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GENERIC COMPETITION AND THE INCENTIVES FOR EARLY-STAGE PHARMACEUTICAL INNOVATION

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ABSTRACT

What impact has rising generic competition had on the nature and direction of pharmaceutical innovation?We find broad-based, strong evidence that pharmaceutical companies have diverted their new drug development efforts away from therapeutic markets already well-served by generic drugs. We also find that increasing generic competition induces firms to shift their R&D activity towards more biologic-based products and away from chemical-based products. We conclude by discussing potential implications of our results for long-run innovation policy.

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1.0 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.[1] 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 (*e.g.*, 2007) supports the view that the gains from pharmaceutical innovation have been very large. In the long run, global investments in pharmaceutical research have proven to be good ones.

These benefits have come with significant costs; pharmaceutical innovation is risky and expensive.[2] These costs are passed on to consumers in the form of higher prices for branded pharmaceuticals.[3] However, in recent years generic products have accounted for an increasing share of prescription drug consumption, collectively accounting for 88 percent of prescription drug sales by volume in 2014 (Aiken *et al*, 2016). While the rise in generic competition has brought benefits to consumers (Branstetter *et al*., 2016), it may have also induced pharmaceutical companies to direct their R&D efforts into therapeutic markets or product categories where competition with generics is less intense (Higgins and Graham, 2009). Changes in the degree of generic competition across therapeutic markets could have strong implications even for non-U.S. drug companies because the global industry relies disproportionately on the U.S. market as a source of its profits. Thus, a natural question becomes, has the increase in generic entry affected pharmaceutical innovation? Our study attempts to address this question and quantify, for the first time, the impact of generic entry on early-stage pharmaceutical innovation.

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[1] 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. Efforts to infer the welfare impact of pharmaceutical innovation using modern models of demand for differentiated products, such as Ellickson *et al*. (2001), Cleanthous (2002), and Dunn (2012), have also yielded large estimates. Acemoglu and Johnson (2007) have documented the role of enhanced life expectancy on population and economic performance.

[2] Recent estimates by DiMasi *et al* (2016) suggest that the costs of developing a drug have risen to almost $2.6 billion. These new cost estimates, along with previous estimates generated through a similar methodology (DiMasi and Grabowski, 2012) have been subjected to considerable criticism and controversy. What we can say with certainty, however, is that costs are high and they continue to increase (Berndt *et al*, 2015).

[3] In 2012, prescription drug spending in the U.S. exceeded $300 billion and accounted for approximately 12 percent of total health care spending (GAO, 2012). Accounting for drugs dispensed in hospitals raises this fraction slightly; more recent data including these expenditures suggest a range of 15-18 percent. We thank an anonymous referee for pointing this out.

We start by constructing a new dataset that allows us to analyze this issue at a disaggregate level over the years 1998 through 2010. Instead of relying on patents as measures of innovation, we focus on early-stage drug development. While patenting is certainly important in the pharmaceutical industry (*e.g.*, Pisano, 2006), it can occur anytime throughout the drug development process, and it often occurs long before the actual therapeutic value of a compound has been demonstrated. As a consequence, patent counts can be imperfect indicators of the real innovative success of pharmaceutical firms, in terms of bringing new drugs to market. Our outcome variable, on the other hand, allows us to measure what is actually happening in the early stages of the drug 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 these different therapeutic markets.[4] This paper considers several potential inference challenges, including the possibility that a decline in research productivity within firms and markets could lower innovative output and raise measured generic penetration. These challenges are met with a range of empirical strategies, including the use of instrumental variables.

We find that the *aggregate* level of new drug development has *not* declined as generic competition in the U.S. market has risen (Appendix Figure A1 and A2); instead, the total number of new compounds (including both small and large molecules) in early-stage development has *risen* over our sample period (Appendix Figure A3 and A4). However, rising generic competition appears to have had a statistically and economically significant impact on *how* pharmaceutical product development is conducted, *where* those efforts are focused, and by *which firms* those efforts are undertaken. Our baseline specifications imply that a 10 percent increase in generic competition in a particular market will *lower* early-stage innovations, in that same market, by 6 to 7 percent. The interpretation that an increase in generic competition within a market lowers early-stage innovation is strengthened by a series of alternative specifications, placebo tests and robustness checks. We find interesting evidence of heterogeneity of response across firms. The firms with the most productive R&D operations appear to be more resistant to this challenge, so that the measured decline is disproportionately driven by firms ratcheting down their less productive research programs. This is all consistent with the view that rising generic competition is inducing firms to refocus drug development efforts in ways that may benefit social welfare, although a full welfare analysis is beyond the scope of the current paper.

[4] We use the phrases *therapeutic area, therapeutic market, therapeutic category* and *markets* interchangeably in this paper. In our empirical work, they correspond to 2-digit categories within the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system (http://www.whocc.no/atc/structure_and_principles/).

Next, we consider the possibility that, within therapeutic markets, a *shift* is occurring out of chemical-based (small molecule) products and into biologic-based (large molecule) products. The regulatory mechanisms that have accelerated generic entry in chemical-based drugs did not extend to biologics during our sample period; biologic-based generics (known in the industry as 'biosimilars') did not enter the U.S. market until 2015.[5] Exploiting this regulatory difference between chemical- and biologic-based innovations, we find a positive relationship between generic entry and a *shift* towards biologic-based products within therapeutic categories. As conjectured by Golec *et al* (2010), this movement suggests that the *nature* of innovation taking place in the pharmaceutical industry is changing in response to rising generic competition.

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

2.0 The U.S. regulatory environment and the rise of generic competition

The current regulatory environment faced by pharmaceutical companies in the U.S. can be traced to the passage of the Drug Price Competition and Patent Term Restoration Act in 1984, informally known as the "Hatch-Waxman" Act. When a pharmaceutical company submits a New Drug Application (NDA) to the FDA for approval, the law requires the company to identify all relevant patented technologies necessary to create the drug; these patents are subsequently listed in the FDA Orange Book.[6] Upon approval, the FDA will grant each new approved product regulatory protection lasting for five years ("data exclusivity") that runs concurrently with patent protection.[7] During this data exclusivity period,

[5] The Affordable Care Act created a legal pathway for biosimilars to enter the U.S. market, but it took several years for the FDA to finalize implementing regulations. The first biosimilar (Zarxio™) entered the U.S. market in March 2015 (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm). Large-molecule drugs have a much longer period of data exclusivity than small-molecule drugs, and their complexity makes them more difficult to copy even after patents expire. These differences could affect the economic incentives for developing generic versions of biologics, even in the long run.

[6] For biologics the initial application is a Biologics License Application. For biologics there is the Purple Book but during our sample period the same patent reporting requirements that are required under Hatch-Waxman for chemical-based drugs did not apply to biologics. In 2019, the Biologic Patent Transparency Act (BPTA) was introduced in the U.S. Senate. Under the BPTA, the Purple Book would become the main source for information on biosimiliarity, interchangeability, approved indications and exclusivities.

[7] There are exceptions; drugs targeting small patient populations (*i.e.*, orphan drugs) receive seven years of data exclusivity. Reformulations of existing drugs receive three years of data exclusivity. New drugs that treat pediatric illnesses receive an additional six months of data exclusivity while GAIN Act antibiotics are eligible for an additional five years of data exclusivity.

regardless of the status of the underlying patent(s), no generic entry may occur. At the conclusion of data exclusivity only patents protect branded products. This period running from the cessation of data exclusivity to the expiration of the patent(s) is commonly referred to as "market exclusivity." At the end of this period, generic manufacturers may enter the market by demonstrating bioequivalence with the branded product.

Throughout our sample period there was no legal mechanism in the U.S. market through which the manufacturer of a biosimilar could demonstrate that its substance was equivalent to the original drug. With no way to establish bioequivalence, any generic version of a biologic-based drug would have to undergo separate clinical trials to receive FDA approval. Under the Obama Administration, passage of the Affordable Care Act (2010) provided the legal basis for biosimilar entry, but that legislation guarantees biologic-based drugs 12 years of data exclusivity - a period of legal monopoly 2.4 times longer than that afforded to chemical-based drugs.[8] Enabling regulations, finalized by the FDA in 2013, generally require limited clinical trials to confirm bioequivalence and similar clinical effects prior to approval. These requirements raise the cost of generic entry relative to what obtains in the case of small molecule drugs. The longer European experience with biosimilars suggests that entry will be much less frequent, occur at a later point in the product lifecycle, and offer a much smaller price discount, relative to the innovator drug, than has been the case for generic entry in chemistry-based drug markets.

While a starkly different statutory treatment of chemical-based and biologic-based drugs has been established in U.S. law since the passage of Hatch-Waxman, the practical impact of these very different regulatory regimes has significantly strengthened in recent years. Generic competition 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 (Berndt *et al*, 2015).[9] Since then, however, generic competition has intensified sharply (*e.g.*, Palermo *et al.*, 2019; Higgins and Graham, 2009; Berndt *et al*., 2007). An important driver of this rise in generic competition has been the growing frequency of so-called Paragraph-IV (Para-IV) challenges, a procedure laid out by Hatch-Waxman whereby a generic company

[8] The section of the Affordable Care Act that details entry provisions for biologics is referred to as the Biologics Products Competition and Innovation Act (BPCIA).

[9] The FDA scandal was widely covered in the media at the time (*New York Times,* Oct. 2 1989). Cockburn (2006) discusses shifts in the measured research productivity of the pharmaceutical industry. A large cohort of new and successful branded products entered in the marketplace in the 1980s and 1990s, limiting the market importance of generic competition. As this wave of products lost patent protection, or was challenged under Paragraph IV, and was not fully replaced by newly introduced branded products, the financial pressure generated by generic competition increased.

could enter the market *prior to* branded patent expiration.[10] By the end of the 2000s, these challenges accounted for more than 40 percent of generic entry (Higgins and Graham, 2009; Berndt *et al*., 2007).

Generic entrants discovered that these shifts had rendered a whole set of pharmaceutical patents susceptible to legal challenges. Since the Hatch-Waxman Act rewarded successful Para-IV challengers with a half-year period of duopoly with the branded incumbent, prospective generic entrants tended to pursue these challenges whether the protected drugs were blockbusters or not (Grabowski and Kyle, 2007). In this way, both the timing of the resulting rise in generic competition and the identity of the patents being targeted were evolving in ways that were plausibly exogenous to the wishes and actions of our sample branded drug firms. We return to this line of argument later in the paper.

3.0 Pharmaceutical innovation and generic competition

After rising significantly in the first half of the 1990s and peaking in 1996, the number of new drug approvals began to decline gradually over the next few years, falling more sharply in the early 2000s, even as R&D expenditures continued to increase. This led to an intense debate about the industry's research "productivity crisis" (Cockburn, 2006; Scherer, 2010). 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 created a rising level of concern within the industry. We do *not* believe generic entry is causally related to measured declines in research productivity. However, changes in research productivity across firms and markets are among the many factors that could lead firms to divert their research efforts away from some therapeutic markets and product categories and toward others. In seeking to quantity the impact of generic competition on the allocation of research effort, we need to control, as best we can, for these other factors.[11]

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. 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 Hatch-Waxman. More recent work includes Reiffen and Ward (2005), Saha *et al* (2006), Grabowski and Kyle (2007), and Berndt and Aitken (2011). Efforts to calculate the welfare impact of generic entry include Bokhari and

[10] The interested reader can see Voet (2013) for a complete discussion of the Paragraph IV challenge process.
[11] Berndt *et al* (2015) identifies other demand side factors that have impacted the profitability of new drugs including: downward pressures on price due to consolidation among payers, wholesalers, and pharmaceutical benefits management firms; increased experience with cost containment; and increased focus on incremental value in coverage decisions. We seek to control for these potential unobserved market-time or time-varying factors in our models using an extensive array of fixed effects.

Fournier (2013) and Branstetter *et al* (2016). The latter study shows that the rising incidence of Para-IV challenges has increased 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 competition could impact 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 branded 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.[12] Other papers have also discussed this possibility, including Grabowski and Kyle (2007), Higgins and Graham (2009), and Knowles (2010). This research stream has provided (mostly indirect or anecdotal) evidence suggesting that an intensification of generic competition has undermined incentives for R&D. However, to the best of our knowledge, no published study has yet provided direct econometric evidence demonstrating that generic entry has induced a change in the nature or direction of new drug development.[13] The extent to which this occurs in practice remains an open question.

4.0 Empirical methodology 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. The dissagregate nature of our data allow us to track both variables by firm *i*, therapeutic market *j*, and year *t*. Over the past decade, other economists have used datasets with firm-market-year dimensions to develop and test formal theories of multiproduct firm behavior (Bernard *et al,* 2006, 2011; Eckel and Neary, 2010; Nocke and Yeaple, 2014; Eckel *et al*, 2015).[14] These models predict (and empirical work finds) striking heterogeneity in firm-level responses to market-level demand shocks, such as those arising from trade liberalization. For example, in response to a more competitive environment, firms tend to cut back on or eliminate product categories in

[12] Goldman *et al* (2011) report results consistent with the view that extending small-molecule data exclusivity to twelve years, matching large-molecule drugs, would lead to an additional 228 new drugs over a 40-year period.
[13] In related work, Budish *et al* (2015) provide evidence that variation in effective patent life distorts incentives for investment in cancer drugs. This study does not consider the impact of rising generic competition. Cook *et al*. (2010) finds evidence consistent with the idea that rising generic competition has reduced pharmaceutical R&D, but this research is undertaken at the economy-wide level; a key variable is the pharmaceutical price index for the entire U.S. economy. This level of aggregation limits the ability of the authors to control for other broad changes in the economy. As we were revising our paper, we became aware of the work of Stephen Murphy (2019), which overlaps with and confirms some of the work presented here.
[14] Given space constraints, we do not replicate the theoretical derivations presented in these papers. A short summary of these models that explains its connection to our empirical specification is provided in Appendix A1.

which they are relatively weak, but expand production in the domains where they are relatively strong. This implies that different firms will respond differently to market-level shocks, depending on their specific capabilities in those markets – a reality that will be completely missed if one adopts a market-year level approach in our context. We find robust evidence of this firm-level heterogeneity in the work presented below.

4.1 Modeling and measuring pharmaceutical innovation

We model early-stage pharmaceutical innovation as a function of generic competition, branded drug competition, scientific opportunity and challenges, firm innovative capability, and a vector of additional controls and fixed effects. Our baseline empirical specification is given below:

$$Inn_{ijt} = \alpha_i + \alpha_j + \alpha_t + \beta_1 Generic_{ijt-1} + \beta_2 Price_{ijt-1} + \beta_3 Tech\ Opp_{jt-1} + \beta_4 Tech\ Challenge_{ijt-1} + \beta_5 Product_{ijt-1} + \beta_6 LatePipe_{ijt-1} + \beta_7 FirmSize_{it} + \varepsilon_{ijt} \quad (1)$$

Our first empirical challenge is to come up with a practical measure of ***early-stage innovation***. Our dependent variable, Inn_{ijt}, measures early-stage innovations by firm *i* in ATC 2-digit (ATC2) market *j* in time *t*.[15] These data come from the Pharmaprojects database and depend on that source's classification of drug candidates into the various therapeutic market categories. Unfortunately, this is consistently reported only at the 2-digit level. Therefore, in our firm-market-year (*ijt*) level of analysis, discussed above, our markets will be constrained to the ATC2 market level.[16]

Firms are included in our sample if they have at least one approved product and at least one early-stage innovation. This limitation necessarily excludes some smaller, research-intensive firms that have yet to market their own products. We impose this exclusion because we seek to quantify the effect of generic competition in the product market on early-stage drug discovery at the firm-market level, and our methods for measuring this effect only work for firms with products in the market place. This exclusion therefore limits what we can say about the impact of generic competition on the research activities of firms without products. However, if these smaller firms license their compounds to larger ones at an early stage of the development process (a strategy frequently employed by smaller firms), we will still capture

[15] Inn_{ijt} counts new compounds only once and that is the first time they appear in either the preclinical stage or the Phase 1 clinical trials stage.

[16] There are 126 different ATC 2-digit level markets which are themselves contained within 14 different ATC 1-digit level markets. The ATC 1-digit market classification "C" represents drugs related to the cardiovascular system. It contains nine ATC 2-digit categories: (1) C01 Cardiac therapy; (2) C02 Antihypertensives; (3) C03 Diuretics; (4) C04 Peripheral vasodilators; (5) C05 Vasoprotectives; (6) C07 Beta blockig agents; (7) C08 Calcium channel blockers; (8) C09 Renin-angiotensin system; and (9) C10 Lipid modifying agents.

that product in our empirical work, effectively assigning it to the firm that develops the drug rather than the one initially identifies the candidate therapy. We argue below that the bias introduced by the sample selection in our source data, to the extent that it exists, may actually weaken our estimated results relative to what holds in reality.[17] The current measure of Inn_{ijt} counts new compounds in the year they first appear in preclinical or Phase 1 clinical trials. Importantly, compounds are not double-counted; if a compound first appears in preclinical it is not counted again as it transitions to Phase 1; thus Inn_{ijt} can be viewed as a flow rather than a stock.[18] This treatment of the data vastly increases the number of firm-market-year observations for which our count of early-stage innovations is zero, and therefore subjects our main hypothesis to a more stringent empirical test than if we relied on the corresponding stock measure.

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, changes in perceived scientific opportunity, or changes in expected market opportunity, we would expect a measurable impact to show up at this stage. In contrast, for drugs that have already successfully moved on to Phase 2 or Phase 3 trials, firms may be more likely to move them through the development process to the end, even if the firm plans to limit future research in that area in response to rising competition or diminished technological opportunity.[19] Because the outcome variable is a count variable, at least some of the statistical models employed in our regression should be ones designed to handle count data. As such, we use fixed effects Poisson and negative binomial estimators (Hausman *et al*., 1984; Woolridge, 1999).

4.2 Measuring generic competition (*$Generic_{ijt-1}$*)

Our next empirical challenge is to measure the ***incidence of generic competition***. This incidence is quite uneven across firms, therapeutic categories and time. Fortunately, we are able to employ disaggregated data from the IQVIA MIDAS™ database that tracks the sales (in quantity terms) of nearly every pharmaceutical product sold in the U.S. by firm, product, and quarter, mapped to ATC categories.

[17] This is particularly true for the results based on Equation 7, described below.
[18] If a compound is licensed, it could appear in Phase 1 clinical trials without ever having appeared as a compound under preclinical investigation by our sample firms.
[19] We present empirical results later in the paper that are consistent with this view. We are not suggesting here that firms would never cancel a compound in Phase 2 or Phase 3 clinical trials. For example, as a result of *branded* competition from Gilead in the Hepatitis C market, both Vertex and Merck ended their products in development. This example, however, is due to branded competition and not due to generic competition, which is the focus of this paper. Rather, we are suggesting that, given the success of the compound in progressing through risky and expensive later phases of the drug development process, firms may be less likely to discontinue development just because the downstream market has become more competitive due to an increase in *generic competition*.

We note that IQVIA creates a 'standard unit' of quantity that equates capsules, tablets and liquid dosages; this is the measure of quantity used in our analysis. Our data are limited to the years 1998-2010, and this data restriction determines the time dimension of our study. However, this window covers a period of intensifying generic competition.[20] Within this period, we are able to determine the extent of generic competition that firm *i* faces in therapeutic area *j* in time *t-1*. We define our measure of generic competition, $Generic_{ijt-1}$, as the sum of generic sales (in quantities) in therapeutic area *j* at time *t-1* divided by the sum of generic and firm *i* branded sales in therapeutic area *j* at time *t-1*.[21] A negative coefficient implies that as generic competition faced by firm *i*, in therapeutic market *j* increases, the flow of early-stage innovation decreases.[22]

The time subscript on our generic competition variable is *t-1*; this effectively imposes an assumption about the timing of a pharmaceutical firm's response to observed changes in the exposure of a firm to generic competition. While we note that the estimated impact of generic competition is robust to alternative lags, we believe the timing assumption implied by Equation (1) is a reasonable one. Recall that our dependent variable measures *early-stage* innovations by firm *i* in ATC2 market *j* in time *t*. Compounds tend to progress through these earlier stages of the development process relatively quickly, and substances that fail early tests can be discarded at low cost. It is the later, larger scale clinical trials that tend to be more time-consuming, expensive, and therefore risky. Precisely because of the costs that are born at these later stages, however, compounds that survive Phase 2 and 3 clinical trials are likely to be introduced into the market place, even if rising generic competition is judged likely to crowd the market and limit future sales. In private conversations, pharmaceutical executives strongly asserted that a significant increase in generic competition in a particular therapeutic area often leads to a rapid response, in terms of a *reduction* in early-stage drug development in *that* domain and a *redirection* of research resources that would have been required to support the progress of those early-stage compounds through more stringent and expensive clinical trials to *other therapeutic areas*.[23] On the other hand, compounds

[20] In 1996, generics accounted for only 43 percent of U.S. prescriptions. By 2002, this share had increased to 53 percent, and by 2008 it had grown to 72 percent (IQVIA, Inc).

[21] As a robustness check, we defined a second measure of generic competition, $G_{jt-1}M_{ijt-1}$, as the ratio of generic sales to total sales in therapeutic area *j* in time *t-1* multiplied by the ratio of branded sales by firm *i* in therapeutic area *j* in year *t-1* divided by total branded sales of firm *i* in year *t-1*. Our earlier working paper (Branstetter *et al.*, 2014) demonstrates that this alternative measure yields results qualitatively similar to the ones obtained with $Generic_{ijt-1}$. For that reason, we focus on the latter measure in this version of the paper.

[22] To be precise, $Generic_{ijt-1}$ was constructed at the ATC 4-digit market level for each firm-year and then aggregated to the ATC 2-digit market level for each firm-year. Hence, two firms, A and B, both operating within the same ATC 2-digit market could face different degrees of measured generic competition, depending on the degree to which each firms' sales within a 2-digit aggregate in a given year is distributed across 4-digit markets within that same year.

[23] Once physicians, insurance companies, and pharmaceutical benefits managers become aware of low-cost, effective generic drugs in a particular domain, this "raises the bar" for new branded drugs – they are likely to secure

that are already in the later stages of development are less sensitive to these changes. Later in the paper, we test this assertion with data, and find strong empirical evidence supporting it, confirming our presumption that the response of drug development efforts to rising generic competition is concentrated in the early stages of the process.

To the extent that pharmaceutical executives take sources of information (unknown to the econometrician) other than current generic competition into account in forming their expectations of what generic competition would be at the time drugs currently in the early stages of development might be introduced, our current specification measures the variable of interest with error. If that measurement error takes the classical form, then it is likely to yield a downward bias in our regression estimates. If we nevertheless find large effects, we do so in the presence of statistical biases against such a finding, giving us some assurance regarding the validity of our inference.[24]

4.3 The impact of generic competition on subsequent innovation[25]

As generic competition rises within a particular drug market, the number of effective therapies currently available at low cost to treat the prevalent diseases in a given market expands. Branded companies contemplating further (expensive and risky) drug development in this market confront a growing array of established, low-cost competing therapies that would be attractive substitutes for any new drug which did not possess clear therapeutic advantages over existing drugs. Rising generic competition therefore "raises the bar" for future branded entry, both because average drug prices are declining *and* because the degree of unmet medical need a new branded drug could address is logically dimishing as the number of available generic therapies grows. Obviously, it would be useful and interesting if we could separate out these two effects of generic competition on subsequent branded innovation, because the theoretical possibility exists that a relatively crowded product space full of low-cost generics could deter entry when the potential exists for a new, different drug to raise consumer welfare even if it were only available at a high price.

