Dear Colleagues:

Our conference paper will examine whether patent thickets in pharmaceuticals affect the timing or extent of generic entry. Pharmaceuticals is typically classified as a “discrete product” industry, in which a single patent covers a single product. The starting point for our paper is that this label is an increasingly poor fit. In Europe, a recent sector report prepared by the Directorate General for Competition found a dramatic rise in the number of patents per drug, with some individual drugs having dozens of patents. Our previous work traces a similar rise in the United States. This increase has led to growing concern about drug patent thickets. Brand-name firms have allegedly sought increasing recourse to ancillary patents to protect their market positions, including patents on chemical variants, alternative formulations, methods of use, and relatively minor aspects of the drug. As in other sectors, the worry is that these thickets can create uncertainty for potential entrants and delay competition.

While we won't have a paper ready for the pre-conference, the attached paper gives a sense of our approach and work so far. The paper reports a sharp rise in patents per drug in the United States over the past quarter century. We also examine how the number of patents on a drug, and other characteristics of drug patent portfolios, affect whether (and when) a drug draws a “Paragraph IV” patent challenge by a competing generic drug maker. (These patent challenges are a legal mechanism by which generic drug makers challenge the patents of brand-name drug makers as a means to secure early market entry.)

For the conference paper, we plan to use the same dataset and empirical approach to examine the effects of the number of patents on the timing of generic entry. As in the background paper, we will separately identify a thicket effect, reflecting the number of patents on a drug, and an “evergreening” effect, which reflects incremental market life created by later-expiring patents.

The opportunity for both thickets and evergreening is set in part by the FDA, in the standard it establishes for which patents may be “listed” as pertinent to a particular brand-name drug. The FDA deems only certain types of patents to be sufficiently pertinent to be included in the Orange Book, an FDA document that records the set of pertinent patents. Orange Book listing has important consequences, including reducing uncertainty about the patent landscape for a particular drug. However, not all patents are listed on the Orange Book: method of manufacture patents, in particular, are excluded. For example, while Merck’s lucrative statin Zocor had only 3 Orange Book-listed patents, 326 patents with the word “simvastatin” in their claims have been issued by the US Patent and Trademark Office, 43 of which are owned by Merck.

Non-Orange Book patents may be a significant source of thickets. Since there is no “official” listing of these patents, they are less apparent. Moreover, their absence from the Orange Book may create uncertainty for a generic firm about whether a proposed generic drug infringes any non-Orange Book patent. In this respect, non-Orange Book patents potentially create problems analogous to the traditional thicket concerns in, for example, the information, communications, and semiconductor industries.

The conference paper will also go beyond previous work on brand-generic competition in

pharmaceuticals and examine whether patents not listed on the Orange Book deter or delay generic drug competition in the United States. We will then determine the extent to which these patents are actually asserted in generic patent litigation, and whether they—by this or another means—have the effect of deterring entry. One goal is to determine whether these patents lead to less generic entry than we would expect by observing only the Orange Book-listed patents, sales, and other observable drug characteristics.

At the pre-conference, we plan to present some initial results about the effects of patent portfolios on generic entry, and to discuss some opreliminary data about non-Orange Book patents.

We look forward to your feedback, and to seeing you soon.

Sincerely

Scott Hemphill
Bhaven Sampat

When Do Generics Challenge Drug Patents?

C. Scott Hemphill[*] and Bhaven N. Sampat[†]

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The Hatch-Waxman Act regulates competition between brand-name and generic drugs in the United States. We examine a feature of the Act that has attracted great controversy but little systematic attention. "Paragraph IV" challenges are a mechanism for generic drug makers to challenge the patents of brand-name drug makers as a means to secure early market entry.

We first present descriptive results that chart the rise of brand-name patent portfolios and Paragraph IV challenges. Over time, patenting has increased, measured by the number of patents per drug and the length of the nominal patent term. Meanwhile, the fraction of drugs subjected to patent challenges has increased. Drugs are also challenged sooner, relative to brand-name approval.

Our econometric analyses of challenges over the past decade show that brand-name sales have a positive effect upon the likelihood of generic challenge. The likelihood of challenge also varies with the nature of the patent portfolio. A drug with weaker patents faces a significantly higher likelihood of challenge, conditional on sales and other drug characteristics. That is not because the drug's patent protection is weaker *overall*; additional patents, even weak ones, generally strengthen a brand-name firm's ability to exclude. Rather, a weak patent, particularly if it expires later than the basic patents, disproportionately attracts a challenge to the pertinent drug. Overall, our results suggest these challenges serve a useful purpose by promoting scrutiny of low quality and late-expiring patents.

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When Do Generics Challenge Drug Patents?

