Killing the Golden Goose or Just Chasing it Around the Farmyard?: Generic Entry and the Incentives for Early-Stage Pharmaceutical Innovation[†]

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Version: 16 January 2014

[†]**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 the USPTO Conference on Patents, Entrepreneurship and Innovation (Washington, DC) and the 2013 Asia Pacific Innovation Conference (APIC), 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. Higgins acknowledges funding from The Imlay Professorship. Chatterjee acknowledges IIM Bangalore for supporting his extended research visit to Georgia Tech. 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. What impact has this rise in generic penetration had on the rate and direction of early stage pharmaceutical innovation? 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, firm innovative capability, and additional controls. While the overall aggregative level of drug development activity has remained fairly stable, our estimates suggest a sizable, robust, negative relationship between generic penetration and early-stage pharmaceutical research activity within therapeutic markets. A 10% increase in generic penetration *decreases* early-stage innovations in the same market by 7.9%. This effect is weaker, but still economically and statistically significant in top therapeutic markets where an increase in generic penetration by 10% decreases the flow of early-stage innovations by 2.1%. 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 biologics-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 the consumption increases from all other sources put together. Victor Fuchs (1982) has 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 risky and expensive. These costs are passed on to consumers in the form of higher prices for branded pharmaceuticals. 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 have accounted for an increasing share of prescription drug expenditures, saving consumers an estimated $1 trillion (GAO, 2012). Current regulation attempts to strike the right balance between access to lower cost generics on the one hand and adequate incentives to promote pharmaceutical innovation on the other. While the rise in generic penetration has brought substantial benefits to consumers (Branstetter *et al*., 2013), some have argued that the regulatory "balance" has shifted so far in the direction of access to inexpensive drugs that is has undermined the incentives for new drug development (Higgins and Graham, 2009; Knowles, 2010). Such a shift could have strong implications, even for drug companies outside the United States, because the global industry relies disproportionately on the U.S. market as a source of its profits. Has the increase in generic entry caused a decline in innovation? Our study attempts to address this question and quantify, for the first time, the impact of generic entry on early-stage drug development.

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 early-stage drug development. While patenting is certainly important in the pharmaceutical industry, it can occur anytime throughout the drug development process, and it often occurs long before the actual therapeutic value of a compound has been tested. Our outcome variable, on the other hand, allows us to analyze what is actually happening in the early stages of the clinical development process. We also utilize comprehensive data on branded and generic drug sales across all therapeutic categories in the U.S.

market, obtained at the firm-product-year level, such that we can measure the differential exposure of individual firms to generic competition across different therapeutic markets. Finally, we seek to control for changes in scientific opportunity by building a comprehensive database of citation-weighted scientific journal articles in the medical sciences and mapping it to our pharmaceutical product categories.

Using these data, we find that the *aggregate* level of new drug development has not declined as generic penetration in the U.S. market has risen. However, rising generic competition has had a statistically and economically significant impact on how pharmaceutical product development is undertaken and where those efforts are focused. We show this by using an empirical framework that models 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. Using this framework, we document a negative and significant relationship between generic entry (penetration) and early-stage innovation at the ATC 2-digit therapeutic category level. 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 7.9%. When, we limit our sample to the top-selling pharmaceutical categories, and find that this negative effect remains weakens slightly, but remains statistically and economically significant.

Branstetter *et al*. (2013) document the high-degree of cross-molecular substitution in the hypertension market. As defined in that study, cross-molecular substitution occurs when patients shift their drug consumption from a branded product to the generic version of a *different* branded product, based on a different molecule. In many therapeutic markets, practicing physicians have long regarded different drugs, based on different molecules, and sometimes utilizing different biochemical pathways to attack the disease, as equally effective therapies for the underlying illness. In such markets, physicians would generally consent to switching drugs if it saved their patients money. This switch also saves insurance companies money, and Branstetter et al. (2013) present evidence that insurance companies have moved aggressively to incentivize cross-molecular substitution. The implications of this are profound; a branded product's intellectual property protection, within a market, is only as strong as their weakest branded competitor's patents. A high degree of cross-molecular substitution thus amplifies the *positive* impact of generic entry on consumer welfare and the *negative* impact of entry on producer profits -- and it potentially also amplifies the impact of generic entry on incentives to develop new drugs. However, not all therapeutic areas are characterized by a high degree of cross-molecular substitution. In this paper, we present evidence from a sub-market, anti-epileptics, where we expect these substitution possibilities 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 cross-molecular substitution.

Finally, we consider the possibility that a *rotation* is occurring out of chemical-based (small molecule) products into biologic-based (large molecule) products. The regulatory changes that have accelerated generic entry in chemicals-based drugs do not extend to biologics; there is still no pathway for biotech-based generics (known in the industry as 'biosimilars') to enter the U.S. market. Exploiting this regulatory difference between chemical and biologic-based innovations, we 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.