Unfortunately, there appears to be no practical way to separately measure "unmet medical need" in a consistent way within and across pharmaceutical markets, and it seems likely that both unmet medical need and average price will decline sharply as generic competition rises. Therefore, we will not

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a high market share only if they are *dramatically* better than previously introduced branded drugs in terms of efficacy, more limited side effects, or ease of use.

[24] Of course, our current analysis also takes seriously the possibility that our measure of generic competition is highly correlated with unmeasured research productivity, leading to a more pernicious kind of bias.

[25] We thank an anonymous referee for raising questions that prompted the writing of this section.

interpret a negative, statistically significant coefficient on our measure of generic competition as representing a social loss, a decline in welfare, or any convincing evidence of unmet medical need. The results we will present are perfectly consistent with a view in which the Hatch-Waxman rules are working as their architects might have intended – market forces are redirecting new drug development efforts away from markets where many effective generic therapies already exist and toward new domains where the stock of effective generic therapies is less developed. The measured negative effect associated with generic competition could very well reflect an efficient (even socially optimal) allocation of research effort across markets. Given these inferential and measurement challenges, we will have little to say about about the welfare implications of the branded firm reactions we quantify, nor will we devote much attention to the normative of question how branded firms should be responding to rising generic competition in order to maximize welfare.

Instead, we will focus on the *positive* questions of how branded firms *are* responding to rising generic competition and whether the estimated relationship can be viewed as being at least partly causal. We view this agenda as interesting in its own right, and we think it constitutes an important first step towards addressing the welfare/normative questions noted in the previous paragraph. The rest of Section 4 presents a range of empirical strategies designed to resolve the more straightforward positive questions to the extent that our data will allow.

4.4 Measuring competition among branded drugs ($Price_{jt-1}$, HHI_{jt-1}, and $Brand_{ijt}$)

Generic competition is not the only form of competition faced by our firms. Branded firms also compete with one another, and the intensity of this competition varies substantially across markets and over time.[26] Excluding this from our estimating equation could lead to a bias in estimates of the impact of generic competition, β_1. To be clear, if we denote our sample estimate of β_1 as $b^*_{Generic}$, and a more inclusive measure of competition that includes branded firms as $Brand_{ijt-1}$, then:

$$b^*_{Generic} = \beta_1 + \beta_{Brand} \frac{\widehat{Cov}\,(Generic_{ijt-1}, Brand_{ijt-1})}{\widehat{Var}(Generic_{ijt-1})} \qquad (2)$$

In this formulation, β_{Brand} could be negative (since a crowding of the product space with other branded products could reduce the private benefits of innovation for firm *i*), and $\widehat{Cov}\,(Generic_{ijt-1}, Brand_{ijt-1})$ is plausibly positive, since branded competition will typically emerge in response to an innovative therapy within an ATC2 market prior to the onset of generic competition, and both variables may be serially correlated within firms and markets. Therefore, omission of a measure that includes branded competition

[26] Authors have long recognized the importance of market competition for innovative activity (*e.g.*, Utterback and Suarez, 1993; Tang, 2006).

could plausibly bias our estimate of β_1 downward, leading to a more negative and perhaps more statistically significant coefficient.

We took several approaches to the empirical measurement of the competition from branded drug makers facing firm *i* in product market *j* at time *t*, focusing first on standard measures of competition at the market level. $Price_{jt-1}$ is the average price (per dose) of all drugs in market *j* at time *t-1*, and this is the control variable featured in the paper's main regression tables.[27] Note that we have constructed our price measure to reflect all drug sales, branded and generic. Inclusion of this variable in our specifications helps us isolate the impact of generic competition – and that impact will remain negative and statistically significant in our baseline specifications. In regressions not shown in the main table, but included in the Appendix, we also include HHI_{jt-1}, the conventionally defined Herfindahl-Hirschman index of drug sales in market *j* at time *t-1*, as an alternative measure of "total" (generic plus branded) competition. Inclusion of this alternative control does not qualitatively change our results, as the results in our Appendix show.

Finally, we constructed a more direct measure of branded competition that is conceptually similar to our measure of generic competition, and varies by firm, market, and year. $Brand_{ijt}$ measures the branded sales of firm *i* in market *j* in year *t* divided by total branded sales in market *j* at time *t*. If firm *i* is the only branded seller, this measure equals 1. As other branded firms enter, the ratio falls below one. A positive coefficient would imply a negative effect of branded competition on early stage innovation efforts. As the results included in our Appendix indicate, the measured negative impact of generic competition is not qualitatively altered by the inclusion of this variable. Given the complex issues raised by a thorough investigation of the impact of branded competition on early-stage drug development (perhaps better explored in a separate study), we have chosen to relegate the details of these results to the Appendix, and instead emphasize in our main text the result that our measures of generic competition are robust to all of these controls.

4.5 The econometric challenges created by unmeasured research capabilities

Now, it would be convenient to presume that, once $Price_{jt-1}$ or other appropriate measures of branded competition are included in our specifications, the error term in Equation (1) is independently and identically distributed across firm-market-year observations. However, one can imagine that the error term is potentially more complicated than that.[28] To fix ideas and illustrate the inferential challenges that arise, we presume that the error term takes on the following form:

[27] We acknowledge that our measure of price is per (standard) dose, rather than a price that reflects the full cost of the standard treatment regimen and that our price data do not reflect branded manufacturer rebates.
[28] This section was inspired, in part, by Olley and Pakes (1996) and Pavcnik (2002) and the notation used here reflects that influence.

$$\varepsilon_{ijt} = \omega_{ijt} + \mu_{ijt} \qquad (3)$$

The second term on the right-hand side of Equation (3) is presumed to be identically and independently distributed, and causes no econometric problems. The first term on the right-hand side, ω_{ijt}, is a research productivity parameter that determines the effectiveness with which firm *i* translates research resources into new drugs in market *j* at time *t*. It is not fixed – instead, it evolves over time across firms and markets, and is therefore not accounted for by the usual fixed effects.

We think of ω_{ijt} as the innovative capabilities of the part of firm *i*'s drug development team that is focusing on therapies in market *j* at time *t*. These capabilities will reflect the skills and creativity of the individuals in this firm-specific R&D unit. These skills and levels of creativity will vary over time, as incumbent researchers retire or resign, new researchers join the team, and current researchers pursue research paths that lead to a string of valuable discoveries or a series of dead ends. Since the composition of the research team evolves over time, through arrivals and departures, and the research productivity of individual members is likely to be characterized by periods of especially fruitful work that stretch out across years, it is natural to think that ω_{ijt} could exhibit some temporal dependence such that:[29]

$$\omega_{ijt} = \gamma_1\omega_{ijt-1} + \gamma_2\omega_{ijt-2} + \gamma_3\omega_{ijt-3} + ... + \gamma_7\omega_{ijt-7} + \gamma_8\omega_{jt-8} + \tau_{ijt} \qquad (4)$$

where τ is the usual well-behaved error term and:

$$\gamma_1 > \gamma_2 > \gamma_3 > ... > \gamma_7 > \gamma_8 \qquad (5)$$

To the extent that the firm is aware of its ω_{ijt}, it will invest more in markets where ω_{ijt} is high and less where it is low, inducing a positive correlation between early-stage drug development activity and ω_{ijt}. Of course, if ω_{ijt} declines significantly, and remains low, then the flow of new drugs from firm *i* in market *j* will decline and perhaps cease altogether. Measured generic competition may therefore rise as existing products loose patent protection and are not replaced by new patent-protected products, inducing a negative correlation between our measure of generic competition and our measure of early-stage innovation, Inn_{jit}.[30]

[29] It is obviously uncertain exactly how many lags are relevant in predicting current ω, and our empirical strategies are not contingent for their success upon our guessing this with perfect accuracy.

[30] Of course, this line of argument raises the possibility of serial correlation in the error term. Interestingly, the standard Breusch-Godfrey test fails to reject the null of no serial correlation in our data (prob > F: 0.6483). The Breusch–Godfrey serial correlation LM test is a test for autocorrelation in the errors in a regression model. It makes use of the residuals from the model being considered in a regression analysis, and a test statistic is derived from these. The null hypothesis is that there is no serial correlation of any order up to *p*. The test is more general than

To summarize these concerns in more mathematical language, let $Cov(\omega_{ijt}, \omega_{ijt-n}) > 0$, such that there is substantial correlation in ω within firms and markets over time up to lags of length *n*. Further, let $Cov(Inn_{ijt}, \omega_{ijt-n}) > 0$, reflecting the fact that early stage innovation will tend to be high in markets where firm *i*'s past research productivity has been high and low where it has been low, reflecting the presumed temporal dependence in ω. Then, let $Cov(\omega_{ijt-n}, Generic_{ijt-1}) < 0$, reflecting the fact that the level of generic competition encountered by firms will tend to be high in markets where their measured research productivity has been low in the past, meaning that the patents of previously introduced products have had time to expire. Given this, it is possible that $Cov(Inn_{ijt}, Generic_{ijt-1}) < 0$, but the latter relationship could emerge *purely as an artifact of omitted variable bias.* In other words, our estimated coefficient on $Generic_{ijt-1}$ could significantly exaggerate the degree to which a negative relationship truly exists between innovation and generic competition.[31]

Note that it is not contemporaneous realizations of ω that induce this inference problem; movements in $Generic_{ijt-1}$ will reflect *past* realizations of ω, because it takes time for new products to move through the development and approval pipeline. A sudden rise in ω that yields an increase in the number of early-stage drug candidates will only effect branded sales, and, by extension, our measure of generic competition, with a relatively long lag, because of the time required for clinical trials and FDA approval. Likewise, a sudden decline in ω that generates a fall in the number of early-stage drug candidates would not have an immediate effect on $Generic_{ijt-1}$ instead, that variable would be evolving in response to the loss of market exclusivity of previously introduced products, resulting from either patent expirations or successful generic challenges. This highlights the need to somehow control for lagged values of ω in our empirical specifications. We will return to this idea later in the paper.

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the Durbin–Watson statistic (or Durbin's *h* statistic), which is only valid for non-stochastic regressors and for testing the possibility of a first-order autoregressive model (*e.g.,* AR(1)) for the regression errors. The BG test has none of these restrictions, and is statistically more powerful than Durbin's *h* statistic. The standard references are Breusch (1978) and Godfrey (1978). However, this finding does not necessarily invalidate our conceptual approach. Recall from Equation (2) that our error term consists of two components: ω_{ijt}, which is subject to first order serial correlation by assumption, and μ_{ijt}, which is not. We know that our outcome variable, which is an integer count of early stage drug candidates, is discrete, highly variable, and frequently zero, suggesting the variance of μ_{ijt}, and its realized magnitude in many observations, could be sufficiently great as to obscure the serial correlation presumed in ω_{ijt}.

[31] Of course, the possibility that $Cov(Inn_{ijt}, Generic_{ijt-1}) < 0$ is not directly implied by our prior assumptions; the point here is that it is a *possible* outcome which could complicate our inference. We thank an anonymous referee for pointing this out.

In mathematical notation, this line of reasoning implies that we would have omitted variable bias in our sample estimate of the impact of generic competition on innovation, which we again denote $b^*_{Generic}$:

$$b^*_{Generic} = \beta_1 + \beta_\omega \frac{\widehat{Cov}\,(Generic_{ijt-1}, \omega_{ijt-n})}{\widehat{Var}(Generic_{ijt-1})} \qquad (6)$$

Here, β_ω is positive and potentially large because current innovative capacity is correlated with lagged values of ω, while $\widehat{Cov}\,(Generic_{ijt-1}, \omega_{ijt-n})$ is negative, and potentially large. Even if the true effect of generic competition on innovation, β_1, is only modestly negative or close to zero, the omitted variable bias could be large enough to render a spurious finding of a large, negative, statistically significant $b^*_{Generic}$. How can we contend with this plausible bias?

4.6 Controlling (indirectly) for ω_{ijt}

Unfortunately, in the context of our study, ω_{ijt} is unobservable.[32] We cannot incorporate direct measures of ω_{ijt} into our estimating equation, thereby eliminating the omitted variable bias directly. Instead, the only way forward is for us to make (plausible) assumptions about the form, structure, and determinants of ω_{ijt}, and then show that our key results are robust to a portfolio of empirical strategies that would yield unbiased estimates of β_1 (or, at least, less biased estimates), contingent on our assumptions being true. This section is devoted to an explication of these empirical strategies. While no single strategy provides perfect leverage around this challenge, the robustness and consistency of our results across all of them significantly strengthens our inference.

a. Controlling for elements of ω_{ijt} that are correlated across firms within a market through inclusion of a direct measure of technological opportunity

We begin our efforts by focusing on elements of ω_{ijt} that are likely to be correlated *across* firms within a market at any point in time and over time. All firms active in a given market are drawing upon a common reservoir of basic medical knowledge that is yielding greater or lesser applied research opportunities over time (Evenson and Kislev, 1976; Kortum, 1997; Cockburn, 2006). Our measure of scientific/technological opportunity, $Tech\ Opp_{jt-1}$, is meant to control for this, at least in part, by constructing a citation-weighted, depreciated stock of potentially relevant science that varies across ATC2

[32] If pharmaceutical companies reported R&D expenditure by ATC2 markets, this could constitute a reasonable proxy for ω, but such data are not publicly available.

markets and over time. Prior research has demonstrated a link between academic research and industrial R&D (*e.g.*, Mansfield, 1995; Gittelman and Kogut, 2003); these linkages are particularly strong in pharmaceuticals (Iaria *et al.*, 2017). Similar to Furman *et al* (2005), we construct a bibliographic measure that captures publicly available academic research in the life sciences.

We start by merging data from IQVIA MIDAS™ with the IQVIA NDTI™ database, which captures physician prescription behavior. This latter database identifies the diseases for which physicians are actually prescribing the drugs in IQVIA MIDAS™, including off-label uses. IQVIA MIDAS™ is categorized by ATC codes and the IQVIA NDTI™ database is categorized by ATC codes and International Statistical Classification of Disease (ICD-9) diagnostic codes. IQVIA NDTI™ provides us with a concordance between ICD-9 diagnostic codes and ATC product codes (at the 4-digit level).[33] Next, we extracted the top 10 ICD-9 diagnostic codes for each ATC 4-digit (ATC4) market. These ICD-9 codes have unified keywords associated with them that were used as search terms in the National Library of Medicine's PUBMED database. This search yielded journal articles published between 1950 and 2010 relating to our various keywords that we were then able to map back to disaggregate ATC4 markets. Ultimately, we identified a unique sample of 6.5 million journal articles. However, some journal articles were mapped to multiple ATC4 markets, thereby yielding 20.9 million raw article counts.

Next, we used the unique PMID identifiers for these articles to gather their forward citations from the year of publication to the end of 2010 in the SCOPUS Sciverse database (*e.g.*, Catalini, 2017). Our sample of 20.9 million articles generated over 345 million forward citations. Since our unit of observation in a therapeutic market is at the ATC2 level, we aggregate our annual, citation-weighted counts of journal articles up from the ATC4 level to the ATC2 level. Older science is likely to be less relevant for current drug development than more recent science. For this reason, we apply a 15 percent "knowledge depreciation" rate (Griliches, 1984), take natural logs, and lag the log of the stock by one year to create our control variable, $Tech\ Opp_{jt-1}$.[34] By construction, "technology opportunity" is presumed to be the same for all firms active within a market at a point in time, and it evolves over time as the relevant scientific literature accumulates and depreciates.

[33] IQVIA NDTI™ is a dataset built from a physician survey that asks physicians which ICD-9 codes they actually prescribe drugs. This creates a physician-based mapping of ICD-9 codes to ATC 4-digit therapeutic markets. The match between IQVIA NDTI™ and IQVIA MIDAS™ can thus be made via ATC codes.

[34] A 15 percent depreciation rate is a standard assumption in the R&D and innovation literature (Griliches, 1984). Results are not sensitive to alternative assumptions regarding the depreciation rate. Newer science is likely to be more relevant to biologic-based drug development, and any depreciation rate will weight this newer science more heavily.

b. Controlling for elements of ω_{ijt} that are correlated across firms through the inclusion of market-year interacted fixed effects

A large body of empirical evidence suggests that a common base of technological opportunity could drive movements in ω_{ijt} that are correlated across firms within markets and vary over time. Given our data resources, we believe we have created a plausible empirical proxy for this common technological opportunity, thereby extracting at least one component of ω_{ijt} out of the error term. Empirical results shown later confirm that our measure of technological opportunity is significantly correlated with innovation outcomes. However, technological opportunity is only one among many market-level variables that could impact ω_{ijt}, and not all of them can be measured, even approximately, with available data.

That inconvenient truth suggests a more "brute force" approach to the inference problem. If ω_{ijt} is correlated across all firms active in a particular market, *j*, for *any* reason, but it varies widely across different markets and different time periods, then we may be able to largely control for it by including interacted market-year fixed effects. Inclusion of these interacted fixed effects could yield other advantages for our inference. Many characteristics of ATC2 markets *other than* research productivity have shifted in ways that could influence the allocation of innovative effort across markets. These effects could be broadly common across firms. For instance, economists have long understood that changes in expected future market size could influence the distribution of R&D investment across product markets, and recent research has shown this to be true in the pharmaceutical industry (*e.g.*, Acemoglu and Linn, 2004; Finkelstein, 2004; Dubois *et al*, 2015; Murphy, 2019). Changes in expected market size across ATC categories over time can be controlled for by a market-year interacted fixed effect.[35] Finally, to the extent that the demand-side factors impacting drug profitability described by Berndt *et al* (2015) also vary across therapeutic markets and time, these effects should also be controlled for by including the same interaction terms.[36]

c. Controlling for elements of ω_{ijt} that vary across firms within markets

[35] In an earlier version of this paper (Branstetter *et al*, 2014) we controlled for the expected future market size for new drugs in a particular therapeutic class by averaging total sales from IQVIA MIDAS™ in therapeutic area *j* over year *t*, year *t+1*, and year *t+2*, measured in inflation-adjusted dollars. The sign and significance of the coefficients on our measures of generic competition are not sensitive to the inclusion or exclusion of this variable, so it is omitted from the current specification and we rely instead on the market-year interacted fixed effects to control for changes in expected market size.

[36] See Walsh (1984) for a broader discussion on demand-pull factors and their influence on innovation.

We have outlined two separate empirical strategies for dealing with elements of ω_{ijt} (and other factors) that are common across firms within markets but vary over time. However, pharmaceutical companies – even ones active in the same therapeutic markets - differ sharply in the drug development capabilities they have built over time. These differences are likely to evolve over time in ways that will vary across firms within markets. As already noted, persistence in the firm-specific components of these unmeasured capabilities could still induce a spurious negative correlation between our measures of innovation and our measures of generic competition, even in the presence of direct controls for technological opportunity or market-year interacted fixed effects. However, this very persistence also suggests proxy variables that could be introduced into our specification to help us control for the lagged realizations of ω that constitute our main inference challenge.

A given firm is more likely to introduce a new compound in a therapeutic category in which it already has substantial research expertise, as evidenced by its past research performance. To employ our earlier notation, if a firm *i* had high values of ω in a particular market *j* in the recent past, this should be evidenced by larger numbers of compounds in the more advanced Phase 2 and Phase 3 stages of the clinical trials process. To control for this, we use data from Pharmaprojects to define $Late\ Pipe_{ijt-1}$ as the number of compounds under development by firm *i* that are in Phase 2 or Phase 3 clinical trials in therapeutic market *j* at time *t-1*. This additional control is likely to be correlated with the lagged values of ω that are generating our central inference challenge.

Continuing with this chain of logic, we can control for even longer lags of ω by using data from Pharmaprojects to create a three-year moving average of past drug introductions, $Product_{ijt-1}$, by firm *i* in the same therapeutic market *j*. This three-year moving average is lagged one period, (*t-1*). Larger firms are likely to have larger R&D budgets and more early-stage innovative effort, so we control for overall firm size by measuring total pharmaceutical sales by firm *i* in year *t*, $Firm\ Size_{it}$, taking the natural log of sales data from IQVIA MIDAS™. All financial variables are converted into real dollars using a base year 2000 GDP deflator.[37]

In the same way that we are attempting to control for past realizations of ω by using measures of past R&D success, we can also incorporate an interesting measure of past R&D *failure*. 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

[37] In earlier versions of the paper, we included the ratio of firm *i*'s marketing expenditures to product sales in market *j* at time *t* as an additional control, given the likelihood that firms will concentrate their research activities in domains where they have a strong brand. The inclusion of this additional control did not qualitatively change our results.

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. In other words, this could be indicative of a negative shock to ω_{ijt} that persists over several periods. 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, $Tech\ Challenge_{ijt-1}$, as the number of products suspended, discontinued or withdrawn by firm *i*, in therapeutic market *j* at time *t-1*, and we include this in our specification.

By explicitly including multiple covariates in Equation (1) that reflect past realizations of ω_{ijt}, both positive and negative, we significantly reduce the possibility that our inference is driven by omitted variables bias. Recall that our earlier concerns rested on the idea that lagged values of ω were positively correlated, at least to some extent, with current innovation (that is, early-stage drug development), and also negatively correlated, to some extent, with our measures of generic competition. A lengthy period of low draws of ω could induce firms to cut back on investment in new products and, as patents on existing products expire, generate an increase in measured generic competition. Inclusion of the covariates described in this section mitigates this problem of omitted variable bias. It is clear from the preceding paragraphs that these variables are included as controls, and we are not attributing a causal or structural interpretation to the regression coefficients estimated.

4.7 Using an instrumental variables approach

The next element of our empirical strategy involves the use of instrumental variables. Recall that our inference problem stems from the fact that fluctuations in firm-market-period specific measures of research productivity (ω_{ijt}) can affect both our measures of innovation and our measures of generic competition. The ideal instrument or instrument set would feature variables which *are* correlated with generic competition but are *not* correlated with the firm's underlying research productivity. If all generic entry resulted from the expiration of patents, this could reflect, with a lag, the declining research productivity of branded drug companies in a particular market.

Fortunately, a growing fraction of generic entry is *not* driven by patent expiration, but instead by *successful challenges* to existing patents. Drawing upon related research (Palermo *et al.,* 2019; Branstetter *et al*., 2016; Hemphill and Sampat, 2011, 2012), we focus on Para-IV challenges to patent-protected

branded drugs. The Hatch-Waxman Act contained a pathway through which generics companies could compete with branded drugs under patent. To utilize this pathway, generics companies had to demonstrate that the patents were invalid or that the generic product did not actually infringe them. If generics companies successfully challenged the patent or evaded infringement charges, then they were rewarded with a half-year of duopoly, after which any generic entrant could seek permission to enter the market. As described in detail in Branstetter et al. (2016), this feature of the legislation created a potential pathway by which generics companies could challenge branded drugs under patent protection, but the number of challenges remained low until the late 1990s. The acceleration of challenges since then can be tied to a series of court decisions, changes in FDA policy, and passage of the Medicare Act of 2003. These shifts in legislation, in regulatory practice, and in the courts' views of patent validity and patent boundaries had the effect of rapidly increasing generic competition in ways that were arguably *not* highly correlated with changes across fields in the research productivity of branded firms and were also plausibly exogenous to the actions or desires of any one branded firm. The effects were large - the number of Para-IV challenges surged from just one in 1994 to 44 in 2007 and to 230 in 2010. By the end of the 2000s, Para-IV challenges accounted for more than 40 percent of all generic entry (Higgins and Graham, 2009; Berndt *et al*., 2007).