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Introduction

The pharmaceutical industry is the rare setting in which the patent system works as it is supposed to—or so the story goes. Innovative new drugs have supplied dramatic improvements in longevity and quality of life over the past century (Murphy and Topel 2000; Lichtenberg 2007, 2009; Lichtenberg and Virabhak 2007). Effective patent protection has provided a critical stimulus to that lifesaving research. Patents are widely thought to have a unique role in stimulating drug research and development, compared to other industries (Levin et al. 1987; Cohen, Nelson and Walsh 2000). It is easy to see why. A patent on a new drug compound is difficult to invent around, and thus is effective in preventing imitation. Without a patent, imitation is straightforward, without any need to duplicate the innovator's enormous efforts to discover and test a new drug.

The profitability of new drugs is limited—some would say threatened—by the aggressive entry of so-called generic drug makers, which offer a close, lower priced copy of the brand-name drug. Once generic firms enter the market, prices fall, often to less than 10 percent of the price of the brand-name drug. Generic drug utilization has seen explosive growth over the past 25 years, from 20 percent of prescriptions then to 70 percent today (Frank 2007; Engelberg et al. 2009). Generic drugs have saved consumers an estimated $700 billion between 1999 and 2008 (IMS Health 2009). Some of that savings is lost innovator profit, raising concerns that aggressive generic competition, by reducing innovator incentives, might heighten the "current crisis in industry R&D pipelines" (Higgins and Graham 2009, p. 370).

From the standpoint of innovators, the matter is dire enough when generic drug entry occurs after patent protection expires. But generic drug makers often seek Food and Drug Administration (FDA) approval and market entry *prior* to patent expiration, asserting that one or more brand-name patents are invalid or not infringed by the generic product. Such "challenges," often called "Paragraph IV challenges," occur pursuant to a special legislative regime that governs the approval process for generic drugs, commonly known as the Hatch-Waxman Act.[1] Frequently, these challenges result in patent litigation. In many cases, the generic firm wins the challenge, resulting in entry, and lower drug prices, much earlier than would otherwise be the case.

As we describe in detail below, the prevalence of challenges have risen dramatically over the past 25 years, placing them at the center of a vigorous debate about drug innovation and access (Engelberg 1999; FTC 2002; Grabowski 2004; Hemphill 2006). The concern that challenges reduce brand-name patent protection, and hence research incentives, is strongest if drug patents fit the ideal type ascribed to them by Levin et al. 1987 and others, in which a novel molecule is covered by single patent that clearly covers the molecule. In that case, a rise in generic challenges might indicate a rise in "prospecting," in which generic drug makers challenge basic compound patents—or basic compound patents on high-sales drugs—indiscriminately, even though most challenges of this type are long-shots, in the hope of winning a few.[2] And if so, more and earlier challenges might imply less protection and resulting reward for innovative drugs.

[1] The label refers to both the legislative regime set up by the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, which amended the Food, Drug, and Cosmetic Act of 1938, and its subsequent amendments. "Paragraph IV" refers to the statutory provision, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that permits a generic firm to assert that relevant patents are invalid or not infringed.

[2] Voet (2005) is typical: "[T]he validity of virtually all major patented drugs is being challenged not necessarily because they are not meritorious patents, but only because that is the road to riches. Thus major generic

As we show, however, many drug patents do not cover the compound. Brand-name firms have sought increasing recourse to ancillary patents on chemical variants, alternative formulations, methods of use, and relatively minor aspects of the drug. These patents have the effect of extending the total duration of protection for a brand-name drug, compared to the protection offered by the compound patent alone. The parallel rise of generic challenges and brand-name patenting suggests an alternative account, in which challenges provide a means for generic firms to restore the status quo, by challenging and thereby clearing away patents of questionable validity or relevance (Engelberg 1999; Bulow 2003). While the source of much debate, these conflicting accounts have been subject to little systematic empirical work.

In this paper, we examine the growth in generic challenges and contemporaneous increase in brand-name patenting, and the relationship between patent portfolio building and the likelihood of a challenge. We bring novel data to bear by examining a new dataset of brand-name drugs approved by the FDA. Among other advances, we construct detailed measures of the patent protection covering each drug and the timing of a challenge (if any).

We find evidence against the null hypothesis that generic drug makers are indiscriminate in their attacks, or that market size is the only determinant of challenges. Market size (as proxied by sales) does matter, unsurprisingly, as does the technical difficulty of making the drug. Patents, however, matter too, and not in the manner that one would immediately expect. Weak patents make a challenge more likely. That is not because the drug's patent protection is weaker *overall*; additional patents, even weak ones, generally strengthen a brand-name firm's ability to exclude. Rather, weak individual patents, particularly if they expire later than the basic patents, disproportionately attract a challenge. Our results provide support for the proposition that generic

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companies have scores of such suits ongoing and generic companies rely on the law of averages—if you place enough bets, you are sure to win a few of them . . . ."

drug makers use challenges as a route to entry when brand drugs have low-quality patents that would, in the absence of challenges, block competition.