Is this shift in the direction of drug development socially beneficial or socially harmful? At this stage in the research process, it is not yet possible to produce a definitive answer to this question. On the other hand, one could argue that current regulation is 'pushing' innovation toward therapeutic markets for which significant numbers of viable generics do not exist. In other words, R&D efforts and expenditures could potentially be flowing to other therapeutic areas which are relatively underserved, thereby generating welfare gains. On the other hand, our evidence of a significant rotation in the data from chemical-based to biologic-based products may have significant implications for the future, especially since biologics tend to be more expensive, on average, than chemical-based products. Until current regulatory challenges are resolved, these higher prices may persist for long periods of time. As the regulatory playing field tilts sharply in the direction of biologics, and firms respond rationally to the incentives they confront, we cannot rule out the possibility that recent efforts to balance access with incentives for innovation will give us cheaper drugs today, but more expensive drugs tomorrow.

The paper proceeds as follows. Section 2 provides a discussion of the U.S. regulatory environment in which pharmaceutical firms operate and brief description of the rise in generic penetration. Section 3 reviews important features of the drug development process and discusses prior work on the potential impact of rising generic penetration on pharmaceutical innovation. Our empirical specification and data are outlined in Section 4. Results are presented in Section 5, and we conclude in Section 6.

2 The Regulatory Environment and the Rise of Generic Penetration

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 this legislation is the balance it tries to

strike between consumer access to inexpensive generic drugs on the one hand and the protection of adequate incentives for new drug development on the other. The Hatch-Waxman Act 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).

When a pharmaceutical company submits a New Drug Application (NDA) to the FDA for approval, the company is required, by law, to identify all relevant patented technologies necessary to create the drug; these patents are subsequently listed in the FDA Orange Book.[1] 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).[2] 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.[3] 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 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.

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[1] For biologics-based or "large molecule drugs" the initial application is a Biologics License Application. However, a similar requirement to disclose patents exists, and this disclosure also becomes a matter of public record.

[2] 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.

[3] There are exceptions to the general rule of 5 years of data exclusivity. Drugs targeting small patient populations (known in the industry as "orphan drugs") receive 7 years of data exclusivity. Reformulations of existing drugs receive only 3 years of data exclusivity. New drugs that treat pediatric illnesses receive an additional 6 months of data exclusivity.

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.[4] If they are 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).

It is important to emphasize, however, that the multiple avenues provided by Hatch-Waxman for generic entry have applied only to chemicals-based drugs. Throughout our sample period, there was no legal mechanism through which the manufacturer of a "biosimilar" (the industry term for the generic version of a biotech drug) could demonstrate that its substance was equivalent to the original drug. With no way to establish bioequivalence, any generic version of a biotech drug would have to undergo separate clinical trials to receive FDA approval -- a barrier to entry so daunting that no biosimilar has yet been introduced in the U.S. market. This historical absence of an entry pathway for biosimilars reflects, in part, the nascent state of the biotech industry when Hatch-Waxman was passed, as well as the real scientific challenges of determining bioequivalence for biotech-based drugs, which are far more complicated than chemistry-based drugs and interact with human biophysical systems in ways that are not always perfectly understood. Under the Obama Administration, new legislation provided the legal basis for biosimilar entry, but that legislation guarantees biotech-based drugs 12 years of data exclusivity -- a period of legal monopoly 2.4 times longer than that afforded to chemistry-based drugs. Furthermore, the enabling regulations that would practically permit biosimilar entry have yet to issued by the FDA. Some countries outside the U.S. already permit biosimilars, but generally require limited clinical trials to confirm bioequivalence prior to approval. The high cost of these trials -- even when they are limited in

[4] 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.

time and scope relative to those required of innovator dugs -- will likely constrain generic entry in the biotech side of the pharmaceutical market for the foreseeable future.

While a starkly different statutory treatment of chemistry-based and biotech-based drugs has been established in U.S. law since the passage of Hatch-Waxman in 1984, the practical impact of these very different regulatory regimes has significantly strengthened in recent years. Generic penetration at the end of the 1980s and in the early 1990s was constrained by an FDA scandal that temporarily slowed down the processing of new generic drug applications, and by an unusually productive era of new drug introductions by the branded drug companies that extended into the mid-1990s. Since then, however, generic penetration has intensified sharply. This has been partly driven by the rising incidence of Para-IV challenges.