We therefore utilize an instrument set based on Para-IV challenges and Para-IV litigation outcomes. For each firm *i*, we count the number of Para-IV market challenges made against the firm's products in market *j* at time *t*. We also count the number of Para-IV legal successes – that is, first court judgments favorable to the generic challenger – in market *j* at time *t*. We instrument for $Generic_{ijt-1}$ using these two instruments, while retaining our other variables to control for movement in ω. Finally, as an extension of our IV models, we estimate a System GMM version of Equation (1) that incorporates a lagged dependent variable, continues to instrument for generic competition, and allows for serial correlation in the error terms. When we do so, we incorporate into our specification, via the lagged the dependent variable, an additional control that is plausibly correlated with very recent realizations of ω, expanding the degree to which we can potentially extract these recent realizations from our error term.

4.8 An exploration of firm-level heterogeneity in response to generic competition

The firm-product literature referenced earlier in our text generally finds that firms respond very differently to rising competition in the domains where they have a "core competence" than in domains where their market-specific capabilities are less developed. When faced with rising competition, the dominant models imply that firms should diminish their investment in domains where they are weak, but

increase their investment in domains where they are strong. This logic suggests an additional empirical test. The negative affect of generic competition on innovation should be significantly attenuated in markets where the firm in question has strong drug development capabilities. We can therefore estimate an alternative specification of (1) along the lines of:

$$Inn_{ijt} = \alpha_i + \alpha_j + \alpha_t + \beta_1 Generic_{ijt-1} + \beta_2(Generic_{ijt-1} * Product_{ijt-1}) + \beta_3 Price_{ijt-1} + \beta_4 Tech\ Opp_{jt-1} + \beta_5 Tech\ Challenge_{ijt-1} + \beta_6 Product_{ijt-1} + \beta_7 Late\ Pipe_{ijt-1} + \beta_8 Firm\ Size_{it} + \varepsilon_{ijt} \quad (7)$$

where we interact our measure of generic competition with a measure of firm-market-specific research competence – in this case, our moving average of past product introductions ($Product_{ijt-1}$). If the theory upon which we draw is correct, and if our interpretation of the results of preceding specifications is valid, then the coefficient β_2 should be positive and statistically significant, confirming that firms with relatively strong drug capabilities in a particular market are less likely to reduce their development efforts as generic competition rises. On the other hand, if the negative regression coefficient we estimate for β_1 is purely spurious, then it is not clear why β_2 should be positive and significant.

4.9 Empirical specification for measuring the shift into biologic-based drugs

Finally, current regulation suggests an alternative approach to estimating the impact of generics on innovation. Chemical-based pharmaceutical products become susceptible to generic entry after patent expiration (*i.e.*, end of market exclusivity). They also become susceptible to early generic entry via Para-IV challenges only five years after approval (*i.e.*, end of data exclusivity). As discussed above, biologic-based drugs face a different regulatory regime. During our sample period, there was no legal pathway through which biosimilars could enter the U.S. market, nor was (or is) there the equivalent of a Para-IV challenge to biologic-based drugs. This suggests that the difference in regulation during our sample period created an incentive for pharmaceutical companies to favor biologic-based therapies over chemical-based therapies, even if the latter was more effective in a purely therapeutic sense. Even as biosimilars begin to enter the U.S. market, for reasons discussed previously, those incentives are likely to remain in the longer run. This suggests an alternative specification:

$$CI_{ijt} - BI_{ijt} = \alpha_i + \alpha_j + \alpha_t + \beta_1 Generic_{ijt-1} + \beta_2(Tech\ Opp_{jt-1}) + \beta_3(CTech\ Challenge_{ijt-1} - BTech\ Challenge_{ijt-1}) + \beta_4(CProduct_{ijt-1} - BProduct_{ijt-1}) + \beta_5(CLate\ Pipe_{ijt-1} - BLate\ Pipe_{ijt-1}) + \beta_6 FirmSize_{it} + \varepsilon_{ijt} \quad (8)$$

Here, the dependent variable measures the difference between chemistry-based innovations (CI_{ijt}) and biologic-based (BI_{ijt}) 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 competition ($Generic_{ijt-1}$) to have an impact on the choice of technology – unless firms' research choices are being affected by the prospect of generic competition.

If current regulation is 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 (Inn_{ijt}) into either biologic-based (BI_{ijt}) or chemical-based (CI_{ijt}) innovation. In operationalizing Equation (8), the dependent variable is the difference between these two types of innovation, $CI_{ijt} - BI_{ijt}$. A negative coefficient on a right-hand side variable 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.[38]

It is possible for firm i to have more biologic-based innovations than chemical-based innovations in therapeutic market j at time t. In this case, our difference variable ($CI_{ijt} - BI_{ijt}$) will become negative, preventing us from using count data models. We therefore create a new variable, $cat(CI_{ijt} - BI_{ijt})$, that equals 1, 2 and 3 if ($CI_{ijt} - BI_{ijt}$) is negative, zero or positive, respectively. This reclassification allows us to use ordered logit and ordered probit specifications. Again, a negative coefficient on an independent variable would imply that as that variable increased, the dependent variable, $cat(CI_{ijt} - BI_{ijt})$, declines. 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 (8), we use the *Origin of Material* field within Pharmaprojects to decompose our measure of late-stage innovations, $Late\ Pipe_{ijt-1}$, past drug introductions, $Product_{ijt-1}$, and our measure of scientific challenges, $Tech\ Challenge_{ijt-1}$, faced by firm i in therapeutic market j, into their chemical-based and biologics-based components. Empirically, we create the variables $diff(Late\ Pipe_{ijt-1})$, $diff(Product_{ijt-1})$, and $diff(Tech\ Challenge_{ijt-1})$, defined as the difference between the chemical- and biologic-based components, respectively.[39]

[38] As a robustness check for this specification we also employ a seemingly unrelated regression (SUR) specification where firms simultaneously decide their innovation decisions in chemicals and biologics (Tables 8 and 9). Results are consistent between our various specifications and will be discussed more fully in Section 5.5. We thank Ivan Png for this suggestion.

[39] Unfortunately, we have not found a credible way to split $Tech\ Opp_{jt-1}$ into chemical-based and biologic-based components. It is extremely difficult to identify all facets of biologic-based research from PubMed. Even after utilizing experts within these respective fields and experts at the U.S. National Library of Medicine (PubMed) to

5.0 Empirical results

5.1 Descriptive statistics and baseline market and firm-market results

Descriptive statistics for our variables are presented in Panels A and B, Table 1, depending on whether they vary at the firm-market-year level (Panel A) or the market-year level (Panel B). In Table 2, we present regression results aggregated up to the ATC 2-digit market year level, as a benchmark against which to compare our firm-market-year level results. In these regressions, standard errors are clustered at the market level. Models 1 through 5 present the results of fixed effects negative binomial regressions (Hausman, Hall, and Griliches, 1984). Model 1 introduces our main variable of interest, and Models 2 through 4 add our main control variables, all aggregated up to the market-year level. The pattern of results suggests a statistically and economically significant negative relationship between generic competition and early-stage innovation, but the magnitude of that relationship and its statistical significance drop sharply as we add the additional controls, suggesting that the omitted variable bias problem discussed earlier in the paper is a real one. The signs of the estimated coefficients for the control variables are generally as expected except for $Tech\ Challenges_{jt-1}$, which is positive rather than negative. This turns out to be robust feature of econometric results, and we discuss how to interpret this finding later in this section. The coefficient on $Generic_{jt-1}$ in Model 4 is significant at the 10 percent level and has an implied elasticity of about 11 percent. Thus, an increase in generic competition of 10 percent implies a decline in early-stage drug development of about 1.1 percent. Model 4 includes year and ATC 1-digit (ATC1) market fixed effects. If we add (ATC1*Year) interacted fixed effects, as in Model 5, the results do not qualitatively change. For comparative purposes, Model 6 provides the results of a Poisson regression. The coefficient on $Generic_{jt-1}$ and its implied elasticity do not change much with this alternative specification.

In Table 3, we present our baseline firm-market-year level results, again employing the fixed-effects negative binomial and Poisson estimators pioneered by Hausman *et al.* (1984).[40] The dependent variable in all specifications is Inn_{ijt}, or the count of firm *i* early-stage innovations in therapeutic market *j* at time *t*, as described in Section 4.2. Model 1 presents results of a regression including only our measure of generic competition and firm, year, and market fixed effects (estimated at the ATC1 market level). The estimated impact of generic competition is negative and statistically significant; the implied elasticity suggests that a 10 percent increase in generic competition lowers early stage innovation by approximately

help construct keywords, we still found examples where our biologic-based measure would be undercounted. Such an undercount is problematic since we are trying to control for biologic-based scientific opportunities. Our alternative solution is to discount $Tech\ Opp_{jt-1}$ in order to deemphasize older research and emphasize more recent research that would be more relevant (and consistent) with the focus on biologic-based products. The removal of $Tech\ Opp_{jt-1}$ does not change our core findings.

[40] As indicated in the regression tables, standard errors are now clustered at the firm level.

6.5 percent. Model 1 omits any consideration of competition between branded drugs. Model 2 rectifies this omission by incorporating our measure of average price, which reflects the impact of branded and generic drugs. The coefficient on $Price_{jt-1}$ is negative but not statistically significant; its inclusion does not qualitatively change the significance or magnitude of our measure of generic competition, strengthening our view that generic competition has a significant and strong impact on early-stage innovation.[41] In Model 3, we incorporate our measure of technological opportunity, $Tech\ Opp_{jt-1}$; the estimated coefficient is positive and statistically significant, but the measured impact of generic competition remains robust.

In Model 4, we incorporate additional firm-market-year controls designed to reflect past research success and failure – $Product_{ijt-1}$ (a three-year moving average of new product introductions), $Late\ Pipe_{ijt-1}$ (a count of compounds in Phase 2 and 3 clinical trials), and $Firm\ Size_{it}$ (total sales of firm *i* in year *t*). The estimated coefficient for generic competition declines slightly in magnitude relative to Model 3, suggesting that the omitted variable bias problem discussed earlier exists, at least to some extent. However, the estimated effect of generic competition remains strongly negative and highly significant. As expected, $Product_{ijt-1}$ and $Late\ Pipe_{ijt-1}$ have positive coefficients, although only the former is consistently significant; $Firm\ Size_{it}$ is also positive but not consistently significant. In Model 5, which serves as our base specification, we add $Tech\ Challenge_{ijt-1}$ and (ATC1*Year) interacted fixed effects. Contrary to expectations, $Tech\ Challenge_{ijt-1}$ is positive and statistically significant – we suspect this reflects the fact that firms with more products in their development pipelines will encounter more challenges. It is also possible that failures can serve as a learning mechanism for future endeavors (Chiou *et al*, 2012). Statin drugs, which today are one of the largest selling therapeutic areas, 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.[42]

Across all specifications, we find negative and statistically significant coefficient estimates for our measure of generic competition. This negative relationship suggests that, at the firm level, increases in generic competition are related to decreases in the flow of early-stage innovation *in that therapeutic market*. Taking the coefficient from our complete negative binomial specification (Table 3, Model 5) as our baseline estimate, we calculate an elasticity equal to -0.674. In other words, a 10 percent increase in

[41] Robustness checks included in our Appendix incorporate *HHI* and *Brand*. Appendix Tables B1 to B8 replicate Tables 2 to Table 9 including *HHI* and *Brand* while Appendix Tables C1 to C4 replicate Appendix Tables A1, A2, A4, and A5 with *HHI* and *Brand.* Inclusion of this additional control does not qualitatively change the estimated impact of generic competition.

[42] In Model 6, we run a linear version of Model 5 for comparative purposes and in Model 7 we employ a fixed effects Poisson model as an additional robustness check. Additional fixed effects Poisson models are reported in Appendix Table A1.

generic competition experienced by a firm in a particular market corresponds to a roughly 6.74 percent decrease in early-stage innovation by that firm in that market. To our knowledge this is the first empirical evidence that documents the effect of generic competition in the U.S. market on early-stage pharmaceutical innovation. Other things equal, if fewer candidates are entering a given therapeutic pipeline within a given firm, then fewer approved drugs will eventually come out. The implied elasticity of the Poisson specification (Model 7) is quite similar to the negative binomial baseline (Model 5). The linear specification in Model 6 suggests a somewhat smaller effect - a 3.34 percent decline in innovation in response to a 10% increase in generic competition - but one that is still quite economically, as well as statistically, significant.

Generic competition into a market is clearly harmful for branded producers. From a social welfare perspective, however, we cannot necessarily infer any negative impact. If the presence of viable generics in a market rises, our results indicate that innovation will decrease in that market. However, the rising level of early-stage drug development effort at the aggregate level suggests that the decline in innovation within markets facing a high degree of generic competition is more than offset by increased innovative effort elsewhere. Indeed, Pammolli *et al*. (2011) argues that one of the reasons overall pharmaceutical R&D productivity has declined is a shift of R&D resources 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 is occurring. In essence, Hatch-Waxman, by providing mechanisms of entry for generics, creates conditions under which the pharmaceutical industry redirects R&D efforts to markets less served by generics.

If R&D efforts are shifting across therapeutic areas, this can have significant future consequences, with a net impact on social welfare that is difficult to calculate. On the one hand, 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 consequences for the net flow of innovation (either increasing or decreasing). On the other hand, new product development in a domain with few (or no) existing effective therapies may have greater social value than similar development in an area with a broad range of existing effective therapies, even if the R&D success probabilities are lower in the domain with few therapies. In this paper, we *do not* take a stand on the ultimate welfare consequences of this shift. Instead, we seek to document the existence and magnitude of this shift. The welfare consequences of the shift remain the focus of ongoing research.

5.2 ATC market-year interacted fixed effects, instrumental variables, and GMM specifications

In Table 4, we submit our baseline results to a number of alternative specifications designed to significantly sharpen our causal inference and address problems of potential endogeneity or omitted variable bias impacting our measures of generic competition. We begin in Model 1 by incorporating ATC2 market fixed effects and the interaction between ATC2 market and year fixed effects into the specification. This is not feasible in our fixed effects negative binomial models; attempts to estimate these nonlinear specifications with so many fixed effects fail to reach convergence. However it is possible to incorporate firm, year, ATC2 market fixed effects along with the interaction between ATC2 market and year fixed effects into a linear regression specification of Equation (1). We view this an especially strong test of the hypothesis that an increase in generic competition is associated with a decline in innovative activity, because *all* of the factors associated with an ATC2 market that vary over time in a common way across firms are swept out with the interaction terms. For example, recent research by Dubois *et at* (2015) has documented the existence of a strong relationship between the expected future growth of demand in a therapeutic area and new drug introductions. To the extent that expectations of future demand growth are correlated across firms active in a given market, inclusion of this fixed effect will control for that.

Despite the imperfect fit between the count data in our dependent variable and the statistical assumptions undergirding our linear specification, we still find that generic competition is still negatively associated with early-stage drug development, and this effect is statistically significant at conventional levels. The elasticity from Model 1 implies that a 10 percent increase in generic competition in a particular market will *lower* early-stage innovations, in that same market, by about 4 percent – an elasticity broadly comparable in magnitude to our baseline estimates from the previous table. Recall that our unit of observation is the firm-market-year level, where market *j* is defined at the ATC2 market level. When we include ATC2 market fixed effects and the interacted fixed effect between ATC2 market and year, $Price_{jt-1}$, and $Tech\ Opp_{jt-1}$ are no longer informative. So, we omit them from Model 1, and we do so in every specification that follows where we include interacted fixed effects between ATC2 market and year dummies.[43]

In Models 2 to 5, we take yet another approach to testing the robustness of our results: the use of instrumental variables. Here, we drop the interacted fixed effects and utilize the instruments described previously. Model 2 presents the results of a two-stage least squares linear regression with firm, year, and ATC1 market fixed effects, along with an interaction between ATC1 market and year fixed effects. The effect of rising generic competition is still negative and statistically significant at conventional levels. The

[43] In one further robustness check we split the sample in order to determine whether results are driven by observations either early or late in the sample period. In short, they are not. Results are reported in Appendix Table A2.

estimated magnitude of the coefficient rises significantly, compared to the coefficient in Mode1, and that estimated coefficient implies that a 10 percent increase in generic competition leads to a 12.5 percent decline in early-stage innovation.

Model 3 incorporates the more disaggregate ATC2 market fixed effects and the interaction between ATC2 market and year fixed effects into our two-stage least squares linear specification; the measured impact of rising generic competition remains negative and statistically significant. The new estimated coefficient implies that a 10 percent increase in generic competition leads to a 13.9 percent decline in early-stage innovative activity. Model 4 drops the interacted fixed effects and employs an Arellano-Bond System GMM linear specification, in which we instrument for generic competition, incorporate a lagged dependent variable, and allow for serial correlation in the error terms.[44] The magnitude of the key coefficient remains negative and statistically significant here as well, implying an elasticity of -0.296. Finally, Model 5 retains the System GMM specification, but drops the additional controls $Product_{ijt-1}$ and $Late\ Pipe_{ijt-1}$. Yet again, the key coefficient remains negative and significant; in Model 5, it implies an elasticity of -0.363.[45]

5.3 Additional robustness checks

In Table 5, we return to our negative binomial specifications and subject these results to an additional series of robustness tests, starting with an alternative dependent variable. Our baseline measure of innovation, Inn_{ijt}, which is the count of products in early-stage development, does not discriminate between "breakthrough" pharmaceutical products and those that come much later in the history of a therapeutic area. This reflects, in part, the difficulty of drawing a clear or meaningful line between "truly innovative" drugs and "me-too" drugs. The history of the industry provides several examples in which the first products in a class had significant shortcomings or side effects - and the real breakthroughs in terms of therapeutic efficacy came several product introductions later.[46] Even when new products are merely recombinations or reformulations of existing active ingredients, the new products can often provide significant therapeutic benefits to certain categories of patients.

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[44] This was implemented using the STATA procedure based on the work of Arellano and Bond (1991) and Bond and Blundell (1998), who devised the more robust System GMM variant used here, which tends to have better small sample properties. The basic approach is to first-difference data as a way of extracting fixed effects, then use lags as instruments for potentially endogenous realizations of the lagged dependent variable.

[45] Appendix Table A3 presents results of an additional robustness check. We report results from an OLS model with $Generic_{ijt-1}$ along with firm, year, ATC2 market fixed effects, interactions between ATC2 market and year fixed effects, *and* interactions between firm and year fixed effects. The main effect remains negative and statistically significant.

[46] See Arcidiacono *et al* (2013).

Despite these realities, critics of the pharmaceutical industry have accused branded firms of responding to generic entry or the threat of generic entry by coming up with branded "innovations" that are not true innovations, but merely minor modifications of earlier branded products. If the negative impact of rising generic entry on early-stage innovation, identified in our regressions, were limited to incremental innovations with little or no therapeutic value, then that would have different policy implications from an effect that extended to the most novel compounds and drugs.

The Pharmaprojects database includes a variable that grades each product under development in terms of its novelty - the most novel compounds are ones that are first in their class. We can therefore present the results of an alternative specification of Equation (1) in which we replace our comprehensive count of drugs in early-stage development with a count of only novel drugs in early-stage development, *Novel Inn*$_{ijt}$. The elasticity from Model 1 implies that a 10 percent increase in generic competition in a particular market will *lower* early-stage *novel* innovations, in that same market, by 5.99 percent. Put another way, our results are not driven by a crowding out of purely incremental inventions or reformulations.

Next, we can test the robustness of our results and the correctness of our interpretation by applying a series of placebo tests. In our previous regressions, we carefully defined innovation as early-stage product development. As compounds move through the costly, expensive, and risky clinical trials process, they require ever-higher levels of investment by the firm. A drug that has survived Phase 2 and Phase 3 clinical trials is likely to be introduced, even if generic competition is rising sharply in a way that might lead to a throttling back of early-stage research in that therapeutic area. Drugs at these later stages of the development process should be significantly less responsive to our measures of generic competition than our measures of earlier stage innovations.[47] We can directly test this proposition by replacing our current early-stage innovation variable, *Inn*$_{ijt}$, with an alternative late-stage innovation variable and see whether our empirical results remain unaffected.

Following this logic, in Table 5, Model 2, we define a new dependent variable, *Late-stage Inn*$_{ijt}$, as a count of firm *i*'s products in Phase 2 or Phase 3 trials in market *j* at time *t*. In this specification, we find that our measure of generic competition is *not* significantly correlated with late-stage product

[47] We thank Jeff Macher for suggesting this robustness check. Conversations with pharmaceutical executives confirm that later stage drug development should be less responsive to changes in generic competition.

innovation.[48] This is in line with our expectations, and strengthens our interpretation of the results using measures of early-stage product development.

Our third regression is a different sort of placebo test. In many therapeutic markets, practicing physicians have long regarded different drugs, based on different molecules and utilizing different biochemical pathways to attack the disease, as equally effective therapies for the underlying illness. In such cases, when insurance companies incentivize their customers to choose newly available generics, physicians will often willingly switch their customers from a molecule without a generic equivalent to one that has a generic equivalent, especially if it saves their patients money. Where this so-called cross-molecular substitution is high, the implications for branded products can be quite profound. In such markets, the emergence of a generic equivalent to *any* branded product can affect the revenue streams of *all* branded products, leading to wide-ranging declines in revenues and profits.

However, the degree of cross-molecular substitution varies substantially across markets. For example, based on conversations with practicing physicians, we would expect higher substitution in therapeutic areas such as anti-infectives, hypertension and allergies and lower substitution in markets such as depression and epilepsy. In general, the complexity and sensitivity of the human brain and the complicated nature of neurological disorders work to strictly limit the degree of cross-molecular substitution in drugs that treat neurological and psychiatric disorders. They even limit the degree to which practitioners are willing to use (bioequivalent) generic versions of the branded drug. When practitioners find a good match between a drug treatment and a patient in these domains, they are often reluctant to switch to a cheaper generic.

Economic intuition suggests that if a class of branded drugs was less susceptible to cross-molecular substitution and generic competition, then we might expect to see a muted innovation response to rising generic competition in that particular market. Focusing on the markets that include anti-epileptics, anti-depressants, and anti-psychotics, we indeed see this in our results in Table 3, Model 3. Increases in generic competition do not appear to have any statistically significant effect on early-stage innovation in these therapeutic areas.[49] This suggests that there are markets for which direct substitution

[48] In these regressions, our dependent variable is identical to $Late\ Pipe_{ijt-1,}$ so we omit this variable from our set of control variables.

[49] Given the limited number of markets we are able to get convergence with a model that includes firm, year, ATC 2-digit market and an interaction between ATC 2-digit and year fixed effects.

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.[50,51]

5.4 Exploring heterogeneity in firm responses to generic competition

Firms with different levels of R&D capability in a given market could vary substantially in their response to a similar rise in the level of generic competition in that market. A firm with strong R&D capabilities could continue to invest in new product development in this domain, expecting that it can deliver new products with sufficient advantages over existing therapies that it can recoup the cost of product development from future sales, even as the number of effective generic medicines in the space rises. Conversely, a firm with limited (or declining) research capabilities in the same space could respond to rising generic competition by lowering its R&D efforts or diverting them to other markets where competition was less intense or the firms underlying R&D capabilities were stronger.