This paper proceeds in six parts. Part I reviews previous studies of generic drug entry and patent policy that inform our inquiry. Part II describes the regime set up by the Hatch-Waxman Act and the incentives it creates, including a special reward available to certain generic drug makers that challenge brand-name patents. Part III offers new descriptive results that trace the growth of brand-name patent portfolios and the contemporaneous increase in generic challenges. Part IV describes our data and explains our empirical approach, which relates the likelihood of a challenge to a drug's patent portfolio, sales, and other characteristics. Part V reports the results. Part VI assesses the implications of our results for several debates about drug and patent policy.

I. Previous Studies

Though there is a significant theoretical and empirical work on generic entry (Scott Morton 1996; Reiffen and Ward 2005), there is little previous work on Paragraph IV challenges. A few recent papers have discussed patent challenges as part of broader work on the changing length of market exclusivity periods in pharmaceuticals (Grabowski and Kyle 2007; Grabowski 2004). There has also been some work on how sales affect challenges: Berndt et al. (2007b) considers the effect of sales on the intensity of challenge, conditional on a challenge occurring, for a proprietary sample of drugs. Filson and Oweis (2010) use two events in the history of Paragraph IV challenges to evaluate the effect on decision making by pharmaceutical startups.

Our analysis is a large-sample study of the determinants of challenges, and the first to assess the relationship between brand-name patents and generic challenges or entry. By focusing on the role of patents, our project draws on a substantial literature, most of it theoretical,

evaluating the partial protection provided by a patent. As economists understand this regulatory entitlement, a patent is "probabilistic," in the sense that it provides not an absolute privilege to exclude alleged infringers, but only a right to try to exclude, through litigation whose outcome is uncertain ex ante (Lemley and Shapiro 2005).

This uncertainty is due partly to ambiguity in the breadth of patent claims, creating doubt as to whether they cover the product of an alleged infringer (Bessen and Meurer 2008). The uncertainty is also a natural consequence of the light scrutiny that patents receive during the application process, due in part to sharp resource constraints facing patent examiners (Jaffe and Lerner 2004) and differences in strictness across patent examiners (Lemley and Sampat 2011). As a consequence, at the time of issuance it is uncertain whether a patent in fact reflects a nonobvious advance over the prior art, as is necessary for a patent to validly issue.

The question whether light ex ante review is good policy is a specific instance of the more general, longstanding inquiry by legal scholars and economists about the virtues of ex post review relative to its alternatives.[3] The lightness of review ex ante might be a rational response given the substantial cost entailed in reviewing each patent. Such "rational ignorance" is cost-effective provided that most patents have little economic importance, and the set of important patents cannot be identified early (Lemley 2001), but can be identified later. One necessary condition for effective ex post review is that the reviewer must have adequate incentives to review. That condition might not be satisfied for patents generally. The reason is that the alleged infringer, the economic actor in the best position to challenge the validity and scope of a patent, faces a free-rider problem, because other alleged infringers can quickly take advantage of a

[3] The choice between ex ante and ex post resolution of uncertainty about the validity and breadth of a patent is also, at its base, an inquiry about the merits of private litigation compared to alternative modalities of regulation as a means to determine the existence and scope of private rights. Posner (2009) reviews the values at stake, emphasizing the relative strength of ex post litigation and litigation-like regulatory processes in making the most use of situation-specific facts.

favorable judgment. This result has led commentators to conclude that patent challenges are underprovided, both in the decision to bring a challenge and in the incentive to pursue it vigorously (Farrell and Merges 2004; Miller 2004; Thomas 2001). That free-rider problem is overcome in the pharmaceutical industry, due to a special incentive to challenge patents discussed below. A second condition for ex post review to be effective is that the likelihood of intensive review should increase with the deadweight loss associated with exclusion.

Prior to that review, even weak patents can have important effects on competition. They can slow down rivals by obliging them to search for, evaluate, and litigate patents that are unlikely to be found valid and infringed. Moreover, patents do not always exist in isolation as single entities. In some industries, single firms collect extensive portfolios that they assert, or threaten to assert, against other firms (Hall and Ziedonis 2001). In general, portfolios can be expected to discourage entry, permitting the incumbent to exclude substitutes or extract revenue from producers of complements. Portfolio building has not generally been associated with the pharmaceutical industry, which is typically understood as a "discrete product" industry in which a single patent covers a single product (Levin et al. 1987; Cohen et al. 2000). As we report below, however, brand-name drug makers are building patent portfolios, raising the question of what effect this might have on generic competition.

