001 (0.000)	0.005*** (0.000)	0.005*** (0.000)
Z_{ijt-1}	0.302*** (0.014)	0.273*** (0.014)	0.276*** (0.014)
D_{ijt-1}	0.109*** (0.004)	0.105*** (0.004)	0.105*** (0.004)
P_{ijt-1}	-0.065*** (0.011)	-0.094*** (0.010)	-0.094*** (0.010)
$diffSA_{ijt}$	-0.000*** (0.000)	-0.000*** (0.000)	-0.000*** (0.000)
S_{it}	0.002 (0.002)	0.002 (0.002)	0.003 (0.002)
Constant	3.104*** (0.022)	2.954*** (0.020)	2.927*** (0.047)
Firm Fixed Effects	Y	Y	Y
Year Fixed Effects	Y	Y	Y
Therapeutic Fixed Effects	Y	Y	Y
Year*Therapeutic Fixed Effects	-	-	Y
N	31,970	31,970	31,970
R-squared	0.379	0.426	0.430

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1