Table 6 implements several empirical tests based on this logic. Model 1 repeats our baseline negative binomial specification but with the inclusion of an interaction term, $(Generic*Product)_{ijt-1}$, which is defined as the product of $Generic_{ijt-1}$ and $Product_{ijt-1}$. The interaction term is highly significant and positive, indicating that that the impact of generic competition weakens significantly when the firm has better developed innovative capabilities in the therapeutic market in question. Model 2 returns to our linear two-stage least squares specification and inserts the same interaction term, finding broadly similar results. Model 3 modifies the interaction term by creating a dummy variable equal to one if $Product_{ijt-1}$ is greater than the median value, zero otherwise, and multiplying $Generic_{ijt-1}$ by this dummy variable. Inserting this new interaction term $(Generic*Product2)_{ijt-1}$ into the baseline negative binomial specification generates a qualitatively similar, but stronger result. The magnitude and significance level of the interaction term suggests that, for the firms with the most developed R&D capabilities, the usual negative impact of generic competition is dramatically reduced. Similar results are obtained in Model 4 when we insert the same interaction term into our two-stage least squares specification, suggesting that essentially all of the decline in new product introduction comes from firms with less developed R&D capabilities in those markets.

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[50] As a further robustness check, through consultations with practicing physicians we identified markets that they deemed high cross-molecular substitution, namely the anti-infective markets J01-J04. Two additional markets, PPIs (A02) and statins (C10), were added on recommendation by an anonymous referee. When we replicate the findings in Model 3, Table 4 for these high CMS markets the coefficients on $Generic_{ijt-1}$ are negative and significant at the 1 percent level. Results available on request are consistent with our intuition about high CMS markets.

[51] Appendix Table A4 replicates the models in Table 5 excluding $Product_{ijt-1}$, and $Late\ Pipe_{ijt-1}$. Results remain robust.

These results continue to hold in Models 5 and 6. Here, we employ yet another variant of the interaction term. We create a dummy variable equal to one if the firm has a measured R&D capability (as evidenced by our $Product_{ijt-1}$ variable) that is in the top quartile, and interact this new dummy with our measure of generic competition, $(Generic*Product)_{ijt-1}$. In both the baseline negative binomial specification (Model 5) and the linear two-stage least squares specification (Model 6), our results suggest that the decline in early-stage innovation in response to greater generic competition is driven by firms with weaker R&D capabilities. For the most capable firms, the negative impact appears to be negligible.

5.5 Are generics driving a switch to biologics-based drug development?

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 shift could have mixed consequences for future drug development. Biologics are more expensive than chemical-based products, on average (Aitken *et al*., 2009), and biologics are likely to experience far less generic competition than chemical-based drugs for the foreseeable future. If consumer uptake across the two types of products over their entire product lifecycle remains similar, then a shift from chemical-based to biologic-based drugs could imply that, all else equal, the percent of overall health care expenditures spent on pharmaceuticals will increase.

In order to consider whether a shift to biologic-based products may be occurring as a consequence of rising generic competition, we estimate the specification described in Equation (8). 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 prevents us from using count data models. Instead, we create a variable, $cat(CI_{ijt}\text{-}BI_{ijt})$, that equals 1, 2 and 3 if the difference ($CI_{ijt} - BI_{ijt}$) is negative, zero, or positive, respectively, and we estimate Equation (8) using IV and OLS specifications (Table 7, Models 1-3) and for comparative purposes, ordered logit and ordered probit models (Table 7, Models 4-6). Model 1 presents the results from a two-stage least squares linear regression utilizing the same instrument set as before, along with firm, year and ATC1 market fixed effects, including the interacted ATC1 market and year fixed effects. Model 2 retains the two-stage least squares approach, but includes firm, year, and ATC2 market fixed effects, including the interacted ATC2 market and year fixed effects. Model 3 adopts a linear specification without instruments, but retains the interacted ATC2 market and year fixed effects. Across all specifications our measure of generic competition is negatively and significantly related to the difference in types of early-stage innovations. This suggests that as generic competition increases, our dependent variable, $cat(CI_{ijt}\text{-}$

BI_{ijt}), declines which, in turn, implies that the difference, ($CI_{ijt} - BI_{ijt}$) is decreasing (or becoming more negative). In other words, as generic competition increases, the flow of biologic-based innovations rises relative to the flow of chemical-based innovations for firm *i*, in market *j*, at time *t*. Controlling for other factors, it appears that pharmaceutical firms are responding to generic competition by shifting to biologics, where they do not face similar competition.

Model 4 employs an ordered logit regression specification with firm, year, and ATC1 market fixed effects. Model 5 adds interacted ATC1 market-year fixed effects. Finally, Model 6 employs an ordered probit specification. All three specifications incorporate the full set of baseline control variables. Not surprisingly, use of nonlinear models results in larger coefficients. In all cases, however, the estimated effects are negative, statistically significant, and of reasonably large magnitude. All results continue to suggest that higher levels of generic competition push firms in the direction of more biologic-based (large molecule) drug development relative to chemical-based (small molecule) drug development.[52]

Table 8 provides results from an alternative approach - one in which two separate linear models predicting chemical-based product innovations and biologic-based production innovations, respectively, are run as a system, using the seemingly unrelated regressions (SUR) approach. In all specifications, we can see that generic competition is negatively associated with chemical-based innovation, but positively associated with biologic-based innovation, and both relationships are statistically significant at the conventional threshold levels. We noted earlier in the paper 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, over our sample period, these smaller entities tended to be more focused on biologic drug development. Hence, we believe their inclusion in our empirical analysis would, if anything, significantly strengthen the general tenor of our findings, especially those concerning the shift out of chemical-based drugs and into biologic-based drugs.

As a final robustness check we consider markets where there is particularly robust biologic-based early-stage innovation. It should be the case that once we restrict the sample, using the same methodology as Table 8, results should strengthen. That is, we should see a greater negative effect on CI_{ijt} and a greater positive effect on BI_{ijt} in markets where biologic-based innovation is especially well developed, frequent,

[52] In Appendix Table A5 we replicate Models 1, 2, and 3 from Table 7 with an alternate definition of the dependent variable. In these models the dependent variable, $diff(CI_{ijt} - B_{ijt})$, is the difference between CI_{ijt} and BI_{ijt}. This allows $diff(CI_{ijt} - B_{ijt})$ to be positive, negative or zero. Results remain robust to this alternative definition.

and, perhaps, easier for firms with the requisite knowledge capital.[53] Table 9 shows that when we restrict the sample to the top three ATC1 markets (F, J and T) with the largest number of early-stage biologic-based innovations, using a SUR approach, we find a greater negative effect on CI_{ijt} and a greater positive effect on BI_{ijt}.

6.0 Conclusion

For many years, researchers and industry observers have conjectured that rising generic competition 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 competition on early-stage pharmaceutical innovation. While the overall level of early-stage drug development has continued to increase, generics have had a statistically and economically significant impact on *where* that development activity is concentrated, *how* it is done, and by *which firms* it is undertaken. In the full sample, we find that, as our baseline measure of generic competition increases by 10 percent within a therapeutic market, we observe a decrease of 6.74 percent in early-stage innovation in that market. This implies that drug development activity is moving out of markets where generic competition is increasing and into domains where it is relatively less intense.

These results were subjected to a broad range of robustness tests and alternative specifications, with particular attention paid to the possibility of omitted variable bias arising from variation in (unmeasured) research productivity across firms, markets, and time. Our results remained robust to inclusion of a number of firm-market-time covariates designed to control for changes in (lags of) firm research productivity. Our results were also robust to multiple alternative definitions of the dependent variable, including the use of only novel, first-in-class drug candidates. Alternatively, as expected, the results fade into insignificance when we redefined innovation as late-stage or when we limited the scope of our analysis to markets where cross-molecular substitution is low. In linear specifications, we found that the negative relationship between drug development and rising generic competition remains robust to the inclusion of a full set of ATC2 market fixed effects and the interaction between ATC2 market and year fixed effects. Finally, an instrumental variables approach reflecting the rapid rise of Para-IV entry confirmed the robustness of the negative estimated relationship between generic competition and early-stage innovation.

Our rich data allow us to examine the heterogeneity of firm responses to generic competition, in a manner informed by recent theories of competition at the firm-product level. Consistent with these

[53] We thank Ariel Stern for making this suggestion.

theories, we find pronounced asymmetries. Firms with high levels of research productivity, as evidenced by past product introductions in a particular market, show much less decline in their early-stage drug development activity as generic competition rises. In fact, the strongest firms appear to show little to no response in markets where they have the greatest strength. We might be tempted to conclude that the rise in generic competition may have had a mostly benign impact, with the induced decline in in early-stage development largely taking the form of firms reducing their development activities in domains where they have been marginal players, and concentrating their efforts in the domains where they have the most strength.

However, we also probed the economic incentives created by regulation to shift, within therapeutic markets, from chemical-based to biologic-based products — and these results suggest a more nuanced conclusion. Increases in generic competition in market *j* appear to lead to an increase in the relative amount of biologic-based drug development. As generic competition in market *j* rises, firms are not entirely abandoning market *j*, but rather changing the *nature* of the innovation they pursue. Our results are drawn from a period of industry in which there was no practical way for generics to compete with biologic-based drugs. That has changed, but data exclusivity is still longer for biologic-based products, and the regulatory pathway to market biosimilars is likely to be far more challenging than the pathway for small molecule generic drugs. We conjecture that as chemical-based products are pressured by generics, pharmaceutical firms will continue to shift toward biologic-based drugs.

We have shown that the rise of generic competition is reshaping the locus of drug development activity. Is this a good thing? In this paper, we have refrained from taking a strong stand on the welfare impact of this shift. The data we would need to determine this are not yet available, and, at this point, we can only speculate on the sign of the ultimate welfare impact. On the positive side, one can argue that social welfare is enhanced when pharmaceutical firms are induced to shift development efforts away from markets where a broad range of effective and cheap generic therapies already exist to ones with far fewer treatment options. This can be true even if the probabilities of research success are lower in the domains into which research effort is being pushed, because the social returns to expanding the range of treatment options is relatively high. Even an increasing shift to more expensive biologic-based drugs may be beneficial in the long run if further innovation in chemical-based drugs brings little social value.

However, it is equally plausible to imagine a less positive outcome. Rising generic competition could be weakening incentives for the development of new chemical-based (small-molecule) drugs that have all the benefits of existing therapies without the side effects. Such new drugs would have social value, even in markets with an extensive range of existing therapies. The less explored domains into

which the pharmaceutical industry's small-molecule developments are being pushed may yield little or no success. Such pessimism would be consistent with much of the discussion of the pharmaceutical industry's longstanding productivity crisis. Finally, by tilting the regulatory playing field so heavily against chemical-based drug development and in favor of biologic-based drugs, we may be inducing the global industry to give up on the former domain that has done so much to advance global health through the provision of cheap, relatively simple, effective drugs long before the potential benefits of further research have been exhausted.[54]

While we can only speculate on welfare in this paper, we believe the effort to quantify it is not just worthwhile, but necessary. Whether the effect was intended or not, the rise of generics in the U.S. market is significantly reshaping the pattern of global drug development efforts. We need to know if this is pushing that pattern closer to or further away from the social optimum. As is usually the case in research, much remains to be done.

[54] In fact, many industry insiders believe that there are hundreds of small molecule compounds with as yet undiscovered therapeutic benefits. Because the patents on these compounds expired long ago, there is no mechanism by which a branded pharmaceutical company could appropriate the returns from R&D into these new therapeutic benefits. See Higgins *et al*. (2014) and Roin (2013) for an explication of this idea and potential policy solutions.

References

Acemoglu, D., Linn, J., 2004. "Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry." *The Quarterly Journal of Economics* 119: 1049-1090.

Acemoglu, D., Johnson, S., 2007. "Disease and Development: The Effect of Life Expectancy on Economic Growth." *Journal of Political Economy* 115: 925-985.

Aitken, M., Berndt, E., Cutler, D., 2009. "Prescription Drug Spending Trends in the U.S.: Looking Beyond the Turning Point." *Health Affairs* 28: 151-160.

Aitken, M. Berndt, E., Cutler, D., Kleinrock, M., Maini, L, 2016. "Has the Era of Slow Growth for Prescription Drug Spending Ended?" *Health Affairs* 35(9): 1595-1603

Arcidiacono, P., Ellickson, P., Landry, P., Ridley, D., 2013. "Pharmaceutical Followers." *International Journal of Industrial Organization* 31: 538-553.

Arellano, M., Bond, S., 1991. "Some Tests of Specification for Panel Data: Monte Carlo Evidence and an Application to Employment Equations." *Review of Economic Studies* 58 (2): 277-297.

Berg, M., 2007. "What's the Problem with Generic Anti-Epileptic Drugs?" *Neurology* 68: 1245-46.

Bernard, A., J. Redding, S., Schott, P., 2006. "Multiproduct Firms and Product Switching." NBER Working Paper 12293.

Bernard, A., Redding, S., Schott, P., 2011. "Multiproduct Firms and Trade Liberalization. *The Quarterly Journal of Economics* 126(3): 1271-1318.

Berndt, E., Mortimer, R., Bhattacharjya, A., Parece, A., Tuttle, E., 2007. "Authorized Generic Drugs, Price Competition and Consumers' Welfare." *Health Affairs* 26: 790-799.

Berndt, E., Aitken, M., 2011. "Brand Loyalty, Generic Entry, and Price Competition in Pharmaceuticals in the Quarter Century after the 1984 Hatch-Waxman Legislation." *International Journal of the Economics of Business* 18: 177 – 201.

Berndt, E., Nass, D., Kleinrock, M., Aitken, M., 2015. "Decline in Economic Returns from New Drugs Raises Questions about Sustaining Innovation." *Health Affairs* 34: 1-9.

Bokhari, F., Fournier, G., 2013. "Entry in the ADHD Drugs Market: Welfare Impact of Generics and Me-Too's." *The Journal of Industrial Economics* 61: 339-392.

Blundell, R., Bond, S., 1998. "Initial Conditions and Moment Restrictions in Dynamic Panel Data Models." Journal of Econometrics 87 (1): 115-143.

Branstetter, L., Chatterjee, C., Higgins, M.J., 2014. "Starving (or Fattening) the Golden Goose: Generic Entry and the Incentives for Early-Stage Pharmaceutical Innovation." Unpublished working paper, NBER Working Paper No. 20532. http://www.nber.org/papers/w20532.

Branstetter, L., Chatterjee, C., Higgins, M. 2016. "Regulation and Welfare: Evidence from Paragraph IV Generic Entry in the Pharmaceutical Industry." *RAND Journal of Economics* 47(4): 857-890.

Breusch, T. 1978. "Testing for Autocorrelation in Dynamic Linear Models," Australian Economic Papers. 17: 334-355.

Budish, E., Roin, B., Williams, H., 2015. "Do Fixed Patent Terms Distort Innovation? Evidence from Cancer Clinical Trials." *American Economic Review* 105: 2044-2085.

Buvailo, A., 2011. "Will Biologics Surpass Small Molecules in the Pharma Race?" July 11, 2018 Blog Post on BiopharmaTrend.Com.

Carter, P., Berndt, E., DiMasi, J., Trusheim, M., 2016. "Investigating Investments in Biopharmaceutical R&D." *Nature Reviews: Drug Discovery* 15 (10): 673-674.

Catalini, C. (2017). Microgeography and the direction of inventive activity. *Management Science*. Forthcoming.

Caves, R., Whinston, M., Hurwitz, M., 1991. "Patent Expiration, Entry and Competition in the U.S. Pharmaceutical Industry." *Brookings Papers on Economic Activity: Microeconomics*: 1-48.

Ceccagnoli, M., Graham, S., Higgins, M., Lee, J., 2010. "Productivity and the Role of Complementary Assets in Firms' Demand for Technology Innovations." *Industrial and Corporate Change* 19: 839-869.

Chan, T., Nickerson, A., J, Owan, H., 2007. "Strategic Management of R&D Pipelines with Cospecialized Investments and Technology Markets." *Management Science* 53: 667–682.

Chiou, J., Magazzini, L., Pammoli, F., Riccaboni, M., 2012. "The Value of Failure in Pharmaceutical R&D." Unpublished working paper, IMT Lucca EIC Working Paper Series 01.

Cleanthous, P., 2002. "Patient Welfare Implications of Innovation in the U.S. Antidepressant Market." Unpublished working paper, New York University.

Cockburn, I., 2006. "Is the Pharmaceutical Industry in a Productivity Crisis? In A. Jaffe, J. Lerner, and S. Stern, (eds.), *Innovation Policy and the Economy*, Vol. 7: 1-32, Cambridge: The MIT Press.

Cockburn, I., Henderson, R., 1994. "Racing to Invest? The Dynamics of Competition in Ethical Drug Discovery" *Journal of Economics & Management Strategy* 3(3): 481-519.

Cohen, W., 2010. "Fifty Years of Empirical Studies of Innovative Activity and Performance." In B. Hall and N. Rosenberg, (eds.), *Handbook in Economics of Innovation*, North-Holland.

Cohen, W., Nelson, R., Walsh, J., 2002. "Links and Impacts: The Influence of Public Research on Industrial R&D." *Management Science* 48: 1-23.

Cook, J., Hunter, G., and Vernon, J., 2010. "Generic Utilization Rates, Real Pharmaceutical Prices, and Research and Development Expenditures," NBER Working Paper No. 15723.

DiMasi, J., Grabowski, H., 2012. "R&D Costs and Returns to New Drug Development: A Review of the Evidence." Tufts Center for the Study of Drug Development. March/April CSDD Impact Report. *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*: 21-46, Oxford: Oxford University Press.

DiMasi, J. A., Grabowski, H. G., Hansen, R. W., 2016. Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of Health Economics*, 47, 20-33.

Dunn, A., 2012. "Drug Innovations and Welfare Measures Computed from Market Demand: The Case of Anti-Cholesterol Drugs." *American Economic Journal: Applied Economics* 4: 167-189.

Dubois, P., De Mouzon, O., Scott Morton, F., Seabright, P., 2015. "Market Size and Pharmaceutical Innovation." *RAND Journal of Economics* 46: 844-871.

Eckel, C., Neary, J., 2010. "Multi-product Firms and Flexible Manufacturing in the Global Economy." *The Review of Economic Studies* 77(1): 188-217.

Eckel, C., Iacovone, L., Javorcik, B., Neary, J., 2015. "Multi-product Firms at Home and Away: Cost Versus Quality-Based Competence." *Journal of International Economics* 95(2): 216-232.

Ellickson, P., Stern, S., Trajtenberg, M., 2001. "Patient Welfare and Patient Compliance: An Empirical Framework for Measuring the Benefits from Pharmaceutical Innovation." In D. Cutler and E. Berndt, (eds.), *Medical Care Output and Productivity*, Chicago: University of Chicago Press.

Finkelstein, A., 2004. "Static and Dynamic Effects of Health Policy: Evidence from the Vaccine Industry." *Quarterly Journal of Economics* 119: 527-64.

Fuchs, V., 1982. "*Who Shall Live? Health, Economics, and Social Choice*." New York: Wiley.

Furman, J., Kyle, K., Cockburn, I. Henderson, R., 2005. "Public and Private Spillovers, Location, and the Productivity of Pharmaceutical Research." *Annales d'Economie et de Statistique* 79/80: 167-190.

General Accounting Office, 2012. "Research on Savings from Generic Drug Use." GAO-12-371R,, http://www.gao.gov/assets/590/588064.pdf

Gittelman, M., Kogut, B., 2003. "Does Good Science Lead to Valuable Knowledge? Biotechnology Firms and the Evolutionary Logic of Citation Patterns." *Management Science* 49: 366–382.

Godfrey, L., 1978. "Testing Against General Autoregressive and Moving Average Error Models When the Regressors Include Lagged Dependent Variables." Econometrica 46: 1293-1301.

Goldman, D., Lakdawalla, D., Romley, J., & Philipson, T., 2011. "The Benefits from Giving Makers of Conventional Small Molecule Drugs Longer Exclusivity Over Clinical Trial Data." *Health Affairs* 30(1): 84-90.

Golec, J., Hegde, S., Vernon, M. J., 2010. "Pharmaceutical R&D Spending and Threats of Price Regulation." *Journal of Financial and Quantitative Analysis* 45: 239-264.

Gowrisankaran, G., Rysman, M., 2012. "Dynamics of Consumer Demand for New Durable Goods." *Journal of Political Economy* 120(6), 1173-1219.

Grabowski, H., Kyle, M., 2007. "Generic Competition and Market Exclusivity Periods in Pharmaceuticals." *Managerial and Decision Economics* 28: 491-502.

Grabowski, H., Long, G., Mortimer, R., 2011. "Implementation of the Biosimilar Pathway: Economic and Policy Issues," *Seton Hall Law Review* 41(2):511-557

Griliches, Z., 1984. "*R&D, Patents, and Productivity."* Chicago: University of Chicago Press.

Hausman, J., Hall, B., Griliches, Z., 1984. "Econometric Models for Count Data with an Application to the Patents-R&D Relationship." *Econometrica* 52: 909-938.

Hausman, J., Lo, A., MacKinlay, C., 1992. "An Ordered Probit Analysis of Transaction Stock Prices." *Journal of Financial Economics* 34: 83-104.

Hemphill, S., Sampat, B., 2011. "When Do Generics Challenge Drug Patents." *Journal of Empirical Legal Studies* 8: 619-649.

Hemphill, C., Sampat, B., 2012. "Evergreening, Patent Challenges, and Effective Market Life in Pharmaceuticals." *Journal of Health Economics* 31: 327-341.

Higgins, M.J., Graham, S., 2009. "Balancing Innovation and Access: Patent Challenges Tip the Scales." *Science* 326: 370-372.

Higgins, M.J., Thursby, J., Thursby, M., 2014. "Bench-to-Bench Bottlenecks in Translation." *Science Translational Medicine* 6: 250fs32.

Hughes, J., Moore, M., Snyder, E., 2002. "Napsterizing Pharmaceuticals: Access, Innovation and Consumer Welfare." Unpublished working paper, NBER Working Paper No. 9229. http://www.nber.org/papers/w9229.

Iaria, A., Schwarz, C., Waldinger, F., 2017. "Frontier knowledge and scientific production: Evidence from the collapse of international science." *The Quarterly Journal of Economics*, forthcoming.

Knowles, S., 2010. "Fixing the Legal Framework for Pharmaceutical Research." *Science* 327: 1083-1084.

Lichtenberg, F., 2007. "The Impact of New Drug Launches on U.S. Longevity and Medical Expenditure." *American Economic Review* 97: 438-441.

Mansfield, E., 1995. "Academic Research Underlying Industrial Innovation: Sources, Characteristics and Financing." *Review of Economics and Statistics* 77: 55-65.

Mossinghoff, G., 1999. "Overview of Hatch-Waxman Act and its Impact on the Drug Development Process." *Food and Drug Law Journal* 54: 187-194.

Nocke, V., Yeaple, S., 2014. "Globalization and Multiproduct Firms." *International Economic Review* 55(4): 993-1018.

Nordhaus, W., 1999. "The Health of Nations: The Contribution of Improved Health to Living Standards." Unpublished working paper, NBER Working Paper No. 8818, http://nordhaus.econ.yale.edu/health_nber_w8818.pdf

Olley, G., Pakes, A., 1996. "The Dynamics of Productivity in the Telecommunications Equipment Industry." *Econometrica* 64: 1263-1297.

Palermo, V., Higgins, M., Ceccagnoli, M., 2019. "How Reliable is the Market for Technology?" NBER Working Paper No. 21103. *Review of Economics and Statistics* 101(1): 107-120.

Pammolli, F., Magazzini, L., Riccaboni, M., 2011. "The Productivity Crisis in Pharmaceutical R&D." *Nature Reviews Drug Discovery* 10: 428-438.

Pavcnik, N., 2002. “Trade Liberalization, Exit, and Productivity Improvements: Evidence from Chilean Plants.” *Review of Economic Studies* 69: 245-276.