To enter the market under the provisions of Paragraph IV while patents protecting the innovator drug are still in force, the generic manufacture either claims that the initial patents were invalid or that his product, though bioequivalent, does not infringe on those patents. When filing an ANDA with a Para-IV certification, the generic challenger is obligated to notify the incumbent, and the incumbent has the right to sue for patent infringement. If the incumbent does so, this triggers a stay on FDA action pending the judgment of the courts. In the early years, after initial passage of Hatch-Waxman, pharmaceutical firms were allowed to appear initial judgments against the validity of their patents (or findings of non-infringement), and the FDA did not approve any generic entry until all appeals had been exhausted. This was a time consuming process that often held generic manufacturers at bay until patents expired or were about to expire. In more recent years, the FDA has approved entry as soon as courts issue a first ruling in favor of the generic entrant. Throughout the 1990s, incumbents often followed a practice of taking out additional patents after an initial Para-IV filing and invoking non-concurrent stays on FDA approval for each patent allegedly infringed. After passage of the Medicare Act of 2003, pharmaceutical firms have been limited to one 30-month stay per product. Finally, legal experts claim that recent court rulings have made it easier to demonstrate patent invalidity and harder to demonstrate infringement. As a consequence of all of these factors, the number of Para-IV challenges has surged from just one in 1994 to 44 in 2007 and to 230 in 2010. 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). Under Hatch-Waxman, within months of the initial Para-IV challenger's entry into the marketplace, any generic manufacturer is allowed to enter, so the massive rise in Para-IV challenges has brought a sharp intensification of generic penetration.

3 Pharmaceutical Innovation and Generic Entry

We began our paper with the claim advanced by Nordhaus (1999) that the advances in human welfare generated by better medical science over the past half century equal in value 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). The work of Lichtenberg (2001, 2004, 2007) and others has lent credence to Victor Fuchs' (1982) assertion that the most important driver of this improvement has been pharmaceutical innovation. Efforts to infer the welfare impact of pharmaceutical innovation using modern models of demand for differentiated products, such Ellickson et al. (2001), Cleanthous (2002), and Dunn (2012), have also yielded large estimates. Coincident advances in nutrition, pollution abatement, diagnostic techniques, and the gradual decline of unhealthy behaviors like tobacco smoking make it difficult to determine exactly what fraction of the observed improvement in health outcomes is attributable to new drugs, but few would contest the unique importance and impact of pharmaceutical innovation. This implies that public policies affecting the rate and direction of pharmaceutical innovation also take on special importance.

3.1 Pharmaceutical innovation: costs and controversies

Pharmaceutical innovation is not just important -- it also difficult, time-consuming, risky, and expensive. A comprehensive accounting of costs has to include expenditures on drug candidates that fail at some point in the process. Recent estimates by DiMasi and Grabowski (2012) suggest that these costs have risen as high as one billion dollars per approved drug, though these cost estimates have been subjected to considerable criticism and controversy. Previous studies have described the various stages of the drug development process, including DiMasi, Hansen,and Grabowski (1991, 2003), DiMasi and Grabowski (2012), and Mossinghoff (1999). This process is typically divided into the following phases: pre-discovery, drug discovery, preclinical development, and clinical trials. In the pre-discovery phase, drug companies study the basic scientific research of other firms and public science institutions, as they seek to understand the fundamental biochemical mechanisms that underlie diseases and the kind of chemicals or proteins that might work to disrupt or reverse those mechanisms, curing the patient. Drug discovery begins when drug companies start identifying and testing specific compounds. In the early stages, it is common for companies to evaluate thousands of compounds, using chemical tests and other means, before focusing on a few hundred compounds in the pre-clinical stage. The preclinical stage involves more in-depth, focused, comprehensive testing of this smaller number of compounds, including

tests of drugs in animals. The time that it takes a compound to move through the drug discovery and preclinical phases is generally 3-6 years.

When drug companies have identified compounds they wish to subject to clinical trials in human subjects, they submit an Investigational New Drug (IND) application to the FDA; this is legally required in order to move drug samples across state lines for the purposes of clinical testing. Firms must then move through three separate phases of clinical trials, each involving a larger number of human subjects. In Phase 1, a small group is tested to determine a safe dosage level and identify side effects. In Phase 2, the treatment is administered to a larger group, to determine effectiveness and also further evaluate its safety. In Phase 3, the treatment is administered to a still larger group and compared to commonly used treatments. When Phase 3 is successfully completed, the drug company submits a New Drug Application to the FDA, including clinical trials results. The FDA evaluates this information before approving the drug. Once it is approved and sales begin, drug companies continue to do Phase 4 trials to acquire additional information on risks, benefits, and optimal use. DiMasi and Grabowski (2012) contend that only one drug obtains FDA approval for every 5 compounds that enter Phase 1, and it can take 6-7 years for a compound to move through all 3 phases. The total development cycle from discovery through approval can take, on average, nearly 12 years, and the distribution of approved drugs is characterized by highly skewed returns. Pharmaceutical firms rely disproportionately on a small number of very successful products to maintain their financial viability.

Starting in the mid-1990s, the number of drug approvals fell sharply, even as industry R&D expenditures continued to increase. This led to an intense debate about the industry's research "productivity crisis" (Cockburn, 2006). The relatively low level of new product approvals persisted throughout our sample period and beyond. Experts disagree as to the causes or future persistence of this "productivity slowdown." Nevertheless, it has created a rising level of concern (and financial stress) within the industry. Accelerating generic competition has been narrowing the profits of branded firms faster than successful new drug development has expanded them.