As discussed in the introduction, some commentators view challenges as a mode of ex post review that can identify and eliminate low-quality patents (Engelberg 1999). This is particularly important given concerns that the U.S. Patent and Trademark Office (PTO) and FDA are unable to do so (Eisenberg 2007), allegations about "evergreening" of patent portfolios by brand-name drug makers, and the consumer harm from such patents (Thomas 2005). On the other hand, Grabowski and Kyle (2007), Grabowski (2004), and Higgins and Graham (2009)

take the view these challenges are mostly driven by sales, and that they create uncertainty and reduce returns to R&D for brand-name firms. The null hypothesis in this strand of the literature—at least implicitly—is that patent characteristics don't matter.

II. The Regulatory Regime for Pre-Expiration Challenges

Generic patent challenges target brand-name drugs that are already on the market. Under federal law, a brand-name firm must demonstrate that a new drug is safe and effective before the FDA will approve it for marketing. Making that demonstration as part of a New Drug Application (NDA) is a lengthy, expensive process, consuming years and many millions of dollars to conduct the necessary clinical trials (DiMasi et al. 2003).

Once the brand-name firm places a drug on the market, a generic firm may seek to market a competing, "therapeutically equivalent" version of the same drug by filing an Abbreviated New Drug Application, or ANDA, with the FDA. The generic firm must demonstrate that the rate and extent of absorption of the active ingredient (AI) are the same in both drugs.[4] The generic drug maker must also be able to actually make the drug, a task that is easier for some dosage forms of drugs (such as tablets or capsules) than others (such as, say, a transdermal patch). New clinical trials are not required. An ANDA costs about $1 million to prepare (FDA 2003a).

Most new drugs are protected by one or more patents. Those patents are listed by the brand-name firm in an FDA compendium commonly known as the Orange Book. Additional details about the Orange Book, and other regulatory matters, are contained in the Appendix. The

[4] 21 U.S.C. § 355(j)(8)(B). The applicant must also demonstrate that the generic drug contains the same conditions of use, route of administration, dosage form, strength, and labeling. § 355(j)(2)(A).

generic firm, faced with this array of patents, may choose not to challenge any patents, in which case the FDA delays ANDA approval until expiration of the last listed patent.

In many cases, however, the generic firm attempts to enter prior to patent expiration. In that case, the generic firm files an ANDA containing a "Paragraph IV" certification, asserting that one or more listed patents are invalid or not infringed by the proposed generic product. The filing of such an ANDA is an act of patent infringement. In response to the ANDA, the brand-name firm may file a patent infringement suit to establish validity and infringement. This pattern—launch, challenge, sue—is frequent for major drugs, and it has become the norm for the best-selling drugs (Hemphill 2006, 2009). Litigation raises the expense of a Paragraph IV challenge to $10 million or more (Goodman 2004).

A generic drug maker has a special incentive to challenge a patent, particularly if the patent is believed to be invalid or not infringed. That is due to a special feature of the Hatch-Waxman regime. Under certain circumstances, the first generic firm to file an ANDA is entitled, upon FDA approval, to a 180-day exclusive right to market its product in competition with the brand-name firm before other generic firms may enter. This exclusivity period provides a bounty to generic firms that incur the costs of Paragraph IV challenges.

There are two types of brand-name drug that are subject to Paragraph IV challenges. Some drugs, called "new chemical entities" (NCEs), contain a novel active ingredient. NCEs are often thought to be the most innovative drugs (NIHCM 2002). NCEs receive special regulatory protection from challenges, a four-year waiting period, starting at FDA approval, during which no ANDA containing a patent challenge may be filed. Other drugs are essentially improved versions or variants that contain a previously approved AI. For example, the drug may be offered in a liquid dosage form rather than the original tablet, reformulated so that the drug can be taken

just once a day, or combined with another existing drug. Reformulation as a strategy for extending drug life is a particular focus of brand-name drug makers (Perett 2008). For non-NCE drugs, an ANDA may be filed immediately after NDA approval.

III. The Rise in Brand-Name Patent Portfolios and Generic Patent Challenges

To assess changes in brand-name patenting and generic challenges over time, we constructed a new dataset that combines detailed information about brand-name drugs, including patent protection, with detailed data about Paragraph IV challenges for each drug. We start with the set of 1481 new non-injection brand-name drugs approved between 1985 and 2008, collected from an FDA database (FDA 2009). A drug is one or more AIs and a dosage form (e.g., extended-release tablet). We aggregate multiple strengths (e.g., 10 milligrams) of the same drug. For each drug, FDA data discloses the applicant name and approval date. We then match this information to data about patent protection and Paragraph IV challenges.