Peng, B., Tomas, M., 2014. “A Cheat Sheet to Navigate the Complex Maze of Exclusivities in the United States.” *Pharmaceutical Patent Analyst* 3(4): 339-343.

Pisano, G., 2006. “Profiting from Innovation and the Intellectual Property Revolution.” *Research Policy* 35(8): 1122-1130.

Reiffen, D., Ward, M., 2005. “Generic Drug Industry Dynamics.” *Review of Economics and Statistics* 87: 37-49.

Roin, B., 2013. “Solving the Problem of New Uses.” *Michigan State Law Review*, (forthcoming). http://ssrn.com/abstract=2337821.

Roy, A., 2019. “Biologic Medicines: The Biggest Driver of Rising Drug Prices.” *Forbes.com*, March 8, 2019.

Saha, A., Grabowski, H., Birnbaum, H., Greenberg, P., Bizen, O., 2006. “Generic Competition in the US Pharmaceutical Industry.” *International Journal of the Economics of Business* 13: 15-38.

Scherer, M., 2010. “Pharmaceutical Innovation.” In B. Hall and N. Rosenberg (eds.), *Handbook in Economics of Innovation*, North-Holland.

Schiantarelli, F., 1996. "Financial Constraints and Investment: Methodological Issues and International Evidence" *Oxford Review of Economic Policy*, Summer: 70-89.

Tang, J., 2006. “Compeition and Innovation Behaviour.” *Research Policy* 35(1): 68-82.

Utterback, J., Suarez, F., 1993. “Innovation, Competition, and Industry Structure.” *Research Policy* 22(1): 1-21.

Voet, M.A., 2013. *The Generic Challenge: Understanding Patents, FDA and Pharmaceutical Life-Cycle Mananagement*. Brown Walker Press.

Vuong, Quang H. (1989). “Likelihood Ratio Tests for Model Selection and non-nested Hypotheses." *Econometrica* 57 (2): 307–333.

Walsh, V., 1984. “Innvention and Innovation in the Chemical Industry: Demand-pull or Discovery-push?” *Research Policy* 13(4): 211-234.

Wong, G., 2009. “Biotech Scientists Bank on Big Pharma’s Biologics Push.” *Nature Biotechnology*.27: 293-295.

Wooldridge, J., 1999. “Distribution-Free Estimation of Some Nonlinear Panel Data Models.” *Journal of Econometrics* 90: 77-97.

Table 1. Variable definition and descriptive statistics. This table provides definitions, data sources along with descriptive statistics for our variables of interest.

Panel A: Firm - Market - Year (*ijt*)

Variables	Definition	Source	N	Mean	σ	Min	Max
Inn_{ijt}	Early stage innovations: Count of early stage pipeline (pre-clinical + phase 1) at *i, j, t* level.	Pharmaprojects	29,514	0.41	0.52	0	12
$Generic_{ijt-1}$	Generic competition: Ratio of generic sales to sum of focal firm and generic sales at *i, j, t-1* level.	IQVIA MIDAS	29,514	0.54	0.46	0	1
$Tech\ Challenge_{ijt-1}$	Technological challenges: Counts of suspended or discontinued pipeline projects and withdrawn approved products at *i, j, t-1* level.	Pharmaprojects	29,514	0.05	0.26	0	6
$Product_{ijt-1}$	Firm innovative capability I: Moving average of product introductions in *t-1, t-2, t-3* at the *i, j, t-1* level.	Pharmaprojects	29,514	0.24	1.01	0	25.67
$Late\ Pipe_{ijt-1}$	Firm innovative capability II: Count of Phase II and Phase III products at the *i, j, t-1* level.	Pharmaprojects	29,514	0.09	0.35	0	6
$Firm\ Size_{it}$	Firm size: Logarithm of total pharmaceutical sales at the *i, t* level.	IQVIA MIDAS	29,514	12.71	4.44	0	17.23

Panel B: Market - Year (*jt*)

Variables	Definition	Source	N	Mean	σ	Min	Max
Inn_{jt}	Early stage innovations: Count of early stage pipeline (pre-clinical + phase 1) at *j, t* level.	Pharmaprojects	1,500	2.84	6.05	0	66
$Generic_{jt-1}$	Generic competition, baseline measure: Ratio of generic sales to sum of focal firm and generic sales at *j, t-1* level.	IQVIA MIDAS	1,500	0.12	0.21	0	1
$Price_{jt-1}$	Price: Average price of drugs in market *j* in year *t-1*.	IQVIA MIDAS	1,500	11.80	69	0.04	1856.50
$Tech\ Opp_{jt-1}$	Technological opportunity: Logarithm of stock of citation-weighted articles in year *t-1* for j^{th} therapeutic market. Depreciated 15 percent per year.	IQVIA NDTI, IQVIA MIDAS, PubMed & SCOPUS	1,500	8.04	7.30	0	17.74
$Tech\ Challenge_{jt-1}$	Technological challenges: Counts of suspended or discontinued pipeline projects and withdrawn approved products at *j, t-1* level.	Pharmaprojects	1,500	1.04	2.58	0	23
$Product_{jt-1}$	Firm innovative capability I: Moving average of product introductions in *t-1, t-2, t-3* at the *j, t-1* level.	Pharmaprojects	1,500	5.42	11.20	0	51
$Late\ Pipe_{jt-1}$	Firm innovative capability II: Count of Phase II and Phase III products at the *j, t-1* level.	Pharmaprojects	1,500	3.89	4.55	0	43

Table 2. Flow of innovation (Market level). This table presents results from negative binomial and poisson models over our full sample. The unit of observation is at the ATC2 market and year (*t*). Model 5 serves as our base specification as it contains our full array of fixed effects, including an interaction between ATC1 market and time (Year). The dependent variable, $Inn_{jt,}$ is defined as the count early-stage innovations in market *j* at time *t*. Standard errors are clustered at the market level and are in parentheses. *** p<0.01, ** p<0.05, *p<0.10.

	(1) NEGBIN	(2) NEGBIN	(3) NEGBIN	(4) NEGBIN	(5) NEGBIN	(6) POISSON
VARIABLES	Inn_{jt}	Inn_{jt}	Inn_{jt}	Inn_{jt}	Inn_{jt}	Inn_{jt}
$Generic_{jt-1}$	-2.258***	-2.324***	-1.573***	-0.968*	-1.016*	-1.109*
	(0.595)	(0.589)	(0.545)	(0.547)	(0.526)	(0.645)
$Price_{jt-1}$		-0.004	-0.002	-0.002	-0.003*	-0.002
		(0.003)	(0.002)	(0.002)	(0.001)	(0.002)
$Tech\ Opp_{jt-1}$			0.043*	0.051**	0.049**	0.061***
			(0.022)	(0.020)	(0.020)	(0.017)
$Tech\ Challenge_{jt-1}$			0.216***	0.138***	0.147***	0.104***
			(0.027)	(0.025)	(0.030)	(0.018)
$Product_{jt-1}$				-0.021	-0.018	-0.028
				(0.021)	(0.022)	(0.018)
$Late\ Pipe_{jt-1}$				0.036***	0.033***	0.019***
				(0.011)	(0.010)	(0.006)
Constant	Y	Y	Y	Y	Y	Y
Year FE	Y	Y	Y	Y	Y	Y
ATC1 FE	Y	Y	Y	Y	Y	Y
ATC1 x Year FE	N	N	N	N	Y	Y
Log likelihood	-2,753.55	-2,737.57	-2,583.84	-2,466.80	-2,398.11	-2,792.58
Observations	1,500	1,500	1,500	1,500	1,500	1,500

Table 3. Flow of innovation (Firm level). This table presents results from negative binomial and poisson models over our full sample. Model 5 serves as our base specification as it contains our full array of fixed effects, including an interaction between ATC1 market and time (Year). The dependent variable, $Inn_{ijt,}$ is defined as the count of early-stage innovations for firm *i*, in market *j* at time *t*. Standard errors are clustered at the firm level and are in parentheses. *** p<0.01, ** p<0.05, *p<0.10.

	(1) NEGBIN	(2) NEGBIN	(3) NEGBIN	(4) NEGBIN	(5) NEGBIN	(6) OLS	(7) POISSON
VARIABLES	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{jt}
$Generic_{ijt-1}$	-1.194***	-1.229***	-1.429***	-1.254***	-1.241***	-0.090***	-1.189***
	(0.181)	(0.183)	(0.186)	(0.181)	(0.181)	(0.019)	(0.196)
$Price_{jt-1}$		-0.006	-0.005	-0.005	-0.006	-0.000***	-0.009
		(0.005)	(0.004)	(0.006)	(0.006)	(0.000)	(0.012)
$Tech\ Opp_{jt-1}$			0.035***	0.034***	0.033***	0.003*	0.033***
			(0.013)	(0.012)	(0.012)	(0.002)	(0.013)
$Tech\ Challenge_{ijt-1}$					0.520***	0.359***	0.379***
					(0.090)	(0.037)	(0.094)
$Product_{ijt-1}$				0.174***	0.174***	0.086***	0.138***
				(0.037)	(0.035)	(0.013)	(0.021)
$Late\ Pipe_{ijt-1}$				0.096	0.104*	0.104	0.085
				(0.065)	(0.062)	(0.064)	(0.055)
$Firm\ Size_{it}$			0.005	0.013*	0.013*	0.002	0.018**
			(0.007)	(0.008)	(0.008)	(0.001)	(0.007)
Constant	Y	Y	Y	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y	Y	Y	Y
Year FE	Y	Y	Y	Y	Y	Y	Y
ATC1 FE	Y	Y	Y	Y	Y	Y	Y
ATC1 x Year FE	N	N	N	N	Y	Y	Y
Log likelihood/R^2	-10,042.36	-9,993.81	-9,944.25	-9,703.03	-9,602.54	0.19	-9,895.47
Observations	29,514	29,514	29,514	29,514	29,514	29,514	29,514

Table 4. Flow of innovation (Firm level, alternative specifications). Model 1 presents our base specification with our full array of fixed effects, including an interaction between market and time. The market fixed effects are at the ATC2 level as is the interaction between ATC2 and time (Year). As such, $Tech\ Opp_{jt-1}$ and $Price_{jt-1}$ are omitted because they are constructed at the ATC 2-digit market level. Models 2 and 3 present results from two-stage least square regressions where we instrument for $Generic_{ijt-1}$. Both models include our full array of fixed effects, including the interaction between market and time. Model 2 uses the ATC1 market level while Model 3 uses the ATC2 market level. Models 4 and 5 implement an Arellano and Bond system GMM where we also instrument for G_{ijt-1} and incorporate a lagged dependent variable. In all specifications, the dependent variable is defined as a count of early-stage innovation, Inn_{ijt}. Standard errors are clustered at the firm level in Models 1 to 3 and are in parentheses. Robust standard errors in parentheses in Model 4 and 5. *** p<0.01, ** p<0.05, * p<0.10.

	(1) OLS	(2) IV	(3) IV	(4) GMM	(5) GMM
VARIABLES	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}
$Generic_{ijt-1}$	-0.097***	-0.333**	-0.370*	-0.364***	-0.449***
	(0.018)	(0.170)	(0.196)	(0.136)	(0.134)
Inn_{ijt-1}				0.552***	0.655***
				(0.100)	(0.0922)
$Price_{jt-1}$		-0.000***		0.000	0.000715
		(0.000)		(0.001)	(0.00135)
$Tech\ Opp_{jt-1}$		0.007**		0.001	0.000413
		(0.003)		(0.002)	(0.00228)
$Tech\ Challenge_{ijt-1}$	0.317***	0.350***	0.333***	0.613	0.593
	(0.037)	(0.079)	(0.068)	(0.528)	(0.539)
$Product_{ijt-1}$	0.085***	0.081***	0.092***	0.307**	
	(0.015)	(0.015)	(0.015)	(0.138)	
$Late\ Pipe_{ijt-1}$	0.073	0.100***	0.102***	0.450	
	(0.060)	(0.026)	(0.023)	(0.370)	
$Firm\ Size_{it}$	0.002	0.008***	0.010***	0.000*	0.000**
	(0.001)	(0.002)	(0.002)	(0.000)	(0.000)
Constant	Y	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y	Y
Year FE	Y	Y	Y	Y	Y
ATC1 FE	N	Y	Y	N	N
ATC1 x Year FE	N	Y	N	N	N
ATC2 FE	Y	N	Y	Y	Y
ATC2 x Year	Y	N	Y	N	N
First-stage F		125.88	43.12		
R^2/Wald X^2	0.263	0.155	0.207	1,817.72	1,745.58
Observations	29,514	29,514	29,514	21,089	21,089

Table 5. Flow of innovation (Robustness checks). This table presents three placebo tests based on a negative binomial specification. Model 1 redefines the dependent variable as novel early-stage innovation, *Novel Inn*$_{ijt}$ while Model 2 redefines the dependent variable as late-stage innovation, *Late-stage Inn*$_{ijt}$. The sample is restricted in Model 3 to markets where we anticipate low cross-molecular substitution, *Low CMS Inn*$_{ijt}$. These include: anti-epileptics, anti-depressants, and anti-psychotics. Standard errors are clustered at the firm level in parentheses. *** p<0.01, ** p<0.05, * p<0.10.

	(1)	(2)	(3)
	NEGBIN	NEGBIN	NEGBIN
VARIABLES	*Novel Inn*$_{ijt}$	*Late-stage Inn*$_{ijt}$	*Low CMS Inn*$_{ijt}$
Generic$_{ijt-1}$	-1.103***	0.033	-0.234
	(0.221)	(0.068)	(0.307)
Price$_{jt-1}$	-0.002	-0.003	-0.098
	(0.002)	(0.002)	(0.090)
Tech Opp$_{jt-1}$	0.024**	0.032***	0.389***
	(0.012)	(0.009)	(0.123)
Tech Challenge$_{ijt-1}$	0.381***	0.562***	0.167
	(0.076)	(0.048)	(0.120)
Product$_{ijt-1}$	0.081**	0.177***	0.221***
	(0.036)	(0.035)	(0.061)
Late Pipe$_{ijt-1}$	0.063		0.041
	(0.079)		(0.209)
Firm Size$_{it}$	0.008	0.010*	0.001
	(0.011)	(0.005)	(0.048)
Constant	Y	Y	Y
Firm FE	Y	Y	Y
Year FE	Y	Y	Y
ATC1 FE	Y	Y	Y
ATC1 x Year FE	Y	Y	N
Log likelihood	-5,637.78	-23,913.59	-542.40
Observations	29,514	29,514	1,577

Table 6. Flow of innovation (Firm heterogeneity). Three sets of specifications are presented based on our base specification with the inclusion of an interaction between $Generic_{ijt-1}$ and $Product_{ijt-1}$. Each set includes both negative binomial and two-stage least square regressions. In Models 1 and 2, $Product_{ijt-1}$ is defined as a three-year moving average of product introductions. In Models 3 and 4, $Product2_{ijt-1}$ is defined as a dummy variable equal to one if the three-year moving average of product introductions is above the median, zero otherwise. Finally, in Models 5 and 6, $Product3_{ijt-1}$ is defined as a dummy variable equal to one if the three-year moving average of product introductions is in the top quartile, zero otherwise. Standard errors are clustered at the firm level in parentheses. *** p<0.01, ** p<0.05, * p<0.10.

	(1)	(2)	(3)	(4)	(5)	(6)
	NEGBIN	IV	NEGBIN	IV	NEGBIN	IV
VARIABLES	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}
$Generic_{ijt-1}$	-1.463***	-0.293*	-1.667***	-0.272*	-1.710***	-0.272*
	(0.139)	(0.164)	(0.148)	(0.156)	(0.153)	(0.157)
$(Generic*Product)_{ijt-1}$	0.473***	0.102**				
	(0.0918)	(0.047)				
$(Generic*Product2)_{ijt-1}$			1.809***	0.265***		
			(0.204)	(0.085)		
$(Generic*Product3)_{ijt-1}$					1.874***	0.267***
					(0.199)	(0.079)
$Price_{jt-1}$	-0.005**	-0.000***	-0.005**	-0.000***	-0.006**	-0.000***
	(0.002)	(0.000)	(0.002)	(0.000)	(0.003)	(0.000)
$Tech\ Opp_{jt-1}$	0.029***	0.005*	0.026***	0.005*	0.026***	0.005
	(0.004)	(0.003)	(0.004)	(0.003)	(0.004)	(0.003)
$Tech\ Challenge_{ijt-1}$	0.492***	0.349***	0.479***	0.350***	0.475***	0.349***
	(0.040)	(0.078)	(0.037)	(0.077)	(0.037)	(0.077)
$Product_{ijt-1}$	0.124***	0.069***	0.129***	0.073***	0.129***	0.073***
	(0.015)	(0.017)	(0.015)	(0.016)	(0.015)	(0.016)
$Late\ Pipe_{ijt-1}$	0.118***	0.104***	0.123***	0.104***	0.121***	0.103***
	(0.046)	(0.025)	(0.045)	(0.025)	(0.045)	(0.025)
$Firm\ Size_{it}$	0.007	0.008***	0.007	0.008***	0.006	0.008***
	(0.011)	(0.002)	(0.011)	(0.002)	(0.011)	(0.002)
Constant	Y	Y	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y	Y	Y
Year FE	Y	Y	Y	Y	Y	Y
ATC1 FE	Y	Y	Y	Y	Y	Y
ATC1 x Year FE	Y	Y	Y	Y	Y	Y
First-stage F		52.31		60.88		62.01
Log likelihood/R^2	-9,529.36	0.165	-9,457.17	0.169	-9,440.62	0.169
Observations	29,514	29,514	29,514	29,514	29,514	29,514

Table 7. Change in innovation. Across all six specifications the dependent variable *cat(CI_{ijt}-BI_{ijt})*, equals 1, 2 and 3 if the difference ($CI_{ijt} - BI_{ijt}$) is negative, zero, or positive, respectively. CI_{ijt} is defined as chemical-based early-stage innovation while BI_{ijt} is defined as biologic-based early-stage innovation. Models 1 and 2 present results from two-stage least square regressions with a full array of fixed effects. Model 1 includes market fixed effects at the ATC1 market level while Model 2 includes market fixed effects at the ATC2 market level along with an interaction with time (Year). Model 3 presents results from OLS with market fixed effects at the ATC2 level along with an interaction with time. Models 4 and 5 ordered logit models, with Model 5 including a full set of fixed effects, including the interaction between market and time, at the ATC1 level. As a robustness check, Model 6 replicates Model 5 using an ordered probit model. In Models 2 and 3, *Tech Opp*$_{jt-1}$ and *Price*$_{jt-1}$ are omitted because they are constructed at the ATC 2-digit level. Standard errors are clustered at the firm level in parentheses. *** p<0.01, ** p<0.05, * p<0.10.

	(1) IV	(2) IV	(3) OLS	(4) OLOGIT	(5) OLOGIT	(6) OPROBIT
VARIABLES	*cat(CI_{ijt}-BI_{ijt})*	*cat(CI_{ijt}-BI_{ijt})*	*cat(CI_{ijt}-BI_{ijt})*	*cat(CI_{ijt}-BI_{ijt})*	*cat(CI_{ijt}-BI_{ijt})*	*cat(CI_{ijt}-BI_{ijt})*
Generic$_{ijt-1}$	-0.445**	-0.478**	-0.328***	-2.084***	-2.098***	-1.038***
	(0.217)	(0.192)	(0.025)	(0.117)	(0.119)	(0.062)
Price$_{jt-1}$	-0.000***			-0.002***	-0.002***	-0.001***
	(0.000)			(0.000)	(0.000)	(0.000)
Tech Opp$_{jt-1}$	0.006			0.025***	0.025***	0.014***
	(0.004)			(0.006)	(0.006)	(0.003)
diff(Tech Challenge$_{ijt-1}$*)*	0.164***	0.134***	0.138***	2.988***	3.014***	1.533***
	(0.026)	(0.022)	(0.024)	(0.277)	(0.275)	(0.135)
diff(Product$_{ijt-1}$*)*	0.056***	0.031***	0.032***	1.160***	1.159***	0.511***
	(0.009)	(0.007)	(0.008)	(0.111)	(0.110)	(0.048)
diff(Late Pipe$_{ijt-1}$*)*	0.226***	0.177***	0.183***	-1.004***	-0.996***	-0.430***
	(0.021)	(0.019)	(0.018)	(0.155)	(0.155)	(0.070)
Firm Size$_{it}$	0.002	0.003	0.003	0.015	0.018	0.007
	(0.002)	(0.002)	(0.002)	(0.013)	(0.013)	(0.007)
Constant	Y	Y	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y	Y	Y
Year FE	Y	Y	Y	Y	Y	Y
ATC1 FE	Y	N	N	Y	Y	Y
ATC1 x Year FE	Y	N	N	N	Y	Y
ATC2 FE	N	Y	Y	N	N	N
ATC2 x Year FE	N	Y	Y	N	N	N
First-stage F	29.65	29.47				
R^2/Pseudo R^2	0.443	0.542	0.546	0.366	0.369	0.332
Observations	29,514	29,514	29,514	29,514	29,514	29,514

Table 8. Robustness: Change in innovation (SUR). This table presents results from three SUR specifications. CI_{ijt} is defined as chemical-based early-stage innovation while BI_{ijt} is defined as biologic-based early-stage innovation. The specifications differ in the mix of fixed effects included. Model 1 includes firm, year and ATC1 market level fixed effects. Model 2 includes firm, year, ATC1 fixed effects along with the interaction between year and ATC1. Model 3 includes firm, year and ATC2 market level fixed effects. Standard errors are clustered at the firm level in parentheses. *** p<0.01, ** p<0.05, * p<0.10.

	(1) SUR		(2) SUR		(3) SUR	
VARIABLES	CI_{ijt}	BI_{ijt}	CI_{ijt}	BI_{ijt}	CI_{ijt}	BI_{ijt}
$Generic_{ijt-1}$	-0.519***	0.037**	-0.518***	0.039**	-0.533***	0.049**
	(0.018)	(0.017)	(0.017)	(0.017)	(0.021)	(0.021)
$Price_{jt-1}$	-0.000***	-0.000	-0.001***	-0.000	0.194	-0.136
	(0.000)	(0.000)	(0.000)	(0.000)	(2.164)	(2.110)
$Tech\ Opp_{jt-1}$	0.012***	-0.004***	0.012***	-0.004***	-0.248***	0.2944
	(0.001)	(0.001)	(0.001)	(0.001)	(0.087)	(0.846)
$Tech\ Challenge_{ijt-1}$	1.062***	0.373***	1.065***	0.375***	0.907***	0.360***
	(0.024)	(0.022)	(0.024)	(0.023)	(0.022)	(0.022)
$Product_{ijt-1}$	0.160***	0.162***	0.161***	0.162***	0.171***	0.145***
	(0.006)	(0.006)	(0.006)	(0.006)	(0.006)	(0.006)
$Late\ Pipe_{ijt-1}$	0.103***	0.483***	0.102***	0.485***	0.054***	0.409***
	(0.019)	(0.018)	(0.019)	(0.018)	(0.017)	(0.017)
$Firm\ Size_{it}$	0.008**	-0.000	0.008**	-0.000	0.001***	-0.002
	(0.004)	(0.003)	(0.004)	(0.003)	(0.003)	(0.003)
Constant	Y	Y	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y	Y	Y
Year FE	Y	Y	Y	Y	Y	Y
ATC1 FE	Y	Y	Y	Y	N	N
ATC1 x Year FE	N	N	Y	Y	N	N
ATC2 FE	N	N	N	N	Y	Y
R^2	0.310	0.367	0.314	0.370	0.447	0.472
Observations	29,514	29,514	29,514	29,514	29,514	29,514

Table 9. Robustness: Change in innovation (SUR). In these two SUR specifications we limit the sample to those markets where biologic-based innovation is most active. Based on data from Pharmaprojects, these include ATC1 markets: F, J and T. The intuition behind this approach is simple, if a rotation is taking place from chemical-based to biologic-based innovation, the effects should be amplified in markets where the rotation is easier for firms to undertake. Results are consistent with this intuition. CI_{ijt} is defined as chemical-based early-stage innovation while BI_{ijt} is defined as biologic-based early-stage innovation. Standard errors are clustered at the firm level in parentheses. *** p<0.01, ** p<0.05, * p<0.10.