3.2 The rise of generic penetration and implications for pharmaceutical innovation

A number of recent studies have studied the intensification of generic competition in recent years and the impact of this shift on branded drug companies. Unfortunately, we lack the space here to offer a comprehensive review of all the work in this domain, and, instead, cite selectively the work that is most relevant to our own analysis. Caves *et al*.(1991) offered an influential look at the early impact of the Act. More recent work includes Reiffen and Ward (2005), Saha et al. (2006), Grabowski (2007), Grabowski

and Kyle (2007), and Berndt and Aitken (2010). Efforts to calculate the welfare impact of generic entry include Bokhari and Fournier (2009), and Branstetter et al. (2013). The latter study shows that the rising incidence of Para-IV challenges has brought substantial gains to consumers. Hemphill and Sampat (2011, 2012) also focus on Para-IV challenges, analyzing, among other things, which incumbent firms' patents tend to be challenged.

The possibility that rising generic penetration could undermine the incentives to undertake new drug development has been recognized in prior work. For example, Hughes et al. (2002) show in a theoretical model that providing greater access to a current stock of prescription drugs yields large benefits to existing customers. However, this access comes at a cost in terms of lost consumer benefits from reductions in the flow of future drugs. Other papers have also discussed this possibility, including Grabowski and Kyle (2007), Higgins and Graham (2009), Knowles (2010), and Panattoni (2011). This research stream has provided (mostly indirect or anecdotal) evidence suggesting that an intensification of generic competition has undermined incentives for R&A. However, to the best of our knowledge, no published study has yet provided direct econometric evidence demonstrating that generic entry has caused a change in the rate or direction of R&D investment in new drugs. The extent to which this occurs in practice remains an open question.

4 Empirical Models 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 a useful degree of leverage over some of the econometric and measurement challenges we confront. Since we seek to measure the impact of rising generic penetration on drug development effort, it is especially important to have high-quality measures of pharmaceutical innovation and of exposure to generic competition. Our data allow us to track both variables by firm, by product category, and by year. The paragraphs below describe our data and our empirical approach.

4.1 Measuring and modeling pharmaceutical innovation

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 monitored, and commercial databases contain rich data on these candidates. We

draw our measures of drug innovation from one such commercial database, known as Pharmaprojects. 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, the therapeutic market in which it is likely to be sold, and the development history (some drugs are initially developed to fight one disease but then are discovered to have positive effects against others). The database also records information on product development suspensions and discontinuations as well as product withdrawals from the market after introduction. The richness of the data allows us, in principle, to examine the relationship between rising generic penetration and the emergence of new compounds through various stages of the drug development process across firms, therapeutic categories, and time.

However, 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). Although there has been no measured slowdown in aggregate early stage drug development, new drug approvals peaked in the mid-1990s and were stagnant or falling through the rest of our sample period. While this opinion is by no means universally held, there are some inside and outside the industry who suggest that this decline reflects an emerging exhaustion of research opportunities. In this view, 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 their drug development efforts, 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, as best we can, for contemporaneous changes in research opportunities and other factors that might influence drug development.

We propose to do this using a regression specification that models innovation as a function of scientific opportunity and challenges, firm innovative capability, downstream co-specialized assets, and generic entry, with a vector of additional controls:

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

where I_{ijt}, measures early-stage innovations by firm i in ATC 2-digit market j in time t. We define "early stage innovations" as the count of individual compounds in "preclinical development" or in Phase 1 clinical trials. If firms are responding to changes in the intensity of generic competition or to changes in perceived scientific opportunity, we would expect a measurable impact to show up at this stage. In

contrast, drugs that have already moved on to Phase 2 or Phase 3 trials are likely to continue through the development process to the end, even if the firm plans to curtail or eliminate future research in that area in response to rising competition or diminished technological opportunity. 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 fixed effects Poisson and negative binomial estimators (Hausman *et al*.,1984). Given that not all firms innovate in each therapeutic category in each year, it is possible that the data may contain zeros. Our count data models have the advantage of dealing with this outcome in a natural way. The specification includes fixed effects for year (α_t), firm (α_i), and therapeutic (ATC) category (α_j). There are 13 years, 178 firms, and 126 ATC 2-digit categories in our data. 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). Pharmaprojects assigns drug candidates to the categories of the Anatomical Therapeutic Chemical (ATC) classification system, but the data are consistently reported only at the 2-digit level. Other key variables are available at a greater level of disaggregation, but because we are seeking to relate these to innovative effort, we can disaggregate no further than the level of our innovation data. The regressions that are described below are therefore run at the firm-ATC 2 -year level. Firms are included in our sample if they have at least one approved product and at least one early-stage innovation. This limitation excludes some smaller, research-intensive firms. We argue below that the bias introduced by this sample selection, to the extent that it exists, likely weakens our estimated results relative to what holds in reality.