Patent Portfolios

For each drug, we collected information about applicable patent protection from current and archival editions of the Orange Book (FDA 1985-2009). The Orange Book is a comprehensive account of a drug's patent protection, including any patent containing at least one claim that covers the drug's AI, its formulation, or a "method of use" pertaining to an approved indication (e.g., inhibiting cholesterol biosynthesis). Removing those drugs that have no Orange Book patents, and hence are not subject to Paragraph IV challenges, yields a set of 1032 drugs.

Our first analyses examine the growth of portfolio building by brand-name firms. Our measure is the number of unique patents that are listed in (any edition of) the Orange Book. We collect the drugs into a series of six three-year approval cohorts starting in 1985, the first full

year after the Hatch-Waxman Act was passed, and ending in 2002. We stop with 2002, because later cohorts are censored: some patents are added to the Orange Book years after the drug is approved. 692 new drugs were approved during this 18-year period.

Figure 1 shows trends over time in the number of patents per drug. Drugs in the first cohort, approved between 1985 and 1987, have an average of 1.9 patents per drug. In the final (2000 to 2002) cohort, the mean slightly more than doubles to 3.9 patents per drug. The median increases from 1.5 to 2.5 patents per drug. Much of the growth in patenting is attributable to the right tail. The top quartile point grows steadily, from two patents per drug to five patents per drug. In other words, the top twenty-five percent of patent portfolios, among drug approvals in the first several years of the Act, had two or more patents per drug, while the top portfolios fifteen years later were more than double that size.

Using Orange Book data, we also determine whether the drug received protection as an NCE. As Figure 1 shows, the increase in patenting plays out differently for NCE and non-NCE drugs. For the first three cohorts, NCEs have more patents on average. Starting with the 1994-1996 cohort, non-NCE drugs take the lead. In the top quartile, non-NCE growth is particularly marked.

Not all patents are created equal. Some patents are more likely to exclude generic entry than others. There is a rough hierarchy in patent strength—that is, in the likelihood that a brand-name firm will convince the court that its patent is valid and infringed by the drug proposed to be made in the generic firm's ANDA. Patents that claim the AI—those basic patents that cover the drug compound—are generally the strongest. They are infringed by making the generic drug product, almost by definition; otherwise bioequivalence is lacking. To make an invalidity argument, a generic drug maker is left contending that the drug was previously disclosed or that

the patentee engaged in inequitable conduct during the application process. These are difficult arguments to win.

In comparison to AI patents, patents for particular formulations—for example, a chemical mechanism providing sustained release of the drug substance over time—are more open to attack. In that case, the generic drug maker can argue not only invalidity but also noninfringement. For example, the generic firm can argue, often with success, that it employs a different, noninfringing mechanism for accomplishing the sustained release of the drug. Other patents listed in the Orange Book—for particular salt forms, particle sizes, and methods of use—are also open to challenge.

These patents, though weak, nevertheless have the effect of making the patent portfolio stronger. If they overlap with a strong composition of matter patent, they provide an additional barrier to generic entry prior to expiration of the strong patent, since the generic firm must defeat the weak patent in addition to the strong one. Indeed, the prospect of having to defeat both patents might cause a generic firm to decline or delay a challenge. Moreover, the additional patent strengthens the portfolio in a second way. A patent that expires later than the strong patent potentially provides a substantial temporal extension in a brand-name drug maker's effective exclusivity.

To explore the importance of portfolio building, and the respective roles of AI and non-AI patents, we examined the claims of each Orange Book-listed patent, 3036 patents in all. One of the authors developed a coding guide and worked with a former PTO examiner of drug patent applications to code each patent according to whether it contained at least one AI claim. This coding is arguably overinclusive: as elaborated in the Appendix, certain types of claims are counted as AI claims even though they are weaker than the "classic" compound claim in

significant respects. Thus, there are likely more non-AI patents than our counts suggest. In recent years, the use of non-AI patents has increased substantially. Figure 2 traces out the trend. In the first cohort of NCEs, 61 percent have at least one non-AI patent listed in the Orange Book. By the 2000 to 2002 cohort, 84 percent have at least one such patent. Non-NCEs have seen similar growth. As discussed in Part V, these patents have a significant effect upon the likelihood of a Paragraph IV challenge.

As noted above, multiple patents provide a potential opportunity for temporal extension of the brand-name exclusivity. We call the lag between a drug's approval date and the date of its last-expiring patent the "nominal" patent life for that drug. Brand-name firms and other market participants often use this date in their announcements and discussions of when a drug goes off-patent. Figure 3 shows the increase in nominal patent life over time, again grouped by approval cohort. NCE drugs have seen a more than three-year increase in nominal patent life, from 12.2 years to 15.5 years. Non-NCEs have seen a smaller increase, from 14.8 years to 16.6 years.