	(1) SUR		(2) SUR	
VARIABLES	CI_{ijt}	BI_{ijt}	CI_{ijt}	BI_{ijt}
$Generic_{ijt-1}$	-0.988***	0.190	-0.892***	0.337**
	(0.065)	(0.140)	(0.069)	(0.145)
$Price_{jt-1}$	-0.001***	-0.001*	0.000	-0.000
	(0.000)	(0.000)	(0.000)	(0.001)
$Tech\ Opp_{jt-1}$	0.072***	-0.051***	0.240	-0.069
	(0.004)	(0.009)	(0.179)	(0.376)
$Tech\ Challenge_{ijt-1}$	0.456***	1.153***	0.432***	1.013***
	(0.041)	(0.087)	(0.039)	(0.081)
$Product_{ijt-1}$	0.041***	0.191***	0.066***	0.174***
	(0.008)	(0.018)	(0.008)	(0.017)
$Late\ Pipe_{ijt-1}$	-0.139***	0.732***	-0.111***	0.588***
	(0.026)	(0.055)	(0.025)	(0.052)
$Firm\ Size_{it}$	0.005	-0.003	0.009	-0.008
	(0.007)	(0.016)	(0.007)	(0.015)
Constant	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y
Year FE	Y	Y	Y	Y
ATC1 FE	Y	Y	N	N
ATC1 x Year FE	Y	Y	N	N
ATC2 FE	N	N	Y	Y
R^2	0.276	0.428	0.344	0.508
Observations	4,958	4,958	4,958	4,958

ONLINE APPENDIX

Appendix A1. Sketch derivation of firm-product models and discussion of the connection between this theory and our empirical results.

As noted in the text of the paper, our empirical approach examines the impact of rising generic competition on innovation at the firm-market-year level rather than the market-year level. Our choice is partly data-driven – we are only able to track new drugs in the relatively early stages of development consistently at the ATC2 market level, which provides us with only 126 cross-sectional units. By contrast, there are 178 firms with sufficient data to be incorporated in our data set over our sample period; the presence of larger firms in many product markets substantially expands the cross-sectional dimension of our data set. Adoption of a firm-market-year approach quickly demonstrates that our firms are quite heterogeneous in terms of their overall scope and in terms of their research capabilities within particular pharmaceutical markets. No firm is capable of investing in all 126 ATC2 markets; conversely, some relatively small firms are able to consistently generate new drug candidates in their domains of strength at rates that exceeds that of larger competitors. These dimensions of heterogeneity are certainly not unique to the pharmaceutical industry.

Over the past decade, other economists have used datasets with firm-market-year dimensions to develop and test formal theories of multiproduct firm behavior (Bernard, Redding, and Schott, 2006a, 2006b, 2011; Feenstra and Ma, 2009; Dhingra, 2013; Mayer, Melitz, and Ottaviano, 2014; Arkokakis and Muendler, 2010; Eckel and Neary, 2010; Nocke and Yeaple, 2014; Eckel *et al*., 2015; Manova and Yu, 2017). This stream of literature is motivated, in part, by empirical research documenting statistical regularities that appear to exist across industries, firms, and time periods. This empirical research finds that firms vary enormously in scope (the number of products they produce), they vary in terms of their relative productivity within specific product categories, and these productivity differentials tend to persist over long periods of time (Bernard, Redding, and Schott, 2006a). These patterns are rationalized by a family of models which assume a "management quality" parameter that varies across firms but can apply to all products in a given firm's portfolio, and a separate set of "product productivity" parameters that are unique to every firm-product pair. The paragraphs below provide a brief "sketch derivation" which summarizes the essential mathematical insights presented in Bernard,

Redding, and Schott (2011) and borrows the notation in that highly influential paper. For a full derivation, the reader is directed to the original paper and to the comprehensive NBER working paper (Bernard, Redding, and Schott, 2006b) from which it evolved. Following our sketch derivation, we relate the central concepts in this emerging literature to our main empirical specification.

While Bernard, Redding, and Schott (2011) is focused on multiproduct firms in a global economy, with firms selling in multiple national markets, for expositional simplicity, we focus here solely on sales in a single market, as in Section 3 of their 2006 NBER working paper, hereafter referred to as "B-R-S". Demand structure is standard and a representative consumer derives utility from consumption of a continuum of products normalized to the interval [0,1]. There is a constant elasticity of substitution across product markets, and within each product market, there is a (higher) constant elasticity of substitution across varieties. The structure of demand assumed by B-R-S creates what amounts to a downward-sloping demand curve – firms can only increase sales of an existing variety by cutting its price (and therefore marginal revenue). The assumption of a downward-sloping demand curve is analytically useful, but the assumed demand structure clearly does not conform well to the empirical realities of the pharmaceutical industry, where all products are ***not*** equally good substitutes for one another. In the pharmaceutical context, we have branded drugs that are differentiated from one another to varying degrees, along both vertical and horizontal dimensions, competing (at least in the small molecule side of the product market) with much less expensive generic drugs that are, by assumption, perfect substitutes for at least one of the branded products. That being said, this theoretical literature considers shocks to the competitive equilibrium (like trade liberalization) that significantly raise the competitive intensity faced by some firms; this is analogous, in some ways, to the rising generic penetration that, we have already noted, characterizes the U.S. market for pharmaceuticals over our sample period.

The technology of production follows Melitz (2003), but introduces some new elements to allow for multiproduct firms. There is a competitive fringe of potential firms who are *ex ante* identical prior to entry; in order to enter, firms must incur a sunk cost. Upon payment of this cost, firms draw two productivity parameters –a "managerial ability" parameter $\varphi \in (0, \infty)$ that is common to all products produced by the firm and what B-R-S call an "expertise" parameter $\lambda_i \epsilon (0, \infty)$, drawn from a separate distribution, that is unique to each firm-product pair. B-R-S

make assumptions regarding the distributions of "ability" and "expertise" that ensure that no one firm makes all products and all active firms make some. When a firm pays its sunk cost and realizes its productivity draws, then the realizations of these productivity draws essentially determine whether the firm remains in business, how many products it produces, and which products those are. By assumption, each firm must pay a fixed cost to set up a "headquarters" and a separate fixed cost to commence production of a variety. In the context of our paper, these product-specific fixed costs can be naturally interpreted as R&D costs.

B-R-S assume that any firm active in a product market manufactures one of a continuum of varieties, and so is unable to influence the price index for the product or induce a competitive pricing response from other firms – thus, the equilibrium price of a product variety is a constant mark-up over marginal cost:

$$p_i(\varphi, \lambda_i) = \frac{1}{\rho} \frac{w}{\varphi \lambda_i}$$

Where the wage is chosen as the numeraire, so w=1. Equilibrium revenue and profits from a firm variety thus become:

$$r_i(\varphi, \lambda_i) = R_i(\rho P_i \varphi \lambda_i)^{\sigma-1}, \qquad \pi_i(\varphi, \lambda_i) = \frac{r_i(\varphi,\lambda_i)}{\sigma} - f_p$$

where R denotes aggregate expenditure on product *i*. From this equation, the ratio of revenues of two varieties of the same product depends solely on their relative productivities:

$$r_i(\varphi'', \lambda_i'') = \left(\frac{\varphi''}{\varphi'}\right)^{\sigma-1} \left(\frac{\lambda''}{\lambda'}\right)^{\sigma-1} r_i(\varphi', \lambda_i')$$

A firm with a particular ability draw φ and expertise draw λ_i decides whether or not to produce a product based on a comparison of revenue and fixed production costs for the product. For each firm with ability φ, there is a zero-profit cutoff for product expertise $\lambda^*{}_i(\varphi)$ such that the firm will enter the product market if it draws a value of λ_i equal to or greater than this cutoff value. Expressed mathematically, this zero-profit condition is:

$$r_i(\varphi, \lambda_i^*(\varphi)) = \sigma f_p$$

There will be a related zero-profit cutoff for firm ability, φ^*, that defines the minimum level of ability required to set up a headquarters; the zero-profit cutoff of expertise for a firm with this level of ability is:

$$r_i(\varphi^*, \lambda_i^*(\varphi^*)) = \sigma f_p$$

This implies that only firms with ability equal to or greater than φ^* will enter the market. Combining these equations, B-R-S obtain:

$$\lambda_i{}^*(\varphi) = \left(\frac{\varphi^*}{\varphi}\right)\lambda_i{}^*(\varphi^*)$$

This expression highlights the interaction between firm ability and product expertise, even though both are drawn from separate and independent distributions. A higher ability raises the zero-profit cutoff for expertise, because higher ability raises productivity in each product, ensuring that sufficient revenue is generated to cover fixed costs at a lower level of expertise. In contrast, an increase in the zero-profit cutoff for ability raises a firm's zero-profit cutoff for expertise, because it raises the average productivity of a rival firm's products, intensifies product competition, and increases the value of expertise at which sufficient revenue is generated to cover fixed costs.

While B-R-S assume that draws of product expertise are strictly independent across products and firms, Eckel *et al* (2016) presume that firms possess a "core competence," and that draws of expertise fall as one moves away from that core competence in the product space. Inspection of our raw data on pharmaceutical sales suggest a distribution of outcomes closer to the "core competence" idea, although larger firms appear to have more than one such domain. For analytical convenience, essentially all the theoretical models in this literature assume that firm ability and product expertise are one-time draws that do not vary over time within a product or firm. In the real world, there is every reason to believe that firm ability and product expertise evolve over time.

So long as firms face a downward sloping demand curve for each product (which, as noted above, is true by assumption in B-R-S), this limits expansion along the intensive margin for each product. This creates an incentive to expand along the extensive margin, into new categories of products in which the firm may have lower productivity. The firm must derive sufficient revenue from each product to cover the costs of development and production, and that constrains a firm's incentives to expand along the extensive margin. The interaction of the overall management quality and product-specific productivity parameters ensure substantial heterogeneity across firms in terms of overall scope and the distribution of firm "core competencies" within the product space, replicating important features of real world micro-data.

These models predict (and empirical work finds) striking heterogeneity in firm-level responses to market-level demand shocks, such as those arising from trade liberalization: in response to a more competitive environment, firms tend to cut back on or eliminate product categories in which they are relatively weak, but expand production in the domains where they are relatively strong. The logic behind this shift is clear given the equations reproduced above. In a more competitive environment, fewer firms will meet their zero-profit conditions for particular products, and so, marginal products "drop out." As this happens, the product space becomes less crowded with competing varieties. That allows for an expansion of sales of existing varieties. This implies that different firms will respond differently to market-level shocks, depending on their specific capabilities in those markets – a reality that will be completely missed if one adopts a market-year level approach. Empirical work in this stream also finds that adjustment *within* firms (*i.e.*, increasing production in some markets and exiting others) can account for very large fractions of industry-level shifts in output, productivity, and exports.

Inspired by these recent theoretical developments and by the features of our data set that accord so strongly with it, we adopt an empirical model specified at the firm-market-year level. We are interested in how *firms* are responding to generic competition, and firms differ significantly from one another in terms of their research capabilities and marketing investments in different therapeutic categories. A firm with strong research capabilities in and heavy financial reliance on a particular drug market may respond to generic competition in that market in a very different way than firms with limited research capacity in that domain and limited economic commitments to it. We want to be able to control for these differences, so we choose to utilize all the dimensions of our data – firm, market, and year. Whereas the existing literature treats a firm's productivity in a particular market as time-invariant, our specification will allow this productivity measure to vary over time, and that flexibility informs the empirical strategy described in the paper to contend with some obvious concerns of econometric identification. If we reference our main empirical specification:

$$Inn_{ijt} = \alpha_i + \alpha_j + \alpha_t + \beta_1 Generic_{ijt-1} + \beta_2 TechOpp_{jt-1} + \beta_3 Tech\ Challenge_{ijt-1} + \beta_4 Products_{ijt-1} + \beta_5 Late\ Pipe_{ijt-1} + \beta_6 Down\ Asset_{ijt} + \beta_7 Firm\ Size_{it} + \varepsilon_{ijt} \quad (1)$$

We can relate several of the variables contained therein to the ideas in the emerging firm-market literature. As noted in our text, it is likely that firm-market "expertise" varies across

firms, markets, and time, in ways that are evidenced by late-stage drug development activity (*LatePipe*), successful product launches in the recent past (*Products*), and perhaps, expenditure on marketing recently released (or about-to-be-released) drugs (*DownAsset*). Inclusion of these variables helps control for firm-market expertise, especially if the realizations of this variable are highly correlated within markets, as is presumed by the classes of models featuring "core competence." A firm-level ability measure is likely to be correlated with overall firm size (conditioning on the firm's presence in particular product markets), so inclusion of the variable *FirmSize* helps control for this productivity realization. Theory would suggest that firm's with a high degree of product market expertise would be less likely to reduce their presence in the market through the abandonment of new product introductions – additional regressions run in the main body of our text show that the negative impact of generic competition on new product introductions is significantly attenuated in product markets where the firm in question has a high revealed level of expertise. On the other hand, the impact is especially strong in domains where the firm is relatively weak.

Appendix References

Arkolakis, C., Muendler, M., 2010. "The Extensive Margin of Exporting Goods: A Firm-Level Analysis." *NBER Working Paper, 16641*. http://www.nber.org/papers/w16641

Bernard, A., Redding, S., Schott, P., 2006a. "Trade Costs, Firms and Productivity." *Journal of Monetary Economics* 53: 917-937.

Bernard, A., Redding, S., Schott, P., 2006b. "Survival of the Best Fit: Exposure to Low-Wage Countries and the (Uneven) Growth of US Manufacturing Plants." *Journal of international Economics* 68(1): 219-237.

Bernard, A., Redding, S., Schott, P., 2011. "Multiproduct Firms and Trade Liberalization." *The Quarterly Journal of Economics* 126(3): 1271-1318.

Dhingra, S., 2013. "Trading Away Wide Brands for Cheap Brands." *The American Economic Review* 103(6): 2554-2584.

Eckel, C., Neary, J., 2010. "Multi-product Firms and Flexible Manufacturing in the Global Economy." *The Review of Economic Studies* 77(1): 188-217.

Eckel, C., Iacovone, L., Javorcik, B., Neary, J., 2015. "Multi-product Firms at Home and Away: Cost Versus Quality-Based Competence." *Journal of International Economics* 95(2): 216-232.

Feenstra, R., Ma, H., 2009. "Optimal Choice of Product Scope for Multiproduct Firms" In (eds) Elhanan Helpman, Dalia Marin and Thierry Verdier, *The Organization of Firms in a Global Economy*. Harvard University Press.

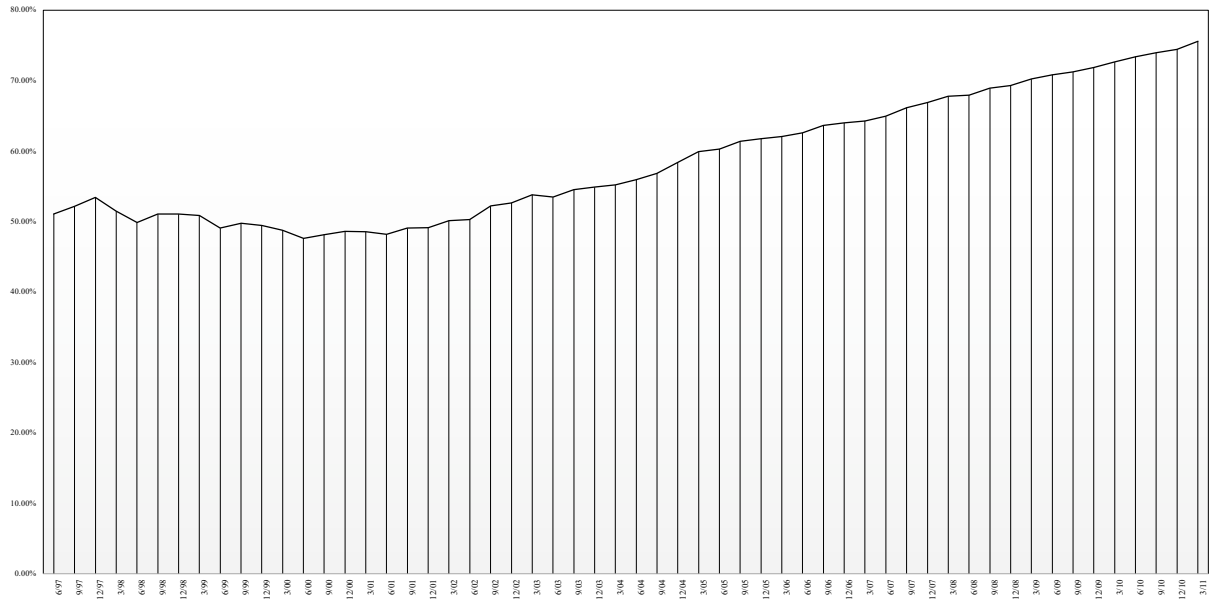
Manova, K., Yu, Z., 2017. "Multi-product firms and product quality." *Journal of International Economics* 109, 116-137.

Mayer, T., Melitz, M., Ottaviano, G, 2014. "Market Size. Competition and the Product Mix of Exporters" *The American Economic Review* 104(2): 495-536.

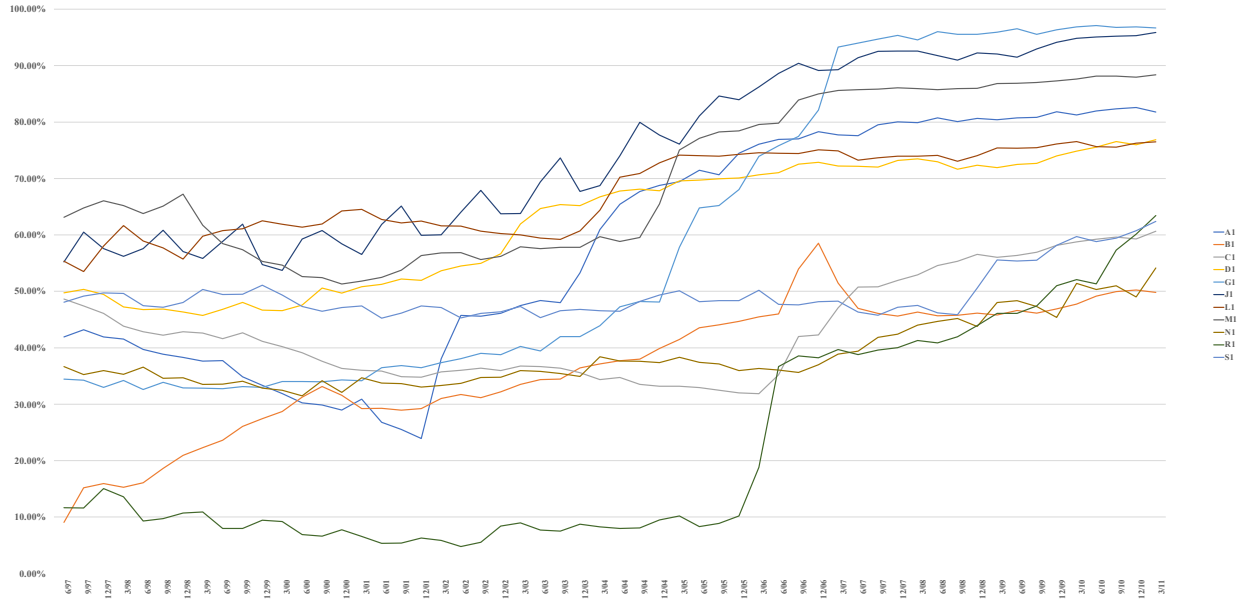
Melitz, M. J., 2003. "The Impact of Trade on Intra-industry Reallocations and Aggregate Industry Productivity." *Econometrica* 71(6): 1695-1725.

Nocke, V., Yeaple, S., 2014. "Globalization and Multiproduct Firms." *International Economic Review* 55(4): 993-1018.

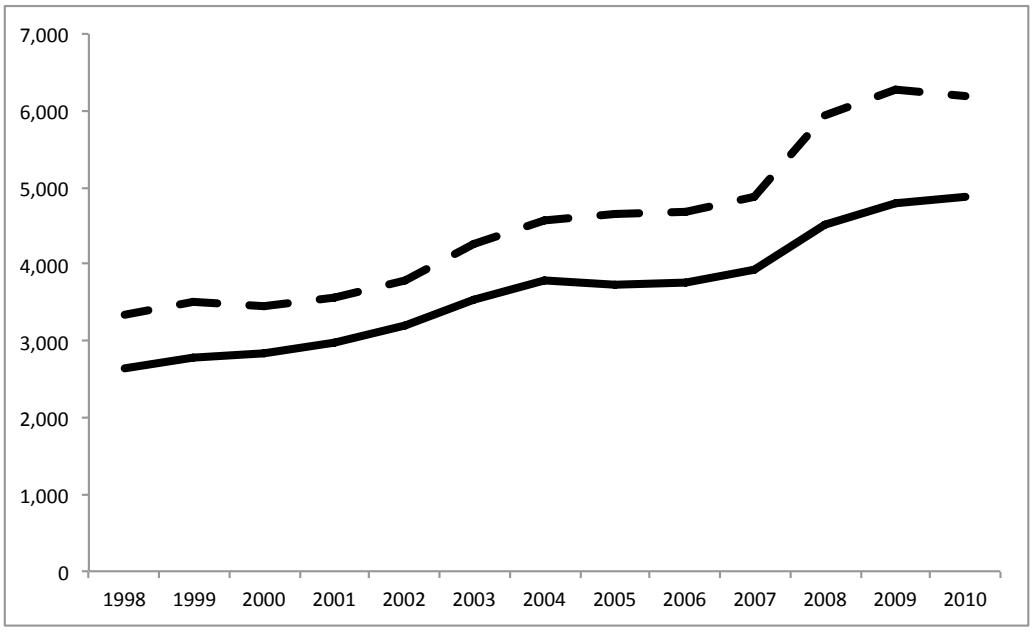
Appendix Figure A1. Percent of generic sales, 1997 to 2011. This figure tracks the growth of generic sales in the U.S., on a quarterly basis, from Q2:1997 to Q1:2011 utilizing proprietary data from IQVIA MIDAS. Sales are measured in standard units (SU) that equate capsules, tablets and liquids. Slightly over 50% of all drugs sold (on a quantity basis) in Q2:1997 were generics, growing to almost 75% of all drugs sold by Q1:2011.