4.2 Measuring generic penetration (GP_{ijt})

The Hatch-Waxman Act 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). However, the incidence of rising generic impact is quite uneven across therapeutic categories and time, and firms differ in terms of their exposure to this competition. Fortunately, we are able to employ disaggregated data from the IMS MIDAS™ database . This database tracks the sales of nearly every pharmaceutical product sold in the United States by firm, product, and quarter, and the data are mapped to ATC categories at the 4-digit level. Our access to these data are limited to the years 1998-2010, and this data restriction determines the time dimension of our study. Fortunately, that window covers a period of intensifying generic competition. Within that period, 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 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 decreases.

4.3 Measuring scientific opportunity (O_{jt-1})

In order to identify the effect of changes in generic competition on innovation, we must also effectively control for underlying scientific opportunities within each therapeutic market j at time t. Prior research has demonstrated the link between academic research and industrial R&D (Mansfield, 1995; Gittelman and Kogut, 2003); these linkages are particularly strong in pharmaceuticals. Similar to Furman *et al*. (2006), we construct a bibliographic measure that captures publicly available academic research in the life sciences.

We start by merging data from IMS MIDAS™, our comprehensive database of pharmaceutical products, categorized by ATC codes, with the IMS NDTI™ database, which captures physician prescription behavior. This latter database tracks the diseases for which physicians are prescribing the drugs in MIDAS, so this linkage enables us to generate a concordance between ICD-9 codes used for diseases in the medical science literature and ATC product codes (at the 4-digit level) used by the drug industry. Next, we pick up the top five keywords listed in the IMS NDTI™ that correspond to each ATC 4-digit category. Using these keywords as search terms in the National Library of Medicine's PUBMED database, we identify scientific articles published between 1950 and 2010 that are connected to these ATC 4-digit categories. This search identified a unique sample of 6.5 million journal articles; because journal articles are often mapped to multiple ATC 4-digit categories, this search yielded 20.9 million raw article counts when mapped into "ATC4 space." Next, we used the unique PMID identifiers for these articles to look each of them up in the SCOPUS Sciverse database, in order to gather forward citations for these articles 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 ATC 2-digit level, we aggregate our annual, citation-weighted counts of journal articles up from the ATC 4-digit level to the ATC 2-digit level, take natural logs, and lag the stock by one year to create our control variable, O_{jt-1}.

4.4 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. The failure of one or more leading products within a broader drug development program could indicate the presence of common or related flaws in the products that are still under development. This, in turn, could lead the firm to scale back, terminate, or redirect research and development efforts in response. Seeking to control for this, we define our proxy for the scientific challenges faced by the firm, Z_{ijt-1}, as the number of products suspended, discontinued or withdrawn by firm *i*, in therapeutic market *j* at time *t-1*.

4.5 Research capabilities (D_{ijt-1} and P_{ijt-1}), marketing assets (SA_{ijt}), and firm size (S_{it})

Clearly, pharmaceutical companies differ in the 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 lagged one period,(*t-1*). 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. 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.

4.6 An empirical specification for measuring rotation into biotech drugs

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. They also become susceptible to early generic entry via Paragraph IV challenges only five years after approval (Figure 1). The same legal frameworks do not (yet) provide a pathway for biosimilar entry after biologic patent expiration, nor is there the equivalent of a Paragraph IV challenge to biotech drugs. Furthermore, biotechnology-based products are now 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:

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

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}) to have an impact on the choice of technology – unless firms' research choices are being affected by the prospect of generic competition.

4.7 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 (such as GP_{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 allows us to use an ordered logit specification (Hausman *et al*., 1992).[5] 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. For our specification in Equation 2 we can use the *Origin of Material* field within Pharmaprojects to decompose our measure of past drug introductions, D_{ijt-1}, and our measure of scientific challenges, Z_{ijt-1}, faced by firm *i* in therapeutic market *j*, into their chemicals-based and biologics-based components. We can also decompose our ratio of promotions to product sales, SA_{ijt}, for firm *i* within therapeutic market *j* at time *t*, into its chemical-based (CSA_{ijt}) and biologic-based (BSA_{ijt}) components.

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.

Inspection of the raw data shows that, in the aggregate, there has been no decline in early-stage innovation over our sample period, even as the level of generic penetration has risen and the number of approved drugs has fallen. This suggests that generics have had limited impact on the overall aggregate rate of early-stage innovation. However, we find strong evidence that generics have had a statistically and economically significant impact on where development activity is concentrated and how it is undertaken.

Generic penetration, GP_{ijt}, as we measure it at the firm-product-year level, was about 54% at the mean and just over 80% at the median. Generic penetration was greatest in ATC S (sensory organs) and

[5] We thank Jerry Thursby for this suggestion.

lowest in ATC J (anti-infectives). Over our sample period, generic penetration increased significantly. 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).

5.2 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). 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.

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 -0.79. In other words, a 10% increase in generic penetration is related to a 7.9% 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. If fewer candidates are entering a therapeutic pipeline then fewer drugs will eventually come out.