Temporal extension complicates the simple story of entry deterrence usually associated with a thicket, i.e. that more patents deter competition. In particular, drugs with weak and later expiring patents may be more likely to attract Paragraph IV challenges. That is not to say overall patent protection on the drug is weak with the addition of such patents; indeed, it is stronger. Rather, the late expiring patent may be a particularly vulnerable target for the generic firm to attack via a Paragraph IV challenge. Compared to the alternative—waiting even longer before generic entry—attacking a weak, late-expiring patent could be an attractive prospect, even if the strong, earlier expiring patent is safe from attack.

The incentive to target weak, late-expiring patents is even stronger once the particular regulatory dynamic of pharmaceuticals is considered. A generic firm is entitled to enjoy the 180-

day exclusivity period if it challenges any patent, even if does not challenge all of them. Moreover, a selective challenge actually benefits the brand-name firm, compared to the patent never having issued. Even if the challenge is successful, the award of 180 days itself provides a measure of protection to the brand-name firm, since it restricts the extent of generic entry for half a year. And of course, the patent might serve to block entry altogether if the challenge is deterred or unsuccessful.[5]

Paragraph IV Challenges

During the same period that patent portfolios have increased, Paragraph IV challenges have grown as well. To explore this trend, we also collected detailed information about Paragraph IV challenges. We determined which drugs attracted challenges between 1984 and December 2009 using a list of such drugs, which we call the "Paragraph IV List," maintained by the FDA (FDA 2010). Comparing the Paragraph IV List to the set of approved brand-name drugs reveals that 299 drugs (out of 692) have been subjected to Paragraph IV challenge by the end of 2009. Overall, the fraction of drugs challenged has increased from 22 percent of drugs approved in the first cohort to 55 percent in the last cohort. We report these trends in Figure 4. Overall, a slightly larger share of NCEs (44 percent) than non-NCEs (43 percent) have been subjected to Paragraph IV challenges. The most striking change, however, has been the rise in challenges against non-NCEs, from just 15 percent of non-NCEs approved in the first cohort, to more than half (58 percent) of those approved in the last cohort.

[5] Including the late-expiring patent might create a risk for the brand-name firm. The generic firm might decide that as long as it is challenging the second patent, it might as well challenge the first patent, too, given that it is already incurring the cost of a challenge and litigation. This spillover effect could be a significant negative consequence of the accumulation of late-expiring patents.

To understand the role of Paragraph IV challenges in reducing effective brand-name patent life, we need to know when these challenges occur relative to FDA approval. The FDA's Paragraph IV List reports the date of first challenges that occur after March 2004. The lack of systematic data before this period has hindered empirical analyses of challenges. To relax this data constraint, we extended this data back to 2000 by hand, using a variety of public sources. (See Appendix for details.)

One benefit of information on timing of challenges is that we can construct a measure of "early" challenges, within one year of challenge eligibility, for a range of drugs. For this analysis, the right truncation is less severe, and so we can use a wider range of approval years. For NCEs, we can construct this measure for drugs approved between 1996 and 2004. (An NCE approved in 1996 can be challenged starting in 2000, on account of the waiting period described above. An NCE approved in 2004 can be challenged starting in 2008.) For non-NCEs, which can be challenged immediately, we can construct this measure for drugs approved between 2000 and 2008. Similarly, we can construct a three-year challenge measure for NCEs approved between 1994 and 2002, and for non-NCEs approved between 1998 and 2006.

Figure 5 reports the results. NCEs have seen a dramatic increase in year-one challenges over the past decade, from seven percent of drugs approved in 1996 (and hence challengeable starting in 2000) to 69 percent of drugs approved in 2004 (and hence challengeable starting in 2008). Non-NCEs are seldom challenged in year one of eligibility. That is not surprising, because it takes time to design a viable challenge, and it may not be immediately clear that a drug is worth challenging. The three-year measure is more appropriate for non-NCEs. On this measure, non-NCEs have seen significant growth from 19 percent of drugs approved in 1998 to 33 percent of drugs approved in 2006.

Patenting and challenges have thus both increased sharply in the quarter century since the passage of Hatch-Waxman. In the next section, we explore how the two are related in the cross-section, examining how patents and other drug characteristics affect the likelihood of challenge, for all drugs eligible for challenge over the past decade.