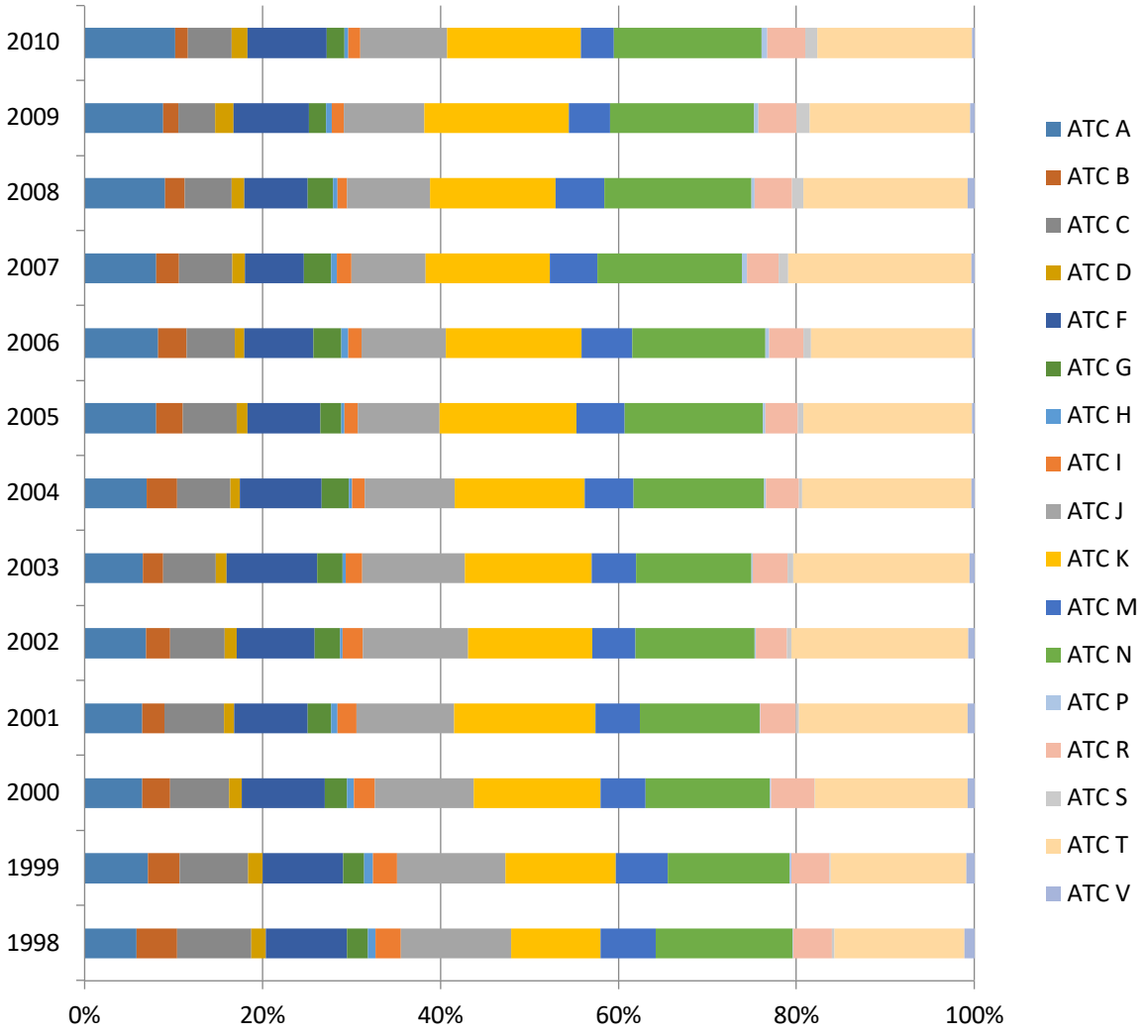
Appendix Figure A2. Percent of generic sales, 1997 to 2011. This figure tracks the growth of generic sales in the U.S., on a quarterly basis, from Q2:1997 to Q1:2011 utilizing proprietary data from IQVIA MIDAS for eleven different ATC 2-digit categories. The figure demonstrates the heterogeneity in generic penetration across therapeutic categories. The eleven categories are: (1) A1 Stomatological preparations; (2) B1 Antithrombotic agents; (3) C1 Cardiac therapy; (4) D1 Antifungals (dermatological); (5) G1 Gynecological anti-infectives and antiseptics; (6) J1 Antibacterials for systemic use; (7) L1 Antineoplastic agents; (8) M1 Anti-inflammatory and antirheumatic products; (9) N1 Anesthetics; (10) R1 Nasal preparations; and (11) S1 Ophthalmologicals. Sales are measured in standard units (SU) that equate capsules, tablets and liquids.



Appendix Figure A3. Early-stage innovations, 1998-2010. This figure tracks the aggregate flow of early-stage pharmaceutical innovations, defined as the annual count of compounds at the preclinical stage or in Phase 1 clinical trials. We provide annual aggregate counts for our sample firms (solid line) and for the entire population (dotted line) of compounds contained in the Pharmaprojects database. Over our time period, 1998-2010, the number of early-stage innovations, including both small- and large-molecules, has increased. Our sample closely tracks the population, with differences being explained by our sample restrictions. Recall, firms must have at least one approved product and one early-stage innovation in order to be incorporated into our sample.



Appendix Figure A4. Relative contribution to total innovations across therapeutic categories. This figure plots the relative contribution of each therapeutic class at the ATC1 market level based on Pharmaprojects data. Data includes all products for which Pharmaprojects identifies a therapeutic category. The figure demonstrates that while the number of overall early-stage innovations has increased (Appendix Figure A3), the relative contributions within each broad therapeutic market has remained relatively stable over time.



Appendix Table A1. Flow of innovation (Poisson). This table presents results from Poisson models across four specifications over our full sample. Model 4 serves as our base specification as it contains our full array of fixed effects, including an interaction between ATC1 market and time (Year). Note, Model 4 is the same as Model 7, Table 3 and is included here for reference. The dependent variable, $Inn_{ijt,}$ is defined as early-stage innovation. Standard errors are clustered at the firm level and are in parentheses. *** p<0.01, ** p<0.05, *p<0.10.

	(1)	(2)	(3)	(4)
	POISSON	POISSON	POISSON	POISSON
VARIABLES	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}
$Generic_{ijt-1}$			-1.200***	-1.183***
			(0.261)	(0.260)
$Price_{jt-1}$	-0.010**	-0.008*	-0.008*	-0.008*
	(0.005)	(0.005)	(0.004)	(0.004)
$Tech\ Opp_{jt-1}$		0.021	0.041***	0.041***
		(0.019)	(0.014)	(0.015)
$Tech\ Challenge_{ijt-1}$		0.399***	0.372***	0.373***
		(0.107)	(0.093)	(0.094)
$Product_{ijt-1}$	0.141***	0.152***	0.139***	0.144***
	(0.020)	(0.021)	(0.020)	(0.022)
$Late\ Pipe_{ijt-1}$	0.194***	0.082	0.076	0.083
	(0.066)	(0.061)	(0.059)	(0.057)
$Firm\ Size_{it}$	0.011	0.014	0.012**	0.018**
	(0.010)	(0.010)	(0.009)	(0.008)
Constant	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y
Year FE	Y	Y	Y	Y
ATC1 FE	Y	Y	Y	Y
ATC1 x Year FE	N	N	N	Y
Pseudo log likelihood	-10,405.77	-10,254.88	-10,016.04	-9,884.69
Observations	29,514	29,514	29,514	29,514

Appendix Table A2. Robustness checks (Split sample). We split the sample at the mean and median observation, which occur in 2004. Models 1 and 4 replicate Table 3, Model 5. Models 2 and 5 replicate these models without the inclusion of $Price_{jt-1}$. Models 3 and 6 replicate Table 4, Model 1. The dependent variable across all specifications is defined as the count of early-stage innovation, Inn_{ijt}. Standard errors are clustered at the firm level and are in parentheses. *** p<0.01, ** p<0.05, *p<0.10.

	(1) NegBin 1999-2004	(2) NegBin 1999-2004	(3) OLS 1999-2004	(4) NegBin 2005 - 2010	(5) NegBin 2005 - 2010	(6) OLS 2005 - 2010
VARIABLES	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}
$Generic_{ijt-1}$	-1.342***	-1.338***	-0.109***	-1.136***	-1.116***	-0.088***
	(0.178)	(0.178)	(0.019)	(0.149)	(0.152)	(0.018)
$Price_{jt-1}$	-0.004**			-0.018***		
	(0.002)			(0.004)		
$Tech\ Opp_{jt-1}$	0.036***	0.039***		0.031***	0.034***	
	(0.005)	(0.005)		(0.005)	(0.005)	
$Tech\ Challenge_{ijt-1}$	0.466***	0.464***	0.212***	0.528***	0.545***	0.035***
	(0.058)	(0.057)	(0.035)	(0.038)	(0.035)	(0.005)
$Product_{ijt-1}$	0.227***	0.229***	0.100***	0.149***	0.143***	0.075***
	(0.030)	(0.031)	(0.014)	(0.025)	(0.028)	(0.014)
$Late\ Pipe_{ijt-1}$	0.101**	0.111**	0.081**	0.101	0.119	0.069
	(0.050)	(0.053)	(0.036)	(0.101)	(0.103)	(0.050)
$Firm\ Size_{it}$	0.023	0.023	0.003	0.021	0.019	0.007
	(0.030)	(0.030)	(0.004)	(0.016)	(0.017	(0.005)
Constant	Y	Y	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y	Y	Y
Year FE	Y	Y	Y	Y	Y	Y
ATC1 FE	Y	Y	N	Y	Y	N
ATC1 x Year FE	Y	Y	N	Y	Y	N
ATC2 FE	N	N	Y	N	N	Y
ATC2 x Year	N	N	Y	N	N	Y
Log likelihood/R^2	-4,763.37	-4,781.26	0.247	-4,728.28	-4,757.80	0.289
Observations	14,870	14,870	14,870	14,644	14,644	14,644

Appendix Table A3. Robustness checks (Flow of innovation). Model 1 presents results from OLS model with $Generic_{ijt-1}$ along with firm, year, ATC2 market fixed effects, interactions between ATC2 market and year fixed effects, ***and*** interactions between firm and year fixed effects. The dependent variable is unchanged and defined as a count of early-stage innovation, Inn_{ijt}. Standard errors are clustered at the firm level in parentheses. *** p<0.01, ** p<0.05, * p<0.10.

	(1)
	OLS
VARIABLES	Inn_{ijt}
$Generic_{ijt-1}$	-0.138***
	(0.014)
Constant	Y
Firm FE	Y
Year FE	Y
Firm x Year FE	Y
ATC2 FE	Y
ATC2 x Year	Y
R^2	0.252
Observations	29,514

Appendix Table A4. Flow of innovation (Robustness checks). This table replicates Table 5 and presents three placebo tests based on a negative binomial specification. Model 1 redefines the dependent variable as novel early-stage innovation, *Novel Inn*$_{ijt}$ while Model 2 redefines the dependent variable as late-stage innovation, *Late-stage Inn*$_{ijt}$. The sample is restricted in Model 3 to markets where we anticipate low cross-molecular substitution, *Low CMS Inn*$_{ijt}$. These include: anti-epileptics, anti-depressants, and anti-psychotics. Excluded from these three specifications are *Product*$_{ijt-1}$, *LatePipe*$_{ijt-1}$, and *Down Asset*$_{ijt}$. Standard errors are clustered at the firm level in parentheses. *** p<0.01, ** p<0.05, * p<0.10.

	(1)	(2)	(3)
	NEGBIN	NEGBIN	NEGBIN
VARIABLES	*Novel Inn*$_{ijt}$	*Late-stage Inn*$_{ijt}$	*Low CMS Inn*$_{ijt}$
Generic$_{ijt-1}$	-1.140***	0.149	-0.246
	(0.223)	(0.132)	(0.533)
Price$_{jt-1}$	-0.001	-0.002	0.037
	(0.001)	(0.001)	(0.058)
Tech Opp$_{jt-1}$	0.023**	0.030***	0.371***
	(0.011)	(0.009)	(0.121)
Tech Challenge$_{ijt-1}$	0.423***	0.627***	0.272**
	(0.066)	(0.053)	(0.112)
Firm Size$_{it}$	0.006	0.007	0.044
	(0.011)	(0.006)	(0.053)
Constant	Y	Y	Y
Firm FE	Y	Y	Y
Year FE	Y	Y	Y
ATC1 FE	Y	Y	Y
ATC1 x Year FE	Y	Y	N
Log likelihood	-5,653.21	-24,384.63	-554.30
Observations	29,514	29,514	1,577

Appendix Table A5. Change in innovation (SUR). This table replicates Models 1, 2, 3 in Table 7 with an alternate definition of the dependent variable. In these models the dependent variable *diff(CI_{ijt}-BI_{ijt})*, is the difference between CI_{ijt} and BI_{ijt}. This allows *diff(CI_{ijt}-BI_{ijt})* to be positive, negative or zero. CI_{ijt} is defined as chemical-based early-stage innovation while BI_{ijt} is defined as biologic-based early-stage innovation. In Models 2 and 3, *Tech Opp*$_{jt-1}$ and *Price*$_{jt-1}$ are omitted because they are constructed at the ATC2 market level. Standard errors are clustered at the firm level in parentheses. *** p<0.01, ** p<0.05, * p<0.10.

	(1) IV	(2) IV	(3) OLS
VARIABLES	*diff(CI_{ijt}-BI_{ijt})*	*diff(CI_{ijt}-BI_{ijt})*	*diff(CI_{ijt}-BI_{ijt})*
Generic$_{ijt-1}$	-1.152**	-1.132**	-0.301***
	(0.533)	(0.514)	(0.055)
Price$_{jt-1}$	-0.001***		
	(0.000)		
Tech Opp$_{jt-1}$	0.021**		
	(0.008)		
diff(Tech Challenge$_{ijt-1}$*)*	1.109***	1.014***	1.039***
	(0.106)	(0.094)	(0.093)
diff(Product$_{ijt-1}$*)*	0.255***	0.249***	0.255***
	(0.021)	(0.022)	(0.037)
diff(Late Pipe$_{ijt-1}$*)*	0.969***	0.879***	0.912***
	(0.053)	(0.048)	(0.089)
Firm Size$_{it}$	0.012***	0.014***	0.014***
	(0.004)	(0.004)	(0.005)
Constant	Y	Y	Y
Firm FE	Y	Y	Y
Year FE	Y	Y	Y
ATC1 FE	Y	N	N
ATC1 x Year FE	Y	N	N
ATC2 FE	N	Y	Y
ATC2 x Year FE	N	Y	Y
First-stage F	85.81	97.06	
R^2	0.464	0.554	0.568
Observations	29,514	29,514	29,514

Appendix B1. Flow of innovation (Market level). This table replicates Table 2 with the inclusion of HHI_{jt-1} and $Brand_{ijt}$. The unit of observation is at the ATC2 market and year (t). Model 5 serves as our base specification as it contains our full array of fixed effects, including an interaction between ATC1 market and time (Year). The dependent variable, $Inn_{jt,}$ is defined as the count early-stage innovations in market j at time t. Standard errors are clustered at the market level and are in parentheses. *** p<0.01, ** p<0.05, *p<0.10.

	(1)	(2)	(3)	(4)	(5)	(6)
	NEGBIN	NEGBIN	NEGBIN	NEGBIN	NEGBIN	POISSON
VARIABLES	Inn_{jt}	Inn_{jt}	Inn_{jt}	Inn_{jt}	Inn_{jt}	Inn_{jt}
$Generic_{jt-1}$	-2.258***	-2.331***	-1.628***	-0.987*	-1.013*	-1.090*
	(0.595)	(0.678)	(0.579)	(0.559)	(0.542)	(0.662)
HHI_{jt-1}		-2.211***	-0.839	-0.376	-0.337	-0.415
		(0.623)	(0.525)	(0.469)	(0.480)	(0.406)
$Brand_{ijt}$		0.794***	0.440**	0.549***	0.642***	0.531**
		(0.288)	(0.220)	(0.200)	(0.214)	(0.221)
$Price_{jt-1}$		-0.003	-0.002	-0.002	-0.002*	-0.002
		(0.004)	(0.002)	(0.002)	(0.001)	(0.002)
$Tech\ Opp_{jt-1}$			0.037*	0.049**	0.047**	0.057***
			(0.022)	(0.020)	(0.020)	(0.017)
$Tech\ Challenge_{jt-1}$			0.205***	0.132***	0.142***	0.098***
			(0.029)	(0.026)	(0.029)	(0.017)
$Product_{jt-1}$				-0.037	-0.039	-0.041*
				(0.024)	(0.025)	(0.022)
$Late\ Pipe_{jt-1}$				0.036***	0.034***	0.020***
				(0.012)	(0.010)	(0.006)
Constant	Y	Y	Y	Y	Y	Y
Year FE	Y	Y	Y	Y	Y	Y
ATC1 FE	Y	Y	Y	Y	Y	Y
ATC1 x Year FE	N	N	N	N	Y	Y
Log likelihood	-2,753.55	-2,708.83	-2,578.32	-2,465.46	-2,396.66	-2,773.45
Observations	1,500	1,500	1,500	1,500	1,500	1,500

Appendix B2. Flow of innovation (Firm level). This table replicates Table 3 with the inclusion of HHI_{jt-1} and $Brand_{ijt.}$ Model 5 serves as our base specification as it contains our full array of fixed effects, including an interaction between ATC1 market and time (Year). The dependent variable, $Inn_{ijt,}$ is defined as the count of early-stage innovations for firm *i*, in market *j* at time *t*. Standard errors are clustered at the firm level and are in parentheses. *** p<0.01, ** p<0.05, *p<0.10.

	(1) NEGBIN	(2) NEGBIN	(3) NEGBIN	(4) NEGBIN	(5) NEGBIN	(6) OLS	(7) POISSON
VARIABLES	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{jt}
$Generic_{ijt-1}$	-1.194***	-1.231***	-1.470***	-1.359***	-1.298***	-0.099***	-1.248***
	(0.181)	(0.184)	(0.192)	(0.185)	(0.183)	(0.021)	(0.195)
HHI_{jt-1}		-1.288***	-1.344***	-1.246***	-1.249***	-0.225**	-1.360***
		(0.339)	(0.352)	(0.351)	(0.329)	(0.107)	(0.346)
$Brand_{ijt}$		1.616***	2.072***	2.553***	2.663***	0.400***	2.349***
		(0.465)	(0.488)	(0.497)	(0.461)	(0.117)	(0.458)
$Price_{jt-1}$		-0.004	-0.004	-0.004	-0.004	-0.000*	-0.004
		(0.004)	(0.003)	(0.004)	(0.003)	(0.000)	(0.004)
$Tech\ Opp_{jt-1}$			0.040***	0.042***	0.040***	0.003	0.041***
			(0.013)	(0.013)	(0.012)	(0.002)	(0.012)
$Tech\ Challenge_{ijt-1}$					0.506***	0.354***	0.365***
					(0.093)	(0.038)	(0.095)
$Product_{ijt-1}$				0.186***	0.176***	0.086***	0.143***
				(0.039)	(0.034)	(0.013)	(0.020)
$Late\ Pipe_{ijt-1}$				0.150**	0.095	0.100	0.068
				(0.072)	(0.066)	(0.063)	(0.064)
$Firm\ Size_{it}$			0.007	0.013	0.015*	0.002	0.019**
			(0.008)	(0.008)	(0.008)	(0.001)	(0.008)
Constant	Y	Y	Y	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y	Y	Y	Y
Year FE	Y	Y	Y	Y	Y	Y	Y
ATC1 FE	Y	Y	Y	Y	Y	Y	Y
ATC1 x Year FE	N	N	N	N	Y	Y	Y
Log likelihood/R^2	-10,042.368	-9,926.77	-9,865.31	-9,702.16	-9,515.73	0.20	-9,769.97
Observations	29,514	29,514	29,514	29,514	29,514	29,514	29,514

Appendix B3. Flow of innovation (Firm level, alternative specifications). This table replicates Table 4 with the inclusion of HHI_{jt-1} and $Brand_{ijt}$. Model 1 presents our base specification with our full array of fixed effects, including an interaction between market and time. The market fixed effects are at the ATC2 market level as is the interaction between ATC2 and time (Year). Models 2 and 3 present results from two-stage least square regressions where we instrument for $Generic_{ijt-1}$. Both models include our full array of fixed effects, including the interaction between market and time. Model 2 uses the ATC1 market level while Model 3 uses the ATC2 market level. Models 4 and 5 implement an Arellano and Bond system GMM where we also instrument for G_{ijt-1} and incorporate a lagged dependent variable. In all specifications, the dependent variable is defined as a count of early-stage innovation, Inn_{ijt}. Standard errors are clustered at the firm level in Models 1 to 3 and are in parentheses. Robust standard errors in parentheses in Model 4 and 5. *** p<0.01, ** p<0.05, * p<0.10.

	(1) OLS	(2) IV	(3) IV	(4) GMM	(5) GMM
VARIABLES	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}
$Generic_{ijt-1}$	-0.113***	-0.865**	-0.631*	-0.527***	-0.517***
	(0.018)	(0.364)	(0.374)	(0.148)	(0.154)
Inn_{ijt-1}				0.397***	0.574***
				(0.129)	(0.116)
HHI_{jt-1}		-0.130**		-0.020	0.057
		(0.065)		(0.087)	(0.089)
$Brand_{ijt}$	0.192**	0.938***	0.520*	1.464	0.939
	(0.078)	(0.300)	(0.304)	(1.075)	(0.855)
$Price_{jt-1}$		-0.000***	-0.008	0.000	0.001
		(0.000)	(0.006)	(0.001)	(0.001)
$Tech\ Opp_{jt-1}$		0.016**		0.001	-0.001
		(0.007)		(0.003)	(0.003)
$Tech\ Challenge_{ijt-1}$	0.317***	0.281***	0.300***	0.452	0.565
	(0.038)	(0.089)	(0.077)	(0.431)	(0.491)
$Product_{ijt-1}$	0.086***	0.065***	0.085***	0.393**	
	(0.015)	(0.019)	(0.015)	(0.180)	
$Late\ Pipe_{ijt-1}$	0.072	0.052	0.056**	0.450	
	(0.060)	(0.038)	(0.027)	(0.427)	
$Firm\ Size_{it}$	0.002	0.015***	0.012***	0.000***	0.000***
	(0.001)	(0.004)	(0.003)	(0.000)	(0.000)
Constant	Y	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y	Y
Year FE	Y	Y	Y	Y	Y
ATC1 FE	N	Y	Y	N	N
ATC1 x Year FE	N	Y	N	N	N
ATC2 FE	Y	N	Y	Y	Y
ATC2 x Year	Y	N	Y	N	N
First-stage F		19.86	16.95		
R^2/Wald X^2	0.263	0.546	0.479	871.34	1,274.96
Observations	29,514	29,514	29,514	21,089	21,089

Appendix B4. Flow of innovation (Robustness checks). This table replicates Table 5 with the inclusion of HHI_{jt}-1 and and $Brand_{ijt}$ and presents three placebo tests based on a negative binomial specification. Model 1 redefines the dependent variable as novel early-stage innovation, *Novel* Inn_{ijt} while Model 2 redefines the dependent variable as late-stage innovation, *Late-stage* Inn_{ijt}. The sample is restricted in Model 3 to markets where we anticipate low cross-molecular substitution, *Low CMS* Inn_{ijt}. These include: anti-epileptics, anti-depressants, and anti-psychotics. Standard errors are clustered at the firm level in parentheses. *** p<0.01, ** p<0.05, * p<0.10.