Generic penetration into a market is clearly harmful for branded producers. 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*.[6] 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 are consistent with this view and provide one possible explanation for why this shift may be occurring. In essence, 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 success probability than the therapeutic category to which expenditures are flowing, this could have eventual consequences for 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 (large molecule) products (we consider this possibility below) then this could have significant consequences for the nations' future prescription drug bill as large molecule drugs are often orders of magnitude more expensive than small molecule drugs. As already noted, under current regulatory settings, biologics-based products have much longer data exclusivity (12 years versus 5 years) than chemicals-based products, and there is currently no regulatory path for "biosimilars" to actually enter

[6]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.

the market. In sum, the current regulatory environment has created an economic incentive to pursue biologic-based products over chemical-based ones.

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 pharmaceutical patenting. Our results take this one step further and document a relationship with actual early-stage drug development. 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 using 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}. As expected, 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).

5.3 The impact of generic competition on innovation in the top-selling 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).[7] In general, results for these top markets are similar to our overall sample, though slightly weaker. The implied elasticity associated with generic penetration, GP_{ijt}, decreases to -.20. In other words, as generic penetration increases by 10%, the flow of early-stage innovations decreases by 2.1%.

5.4 The impact of generic competition on innovation in anti-epileptics

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). Increases in generic

[7]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.

penetration, GP_{ijt} do not 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.

5.5 Are generics enhancing the switch to biologics?

Other researchers 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; Golec *et al*, 2010). As we have noted 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.

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 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.

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.

We noted earlier that our sample is limited to firms with at least one approved product and at least one candidate drug in early stage development. This sampling restriction excludes some small, research-intensive firms. However, these smaller entities are overwhelmingly focused on biotech drug development. We strongly believe their inclusion in our empirical analysis would, if anything, significantly strengthen the general tenor of our findings, especially those concerning the rotation out of chemicals-based drugs and into biologics.

6 Conclusion

For many years, researchers and industry observers have conjectured that rising generic penetration might have an impact on the rate and direction of pharmaceutical innovation. Using a new combination of data sets, we are able to estimate the effects of rising generic penetration on early-stage pharmaceutical innovation. While the overall level of early stage drug development has remained stable, generics have had a statistically and economically significant impact on where and how that development activity is concentrated. In the full sample, we find that, as generic penetration increases by 10% within a therapeutic market, we observe a decrease of 7.9% in early-stage innovation in that market.

We observed in Branstetter *et al*. (2013) 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 statistically significant effect of generics on the early-stage innovation decision. In this particular submarket, and other similar markets with low levels of cross-molecular substitution, 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 therapeutic markets.

We also consider the economic incentives created by regulation to shift, within therapeutic markets, from chemicals-based to biologics-based products. Currently, data exclusivity is much 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* appear to lead to an increase in the relative amount of biologics-based drug development. As generic penetration in market *j* rises, firms do not appear to be abandoning market *j* completely, 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, such as marketing, manufacturing, or 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 current regulation is actually enhancing social welfare in the following sense. 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 a complete analysis of the rotation *between* therapeutic markets is beyond the scope of this paper, what we do observe is that as the thumb of generic competition is pressed down on a particular market, firms appear to be changing the direction and nature of their innovation, and we see a rotation *within* a market from chemicals-based to biologics-based innovation. This rotation could 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*., 2013). Our results seem to suggest that indeed there is an impact on 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.

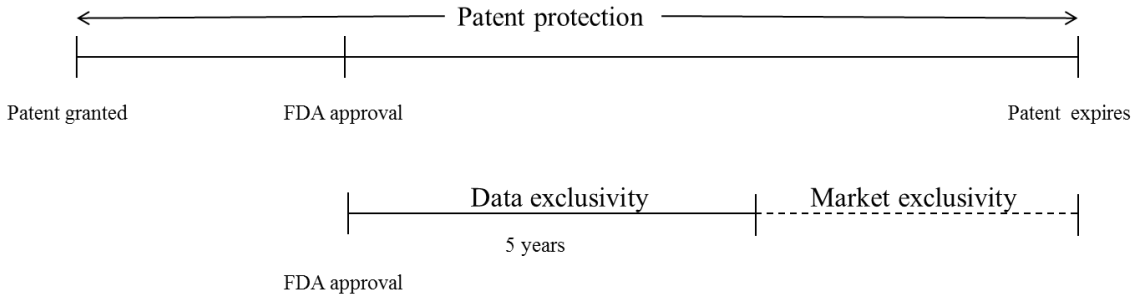

Figure 2. ANDA patent certification options for generic manufacturers. The regulatory pathway for generic entry in the U.S. can occur in one of four ways. Paragraph I, Paragraph II, and Paragraph III are used by generic manufacturers for drugs whose patents are either not listed in the FDA Orange Book 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).