IV. Data and Empirical Approach

Data: Description and Summary Statistics

Our sample consists of prescription drugs that first became eligible for generic challenge between 2000 and 2008. That range reflects the fact that we can observe the timing of challenges that occur between 2000 and 2009, and allow for at least one full year of observation. As a general matter, for non-NCE drugs that can be challenged immediately upon approval, these are drugs approved between 2000 and 2008. For NCEs that become eligible after the four-year waiting period, these are drugs approved between 1996 and 2004. There are two minor exceptions to this generalization, explained in detail in the Appendix.[6]

For each year between 2001 and 2009, we collected January sales from the National Sales Perspective database of IMS Health, the leading provider. For convenience, we convert all sales figures to annualized sales in billions of dollars, inflated to 2010 values using the CPI deflator (BLS 2010). We omit a small number of drugs for which IMS Health lacked sales. The resulting sample contains 479 drugs, half of which were challenged by the end of 2009. Among drugs eligible for challenge in 2006 or earlier, for which we at least three years of observations, 35 percent were challenged in the first three years.

[6] First, a few drugs have an NCE waiting period of less than four years. Second, in 2008, certain previously approved antibiotic drugs were made eligible for Paragraph IV challenge that had previously been ineligible. Some of these drugs were approved as early as 1990. The data have been adjusted to take account of the actual first eligibility for each drug. See the appendix for further details.

What explains which drugs are challenged? Table 1 describes each of the variables we examine. Our main analyses are duration models, following a drug over time. However, for expository convenience, we begin in Table 2 by presenting static descriptive information for each of the 479 drugs. NCEs are 35 percent of the sample. As discussed above, dosage forms differ in their ease of manufacture and replication (Scott Morton 2000) and so may also be important to the likelihood of challenge. Two-thirds of the drugs in our sample are orally administered. We also calculated average sales for each drug (across each year we observe the drug). These range from zero to $5.9 billion, with a mean of $205 million. Nine drugs in our sample have average annual sales exceeding $2 billion (Abilify, Advair Diskus, Celebrex, Cymbalta, Lipitor, Nexium, Protonix, Vytorin, and Zyprexa).

We employ three types of measures of the quality of the patents on a drug. A first set of is based on a suite of widely used measures of patent quality, including the number of times a patent is cited (by later-issued patents) and the number of countries in which patent protection is sought (Hegde and Sampat 2009; Sampat 2010). Forward citations to a patent are commonly used measures of patent value, on the theory that higher quality patents generate more citations. Using information from a private patent data vendor, Delphion, we determined the number of citations for all Orange Book listed patents issued until the end of 2008. For each patent associated with a drug in our sample, we determined whether it is in the bottom quartile of citations for all Orange Book listed patents with the same issue year. (Normalizing by issue year is necessary because more recently issued patents have a shorter window to be cited.) For each drug, we created a variable counting the number of these "low quality" patents. On average, drugs in our sample had 0.98 of such patents. We constructed a similar measure for family size, the number of countries where a patent application was filed. This too is a commonly used

measure of patent quality, on the theory that more important patents will be filed in more jurisdictions (Lanjouw et al. 1998; Lanjouw and Schankerman 2004). On average, the drugs in our sample have 0.79 patents in the bottom quartile of this measure of patent quality.

A second set of measures is based on information from the Orange Book. One measure is the number of patents applied for before or during the calendar year of drug approval—what we call "early" patents—and the number of "late" patents applied for after approval. Late filed patents are generally viewed as being lower quality, since the late-filed patent may not claim any patentable attribute of the approved drug, which by then is part of the prior art. Drugs in our sample have 3.3 early patents, on average, and just 0.36 late-filed patents. We also control for overall "nominal" patent life for each drug, also determined from the Orange Book.

In addition to these measures, we also examine hand-coded information on the type of patents on a drug—whether the drug has only AI patents, only non-AI patents, or both types—using the expert coding described above. (Recall that, by definition, each of the drugs in our sample has at least one patent. Otherwise it would not be eligible for a challenge.) Of the drugs in our sample, 12 percent have only AI patents, 47 percent only non-AI patents, and 41 percent have both.

To examine the hypothesis that late expiring non-AI patents could have distinctive effects, we also determined whether non-AI patents add market life beyond all the AI patents, or are redundant to them. For a drug with both AI and non-AI patents, about three-quarters of the non-AI patents expire after the AI patents. Thus about 8 percent of the drugs in our sample have redundant non-AI patents, and 33 percent have non-AI patents generating extra market life. On average (across all drugs) the extra life from non-AI patents is 1.9 years.