VARIABLES	(1) NEGBIN *Novel* Inn_{ijt}	(2) NEGBIN *Late-stage* Inn_{ijt}	(3) NEGBIN *Low CMS* Inn_{ijt}
$Generic_{ijt-1}$	-1.154***	-1.528***	-0.448
	(0.219)	(0.169)	(0.458)
HHI_{jt-1}	-1.117***	-0.966***	0.114
	(0.417)	(0.297)	(6.590)
$Brand_{ijt}$	3.383***	2.721***	1.594
	(0.883)	(0.469)	(1.842)
$Price_{jt-1}$	-0.001	-0.002	-0.099
	(0.001)	(0.002)	(0.091)
$Tech\ Opp_{jt-1}$	0.033***	0.038***	0.374***
	(0.012)	(0.009)	(0.111)
$Tech\ Challenge_{ijt-1}$	0.347***	0.536***	0.167
	(0.084)	(0.049)	(0.126)
$Product_{ijt-1}$	0.088***	0.179***	0.223***
	(0.033)	(0.033)	(0.064)
$Late\ Pipe_{ijt-1}$	0.025		0.041
	(0.082)		(0.212)
$Firm\ Size_{it}$	0.012	0.013**	0.014
	(0.012)	(0.006)	(0.051)
Constant	Y	Y	Y
Firm FE	Y	Y	Y
Year FE	Y	Y	Y
ATC1 FE	Y	Y	Y
ATC1 x Year FE	Y	Y	N
Log likelihood	-5,615.76	-23,839.27	-542.04
Observations	29,514	29,514	1,577

Appendix B5. Flow of innovation (Firm heterogeneity). This table replicates Table 6 with the inclusion of HHI_{jt-1} and $Brand_{ijt.}$ In Models 1 and 2, $Product_{ijt-1}$ is defined as a three-year moving average of product introductions. In Models 3 and 4, $Product2_{ijt-1}$ is defined as a dummy variable equal to one if the three-year moving average of product introductions is above the median, zero otherwise. Finally, in Models 5 and 6, $Product3_{ijt-1}$ is defined as a dummy variable equal to one if the three-year moving average of product introductions is in the top quartile, zero otherwise. Standard errors are clustered at the firm level in parentheses. *** p<0.01, ** p<0.05, * p<0.10.

	(1)	(2)	(3)	(4)	(5)	(6)
	NEGBIN	IV	NEGBIN	IV	NEGBIN	IV
VARIABLES	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}
$Generic_{ijt-1}$	-1.515***	-0.733**	-1.712***	-0.673**	-1.755***	-0.676**
	(0.129)	(0.319)	(0.140)	(0.303)	(0.146)	(0.311)
$(Generic*Product)_{ijt-1}$	0.455***	0.155**				
	(0.087)	(0.064)				
$(Generic*Product2)_{ijt-1}$			1.752***	0.375***		
			(0.197)	(0.124)		
$(Generic*Product3)_{ijt-1}$					1.820***	0.373***
					(0.192)	(0.118)
HHI_{jt-1}	-1.218***	-0.143**	-1.195***	-0.148**	-1.195***	-0.148**
	(0.139)	(0.061)	(0.138)	(0.0598)	(0.138)	(0.060)
$Brand_{ijt}$	2.636***	0.834***	2.508***	0.782***	2.507***	0.785***
	(0.325)	(0.262)	(0.348)	(0.248)	(0.349)	(0.254)
$Price_{jt-1}$	-0.003***	-0.000***	-0.003***	-0.000***	-0.003***	-0.000***
	(0.001)	(0.000)	(0.001)	(0.000)	(0.001)	(0.000)
$Tech\ Opp_{jt-1}$	0.036***	0.013**	0.033***	0.012**	0.032***	0.012**
	(0.004)	(0.006)	(0.005)	(0.006)	(0.004)	(0.006)
$Tech\ Challenge_{ijt-1}$	0.480***	0.289***	0.467***	0.295***	0.464***	0.293***
	(0.039)	(0.088)	(0.037)	(0.085)	(0.037)	(0.085)
$Product_{ijt-1}$	0.129***	0.049**	0.133***	0.057***	0.134***	0.057***
	(0.015)	(0.023)	(0.015)	(0.021)	(0.015)	(0.021)
$Late\ Pipe_{ijt-1}$	0.107**	0.067**	0.113**	0.069**	0.111**	0.068**
	(0.047)	(0.033)	(0.047)	(0.033)	(0.047)	(0.033)
$Firm\ Size_{it}$	0.009	0.013***	0.009	0.012***	0.008	0.012***
	(0.011)	(0.004)	(0.011)	(0.003)	(0.011)	(0.003)
Constant	Y	Y	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y	Y	Y
Year FE	Y	Y	Y	Y	Y	Y
ATC1 FE	Y	Y	Y	Y	Y	Y
ATC1 x Year FE	Y	Y	Y	Y	Y	Y
First-stage F		23.92		26.71		26.58
Log likelihood/R^2	-9,444.02	0.248	-9,375.31	0.253	-9,358.73	0.255
Observations	29,514	29,514	29,514	29,514	29,514	29,514

Appendix B6. Change in innovation (SUR). This table replicates Table 7 with the inclusion of HHI_{jt-1} and $Brand_{ijt}$. Across all six specifications the dependent variable $cat(CI_{ijt}\text{-}BI_{ijt})$, equals 1, 2 and 3 if the difference ($CI_{ijt} - BI_{ijt}$) is negative, zero, or positive, respectively. CI_{ijt} is defined as chemical-based early-stage innovation while BI_{ijt} is defined as biologic-based early-stage innovation. Models 1 and 2 present results from two-stage least square regressions with a full array of fixed effects. Model 1 includes market fixed effects at the ATC1 market level while Model 2 includes market fixed effects at the ATC2 market level along with an interaction with time (Year). Model 3 presents results from OLS with market fixed effects at the ATC2 level along with an interaction with time. Models 4 and 5 ordered logit models, with Model 5 including a full set of fixed effects, including the interaction between market and time, at the ATC1 level. As a robustness check, Model 6 replicates Model 5 using an ordered probit model. In Models 2 and 3, $Tech\ Opp_{jt-1}$ and $Price_{jt-1}$ are omitted because they are constructed at the ATC2 market level. Standard errors are clustered at the firm level in parentheses. *** p<0.01, ** p<0.05, * p<0.10.

	(1) IV	(2) IV	(3) OLS	(4) OLOGIT	(5) OLOGIT	(6) OPROBIT
VARIABLES	$cat(CI_{ijt}\text{-}BI_{ijt})$	$cat(CI_{ijt}\text{-}BI_{ijt})$	$cat(CI_{ijt}\text{-}BI_{ijt})$	$cat(CI_{ijt}\text{-}BI_{ijt})$	$cat(CI_{ijt}\text{-}BI_{ijt})$	$cat(CI_{ijt}\text{-}BI_{ijt})$
$Generic_{ijt-1}$	-1.410***	-0.478**	-0.328***	-2.240***	-2.256***	-1.104***
	(0.540)	(0.192)	(0.025)	(0.117)	(0.120)	(0.064)
HHI_{jt-1}	0.004			-0.707***	-0.723***	-0.438***
	(0.068)			(0.182)	(0.185)	(0.103)
$Brand_{ijt}$	1.241***			4.009***	4.056***	1.893***
	(0.367)			(0.388)	(0.387)	(0.197)
$Price_{jt-1}$	-0.001***			-0.002***	-0.002***	-0.001***
	(0.000)			(0.000)	(0.000)	(0.000)
$Tech\ Opp_{jt-1}$	0.021**			0.028***	0.028***	0.014***
	(0.009)			(0.005)	(0.005)	(0.003)
$diff(Tech\ Challenge_{ijt-1})$	0.113***	0.134***	0.138***	2.990***	3.016***	1.531***
	(0.034)	(0.022)	(0.024)	(0.281)	(0.281)	(0.135)
$diff(Product_{ijt-1})$	0.057***	0.031***	0.032***	1.161***	1.159***	0.509***
	(0.010)	(0.007)	(0.008)	(0.117)	(0.116)	(0.048)
$diff(Late\ Pipe_{ijt-1})$	0.161***	0.177***	0.183***	-1.055***	-1.049***	-0.448***
	(0.039)	(0.019)	(0.018)	(0.158)	(0.158)	(0.072)
$Firm\ Size_{it}$	0.005	0.003	0.003	0.021	0.023*	0.009
	(0.005)	(0.002)	(0.002)	(0.013)	(0.013)	(0.007)
Constant	Y	Y	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y	Y	Y
Year FE	Y	Y	Y	Y	Y	Y
ATC1 FE	Y	N	N	Y	Y	Y
ATC1 x Year FE	Y	N	N	N	Y	Y
ATC2 FE	N	Y	Y	N	N	N
ATC2 x Year FE	N	Y	Y	N	N	N
First-stage F	14.73	26.47				
R^2/Pseudo R^2	0.490	0.542	0.546	0.366	0.369	0.331
Observations	29,514	29,514	29,514	29,514	29,514	29,514

Appendix B7. Robustness: Change in innovation (SUR). This table replicates Table 8 with the inclusion of HHI_{jt-1} and $Brand_{ijt}$. This table presents results from three SUR specifications. CI_{ijt} is defined as chemical-based early-stage innovation while BI_{ijt} is defined as biologic-based early-stage innovation. The specifications differ in the mix of fixed effects included. Model 1 includes firm, year and ATC1 market level fixed effects. Model 2 includes firm, year, ATC1 fixed effects along with the interaction between year and ATC1. Model 3 includes firm, year and ATC2 market level fixed effects. Standard errors are clustered at the firm level in parentheses. *** p<0.01, ** p<0.05, * p<0.10.

	(1) SUR		(2) SUR		(3) SUR	
VARIABLES	CI_{ijt}	BI_{ijt}	CI_{ijt}	BI_{ijt}	CI_{ijt}	BI_{ijt}
$Generic_{ijt-1}$	-0.550***	0.017	-0.549***	0.019	-0.595***	0.026
	(0.018)	(0.017)	(0.018)	(0.017)	(0.022)	(0.021)
HHI_{jt-1}	-0.981***	0.261***	-1.007***	0.281***	0.406***	-0.326
	(0.038)	(0.014)	(0.039)	(0.039)	(0.097)	(5.764)
$Brand_{ijt}$	1.610***	0.423***	1.630***	0.423***	0.419***	0.286***
	(0.073)	(0.069)	(0.073)	(0.069)	(0.097)	(0.067)
$Price_{jt-1}$	-0.000***	-0.000*	-0.000***	-0.000*	-0.113	-0.052
	(0.000)	(0.000)	(0.000)	(0.000)	(2.164)	(3.186)
$Tech\ Opp_{jt-1}$	0.012***	-0.003***	0.010***	-0.003***	-0.248	0.294
	(0.001)	(0.001)	(0.001)	(0.000)	(0.868)	(0.846)
$Tech\ Challenge_{ijt-1}$	1.044***	0.373***	1.048***	0.376***	0.903***	0.359***
	(0.024)	(0.023)	(0.0237)	(0.023)	(0.022)	(0.022)
$Product_{ijt-1}$	0.157***	0.164***	0.158***	0.164***	0.176***	0.146***
	(0.006)	(0.006)	(0.006)	(0.006)	(0.006)	(0.006)
$Late\ Pipe_{ijt-1}$	0.091***	0.483***	0.089***	0.485***	0.050***	0.408***
	(0.018)	(0.018)	(0.018)	(0.018)	(0.017)	(0.017)
$Firm\ Size_{it}$	0.008**	0.000	0.009**	0.002	0.012***	-0.001
	(0.003)	(0.003)	(0.003)	(0.003)	(0.003)	(0.003)
Constant	Y	Y	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y	Y	Y
Year FE	Y	Y	Y	Y	Y	Y
ATC1 FE	Y	Y	Y	Y	N	N
ATC1 x Year FE	N	N	Y	Y	N	N
ATC2 FE	N	N	N	N	Y	Y
R^2	0.330	0.369	0.334	0.372	0.450	0.472
Observations	29,514	29,514	29,514	29,514	29,514	29,514

Appendix B8. Robustness: Change in innovation (SUR). This table replicates Table 9 with the inclusion of HHI_{jt-1} and $Brand_{ijt}$. In these two SUR specifications we limit the sample to those markets where biologic-based innovation is most active. Based on data from Pharmaprojects, these include ATC1 markets: F, J and T. The intuition behind this approach is simple, if a rotation is taking place from chemical-based to biologic-based innovation, the effects should be amplified in markets where the rotation is easier for firms to undertake. Results are consistent with this intuition. CI_{ijt} is defined as chemical-based early-stage innovation while BI_{ijt} is defined as biologic-based early-stage innovation. Standard errors are clustered at the firm level in parentheses. *** p<0.01, ** p<0.05, * p<0.10.

	(1) SUR		(2) SUR	
VARIABLES	CI_{ijt}	BI_{ijt}	CI_{ijt}	BI_{ijt}
$Generic_{ijt-1}$	-1.024***	0.264*	-0.895***	0.320**
	(0.065)	(0.140)	(0.069)	(0.145)
HHI_{jt-1}	-0.633***	1.925***	-0.088	-1.133*
	(0.145)	(0.326)	(0.229)	(0.584)
$Brand_{ijt}$	0.428*	1.642***	0.109	0.408
	(0.238)	(0.461)	(0.281)	(0.437)
$Price_{jt-1}$	-0.002***	-0.000	0.000	-0.000
	(0.000)	(0.000)	(0.000)	(0.001)
$Tech\ Opp_{jt-1}$	0.064***	-0.028***	0.240	-0.059
	(0.005)	(0.009)	(0.179)	(0.375)
$Tech\ Challenge_{ijt-1}$	0.461***	1.139***	0.432***	1.016***
	(0.040)	(0.087)	(0.038)	(0.081)
$Product_{ijt-1}$	0.037***	0.204***	0.066***	0.176***
	(0.008)	(0.018)	(0.008)	(0.017)
$Late\ Pipe_{ijt-1}$	-0.136***	0.717***	-0.111***	0.587***
	(0.026)	(0.055)	(0.025)	(0.052)
$Firm\ Size_{it}$	0.004	-0.003	0.008	-0.008
	(0.007)	(0.016)	(0.007)	(0.015)
Constant	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y
Year FE	Y	Y	Y	Y
ATC1 FE	Y	Y	N	N
ATC1 x Year FE	Y	Y	N	N
ATC2 FE	N	N	Y	Y
R^2	0.279	0.433	0.344	0.509
Observations	4,958	4,958	4,958	4,958

Appendix C1. Flow of innovation (Poisson). This table replicates Appendix Table A1 with the inclusion of HHI_{jt-1} and $Brand_{ijt.}$ This table presents results from Poisson models across four specifications over our full sample. Model 4 serves as our base specification as it contains our full array of fixed effects, including an interaction between ATC1 market and time (Year). The dependent variable, $Inn_{ijt,}$ is defined as early-stage innovation. Standard errors are clustered at the firm level and are in parentheses. *** p<0.01, ** p<0.05, *p<0.10.

	(1)	(2)	(3)	(4)
	POISSON	POISSON	POISSON	POISSON
VARIABLES	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}
$Generic_{ijt-1}$			-1.532***	-1.253***
			(0.307)	(0.267)
HHI_{jt-1}	-1.393***	-1.352***	-0.808*	-1.352***
	(0.540)	(0.484)	(0.489)	(0.484)
$Brand_{ijt}$	1.539***	1.671***	2.493***	2.259***
	(0.566)	(0.505)	(0.531)	(0.465)
$Price_{jt-1}$	-0.005	-0.004	-0.008	-0.004
	(0.005)	(0.004)	(0.007)	(0.004)
$Tech\ Opp_{jt-1}$		0.024	0.012	0.047***
		(0.018)	(0.015)	(0.014)
$Tech\ Challenge_{ijt-1}$		0.379***	0.445***	0.354***
		(0.112)	(0.095)	(0.099)
$Product_{ijt-1}$	0.140***	0.154***	0.130***	0.143***
	(0.018)	(0.020)	(0.021)	(0.020)
$Late\ Pipe_{ijt-1}$	0.178***	0.070	0.167*	0.061
	(0.067)	(0.062)	(0.090)	(0.064)
$Firm\ Size_{it}$	0.009	0.012	0.023**	0.020**
	(0.009)	(0.010)	(0.010)	(0.008)
Constant	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y
Year FE	Y	Y	Y	Y
ATC1 FE	Y	Y	Y	Y
ATC1 x Year FE	N	N	N	Y
Pseudo log likelihood	-10,295.61	-10,149.39	-10,435.36	-9,891.41
Observations	29,514	29,514	29,514	29,514

Appendix C2. Robustness checks (Split sample). This table replicates Appendix Table A2 with the inclusion of HHI_{jt-1} and $Brand_{ijt}$. We split the sample at the mean and median observation, which occur in 2004. Models 1 and 4 replicate Table 3, Model 5. Models 2 and 5 replicate these models without the inclusion of $Price_{jt-1}$. Models 3 and 6 replicate Table 4, Model 1. The dependent variable across all specifications is defined as the count of early-stage innovation, Inn_{ijt}. Standard errors are clustered at the firm level and are in parentheses. *** p<0.01, ** p<0.05, *p<0.10.

	(1) NegBin 1999-2004	(2) NegBin 1999-2004	(3) OLS 1999-2004	(4) NegBin 2005 - 2010	(5) NegBin 2005 - 2010	(6) OLS 2005 - 2010
VARIABLES	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}	Inn_{ijt}
$Generic_{ijt-1}$	-1.397***	-1.338***	-0.109***	-1.198***	-1.116***	-0.088***
	(0.168)	(0.178)	(0.018)	(0.134)	(0.152)	(0.018)
HHI_{jt-1}	-1.273***			-1.192***		
	(0.175)			(0.215)		
$Brand_{ijt}$	2.237***			3.232***		
	(0.458)			(0.461)		
$Price_{jt-1}$	-0.002*			-0.009***		
	(0.001)			(0.003)		
$Tech\ Opp_{jt-1}$	0.043***	0.039***		0.037***	0.035***	
	(0.005)	(0.005)		(0.006)	(0.005)	
$Tech\ Challenge_{ijt-1}$	0.443***	0.464***	0.212***	0.530***	0.545***	0.413***
	(0.054)	(0.057)	(0.035)	(0.038)	(0.035)	(0.098)
$Product_{ijt-1}$	0.227***	0.229***	0.099***	0.148***	0.143***	0.075***
	(0.030)	(0.031)	(0.014)	(0.026)	(0.028)	(0.014)
$Late\ Pipe_{ijt-1}$	0.112**	0.111**	0.081**	0.076	0.119	0.069
	(0.046)	(0.053)	(0.036)	(0.103)	(0.103)	(0.050)
$Firm\ Size_{it}$	0.021	0.023	0.003	0.024	0.019	0.007
	(0.029)	(0.030)	(0.004)	(0.016)	(0.017)	(0.005)
Constant	Y	Y	Y	Y	Y	Y
Firm FE	Y	Y	Y	Y	Y	Y
Year FE	Y	Y	Y	Y	Y	Y
ATC1 FE	Y	Y	N	Y	Y	N
ATC1 x Year FE	Y	Y	N	Y	Y	N
ATC2 FE	N	N	Y	N	N	Y
ATC2 x Year	N	N	Y	N	N	Y
Log likelihood/R^2	-4,721.07	-4,781.26	0.247	-4,686.17	-4,757.80	0.289
Observations	14,870	14,870	14,870	14,644	14,644	14,644

Appendix C3. Flow of innovation (Robustness checks). This table replicates Appendix Table A4 with the inclusion of HHI_{jt-1} and $Brand_{ijt}$. Model 1 redefines the dependent variable as novel early-stage innovation, *Novel* Inn_{ijt} while Model 2 redefines the dependent variable as late-stage innovation, *Late-stage* Inn_{ijt}. The sample is restricted in Model 3 to markets where we anticipate low cross-molecular substitution, *Low CMS* Inn_{ijt}. These include: anti-epileptics, anti-depressants, and anti-psychotics. Excluded from these three specifications are $Product_{ijt-1}$, $LatePipe_{ijt-1}$, and $Down\ Asset_{ijt}$. Standard errors are clustered at the firm level in parentheses. *** p<0.01, ** p<0.05, * p<0.10.

VARIABLES	(1) NEGBIN *Novel* Inn_{ijt}	(2) NEGBIN *Late-stage* Inn_{ijt}	(3) NEGBIN *Low CMS* Inn_{ijt}
$Generic_{ijt-1}$	-1.187***	-1.602***	-0.776
	(0.222)	(0.175)	(0.529)
HHI_{jt-1}	-1.144***	-1.044***	-1.445
	(0.412)	(0.294)	(3.609)
$Brand_{ijt}$	3.186***	2.250***	2.250
	(0.839)	(0.468)	(2.426)
$Price_{jt-1}$	-0.001	-0.002	0.048
	(0.001)	(0.002)	(0.062)
$Tech\ Opp_{jt-1}$	0.032***	0.035***	
	(0.012)	(0.009)	
$Tech\ Challenge_{ijt-1}$	0.382***	0.603***	0.267**
	(0.076)	(0.059)	(0.112)
$Firm\ Size_{it}$	0.010	0.009	0.051
	(0.012)	(0.007)	(0.053)
Constant	Y	Y	Y
Firm FE	Y	Y	Y
Year FE	Y	Y	Y
ATC1 FE	Y	Y	Y
ATC1 x Year FE	Y	Y	N
Log likelihood	-5,584.34	-24,101.26	-553.62
Observations	29,514	29,514	1,577

Appendix C4. This table replicates Appendix Table A5 with the inclusion of HHI_{j-1} and $Brand_{ijt}$ and also replicates Models 1, 2, 3 in Table 7 with an alternate definition of the dependent variable. In these models the dependent variable $diff(CI_{ijt}\text{-}BI_{ijt})$, is the difference between CI_{ijt} and BI_{ijt}. This allows $diff(CI_{ijt}\text{-}BI_{ijt})$ to be positive, negative or zero. CI_{ijt} is defined as chemical-based early-stage innovation while BI_{ijt} is defined as biologic-based early-stage innovation. In Models 2 and 3, $Tech\ Opp_{jt-1}$ and $Price_{jt-1}$ are omitted because they are constructed at the ATC market level. Standard errors are clustered at the firm level in parentheses. *** p<0.01, ** p<0.05, * p<0.10.

	(1) IV	(2) IV	(3) OLS
VARIABLES	$diff(CI_{ijt}\text{-}BI_{ijt})$	$diff(CI_{ijt}\text{-}BI_{ijt})$	$diff(CI_{ijt}\text{-}BI_{ijt})$
$Generic_{ijt-1}$	-0.559***	-0.410***	-0.313***
	(0.101)	(0.079)	(0.056)
HHI_{jt-1}	-0.636**		
	(0.262)		
$Brand_{ijt}$	0.236*	0.223*	0.144
	(0.130)	(0.133)	(0.129)
$Price_{jt-1}$	-0.001		
	(0.001)		
$Tech\ Opp_{jt-1}$	0.043		
	(0.032)		
$diff(Tech\ Challenge_{ijt-1})$	1.030***	1.037***	1.040***
	(0.193)	(0.091)	(0.094)
$diff(Product_{ijt-1})$	0.256***	0.255***	0.255***
	(0.043)	(0.036)	(0.037)
$diff(Late\ Pipe_{ijt-1})$	0.864***	0.907***	0.911***
	(0.190)	(0.086)	(0.089)
$Firm\ Size_{it}$	0.017	0.014***	0.014***
	(0.016)	(0.005)	(0.005)
Constant	Y	Y	Y
Firm FE	Y	Y	Y
Year FE	Y	Y	Y
ATC1 FE	Y	N	N
ATC1 x Year FE	Y	N	N
ATC2 FE	N	Y	Y
ATC2 x Year FE	N	Y	Y
First-stage F	47.03	57.77	
R^2	0.320	0.568	0.568
Observations	29,514	29,514	29,514