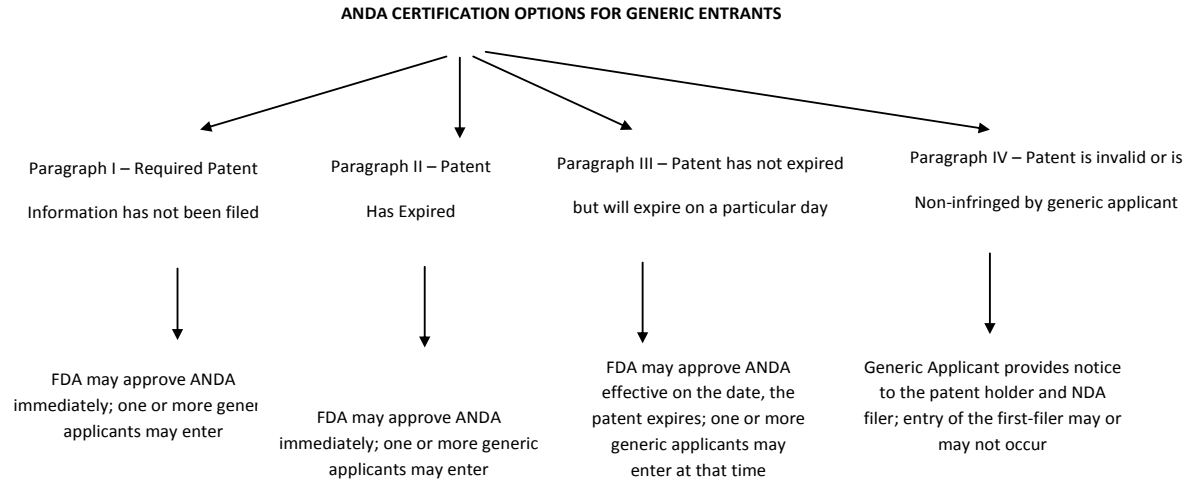

FIGURE 3.RELATIVE CONTRIBUTION TO TOTAL INNOVATIONS ACROSS THERAPEUTIC CATEGORIES

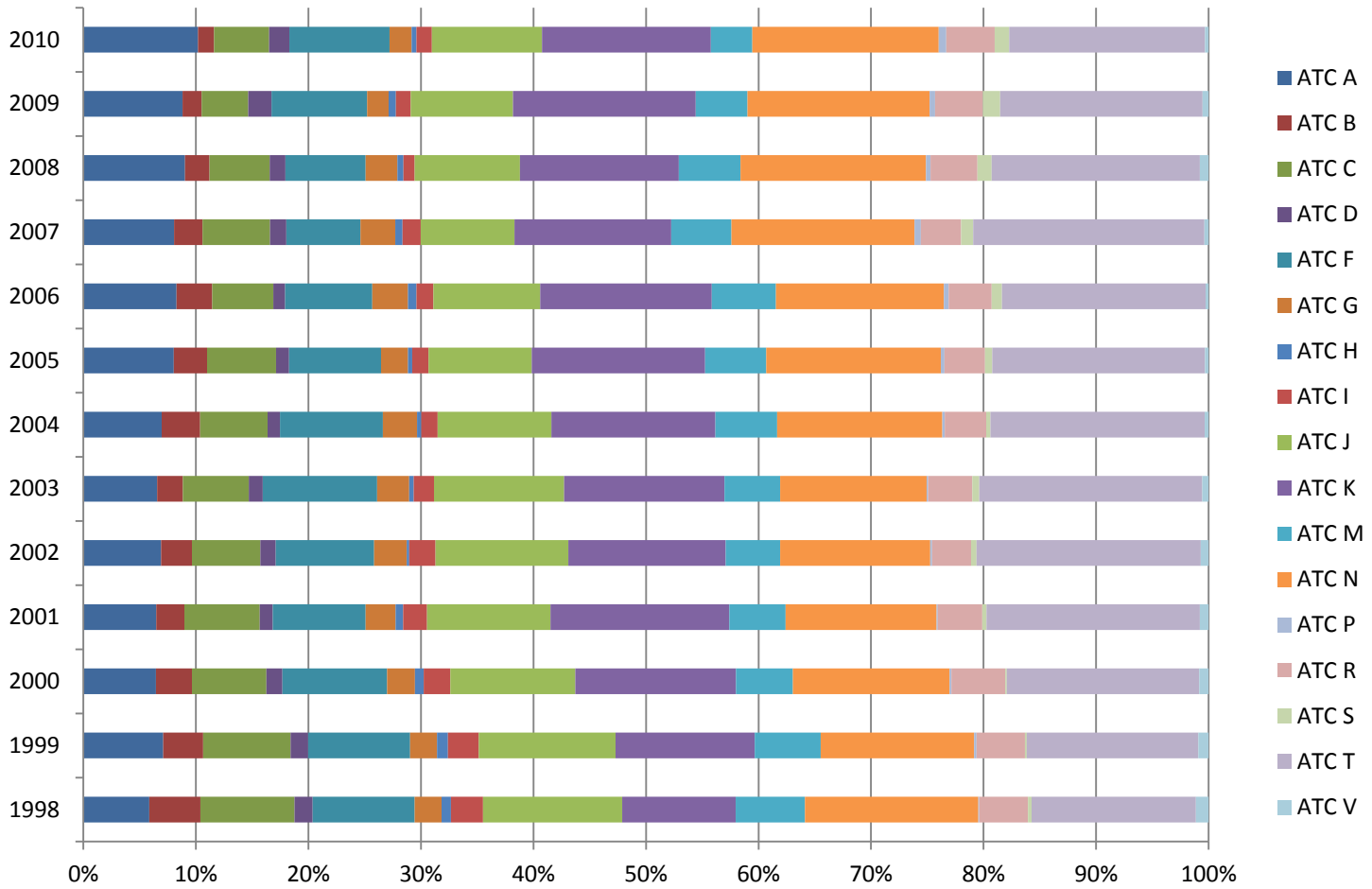

TABLE 1. VARIABLE DEFINITION AND DESCRIPTIVE STATISTICS

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
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}	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						
O_{jt-1}	-0.143	0.447	1.000					
Z_{ijt-1}	0.361	-0.139	-0.036	1.000				
D_{ijt-1}	0.357	-0.180	-0.083	0.152	1.000			
P_{ijt-1}	0.334	-0.225	-0.127	0.198	0.357	1.000		
SA_{ijt}	-0.007	0.018	-0.001	-0.004	-0.005	-0.005	1.000	
S_{it}	0.068	0.101	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)
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_{ijt-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_{ijt}	-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)
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

Standard errors 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)	-1.449*** (0.029)
O_{it-1}		0.003** (0.002)	0.009*** (0.001)	0.029*** (0.002)	0.035*** (0.002)
Z_{ijt-1}		0.448*** (0.013)	0.469*** (0.014)	0.398*** (0.013)	0.571*** (0.021)
D_{iit-1}	0.103*** (0.004)	0.106*** (0.004)	0.090*** (0.004)	0.094*** (0.004)	0.174*** (0.007)
P_{ijt-1}	0.142*** (0.016)	0.036** (0.015)	0.074*** (0.016)	0.028* (0.015)	0.113*** (0.017)
SA_{ijt}	-0.010 (0.006)	-0.008 (0.006)	-0.005 (0.004)	-0.001 (0.002)	-0.002 (0.002)
S_{it}	-0.043*** (0.003)	-0.040*** (0.003)	-0.043*** (0.003)	-0.028*** (0.003)	0.013*** (0.005)
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	-26833.96	-27135.10
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_{ijt}			-0.794*** (0.082)	-0.274*** (0.079)
O_{jt-1}		0.874*** (0.176)	0.239*** (0.017)	0.890*** (0.181)
Z_{ijt-1}		0.220*** (0.032)	0.256*** (0.039)	0.242*** (0.038)
D_{iit-1}	0.143*** (0.015)	0.149*** (0.015)	0.168*** (0.016)	0.151*** (0.016)
P_{iit-1}	0.093* (0.051)	0.111** (0.050)	0.096 (0.063)	0.120* (0.051)
SA_{ijt}	-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)	0.027** (0.011)
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	-2203.44
N	3,919	3,919	3,919	3,919

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

TABLE 6.CASE STUDY OF ANTI-EPILEPTIC DRUGS

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_{ijt}			-1.630*** (0.167)	0.155 (0.330)
O_{jt-1}		-0.238 (0.269)	-0.230 (0.250)	-0.189 (0.171)
Z_{iit-1}		0.423*** (0.135)	0.290** (0.117)	0.142** (0.062)
D_{iit-1}	0.137*** (0.034)	0.445*** (0.045)	0.289*** (0.039)	0.116*** (0.037)
P_{iit-1}	-0.036 (0.100)	0.464*** (0.156)	0.559*** (0.144)	-0.084 (0.104)
SA_{iit}	-0.335 (0.533)	0.214 (0.714)	0.906 (0.653)	-0.399 (0.623)
S_{it}	0.021 (0.016)	0.062*** (0.014)	0.115*** (0.015)	0.026 (0.020)
Year Fixed Effects	Y	Y	Y	Y
Firm Fixed Effects	Y	N	N	Y
Log Likelihood	-426.29	-719.46	-669.94	-352.91
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)	-2.069*** (0.045)
O_{jt-1}	0.006** (0.002)	0.030*** (0.002)	0.030*** (0.002)
$diffZ_{ijt-1}$	3.111*** (0.169)	3.065*** (0.188)	3.095*** (0.191)
$diffD_{ijt-1}$	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)
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	-16817.58
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)
O_{jt-1}	0.001 (0.000)	0.005*** (0.000)	0.005*** (0.000)
$diffZ_{ijt-1}$	0.302*** (0.014)	0.273*** (0.014)	0.276*** (0.014)
$diffD_{ijt-1}$	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)	0.002 (0.002)
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