Empirical Framework

Our estimation strategy relates the likelihood of a first challenge to a drug at a point in time to the extent and type of patent protection, drug sales, and other drug characteristics. For each drug, we have an observation for each year following its initial eligibility for challenge, until it either receives its first challenge or is censored when our data ends on the last day of 2009. We specify the probability of challenge for drug i at time t, P_{it}, as

$$\text{Logit}(P_{it}) = \alpha + \beta SALES_{it} + \gamma PATENTQUAL_i + \delta_i + \lambda(t) + \theta_t.$$

SALES is a set of time-varying sales measures for each drug (e.g., sales in the past year). *PATENTQUAL* includes the patent measures discussed above. δ is a set of measures of drug characteristics, including chemical type, therapeutic class, and dosage form. The last two terms capture the timing of the challenge. λ is a measure of duration dependence, years since eligibility, which is operationalized as a set of dummy variables. θ is a set of challenge year dummies. We are thus estimating discrete-time duration models of the likelihood of challenge.[7] These models will be estimated using logistic regressions, with standard errors clustered by drug.

The dependent variable is whether, in a given year after eligibility, the drug receives a challenge. Each drug in our sample has an observation for each year after eligibility, until it is either challenged or censored. We also drop a small number of observations (60 observations) in which no challenge has yet occurred, but all patents have expired. After that point, the drug is not at risk of challenge. The resulting dataset has 1807 drug-year observations.

[7] Allison (1982) and Jenkins (1995) show that estimates from these models are similar to hazard rates obtained from continuous time models. In addition to these duration models, we estimated static models relating the probability that each of the drugs was challenged within five years of eligibility to the same covariates. Results are similar, and available on request.

Table 3 describes the data structure. In year one after eligibility, all 479 drugs are at risk of challenge. Of these, 77 drugs, or 16 percent, receive a challenge. Of the remaining 402 drugs, 40 are censored: these are drugs that were eligible in 2008, and 2009 is the last observed year of possible challenge. Five more drugs leave the dataset because their patents expire. That leaves 357 drugs at risk of challenge in year 2. Of these, 43 drugs (12 percent) were challenged and 22 (6 percent) were censored. And so on. The first column can thus be interpreted as a discrete time hazard rate, without conditioning on additional predictors.

V. Results

Table 4 shows results from the baseline models. In the most parsimonious specification, Model 1, we relate whether a drug is challenged to indicators for sales of the drug in that year, time elapsed since eligibility, indicators for each potential challenge year, and therapeutic class effects. Sales have a large, positive, and statistically significant impact on the hazard of challenge. Marginal effects calculations (unreported) indicate that a billion-dollar increase in annual brand-name sales is associated with a 10 percentage point increase in the hazard of challenge.[8] Neither the NCE indicator nor the control for antibiotics is significant. Consistent with the view that oral drugs are generally easier to copy as a technical matter, oral drugs have a much higher hazard of challenge than others, raising the probability of challenge by 9 percentage points.

Model 2 introduces the total number of patents. The total number of patents has no significant effect on the likelihood of challenge, indicating that the usual "thicket" story does not accurately capture what is going on. Models 3 and 4 explore the nature of the patent portfolio

[8] We calculate marginal effects at the mean values of continuous variables, and the most common categories for categorical variables (e.g. the eligibility year and observation year indicators).

using standard patent quality measures: the number of patents with low citations, and the number of other patents on the drug; the number of patents with low family size, and the number of other patents on the drug. They show that drugs with more patents in the first quartile of citations, or the first quartile of the family size distribution, are associated with significantly higher rates of challenge. These standard measures of quality may be more related to the private value of patents than patent quality in a legal sense, e.g. the likelihood that the patents are valid (Sampat 2010). While we will focus on our own hand-coded measures of patent quality in most of the analyses reported below, we start by observing that even these "off the shelf" measures show that low-quality patents are significantly related to the probability of challenges.

The third readily available measure of patent quality is based on whether the patents were filed early or late. Model 5 shows that the number of late patents has a strong, positive, and statistically significant effect, while the number of early patents has a negative and statistically insignificant association with the likelihood of challenge. For example, drugs with one late patent have a 3 percentage point higher likelihood of challenge than drugs with none. Late patents are both weaker, as explained above, and also generally expire later, so the fact that they are associated with higher challenges suggests that an aggressive patent position may be attracting challenges.

Model 6 considers the effect of a long nominal patent term on the likelihood of challenge. A longer term has a positive and significant effect. This result again indicates, as suggested in Part III, that an aggressive patent position, composed of weaker, later expiring patents, might be attracting challenges.

Table 5 introduces our hand-coded quality measures. As Model 7 indicates, having only non-AI patents has a positive and statistically significant effect on the likelihood of challenge,

relative to the left out category (AI patents only). Drugs with both types of patents also have a higher likelihood of challenge. Having at least one non-AI patent in addition to having at least one AI patent raises the probability of challenge by 6 percentage points, compared to having no non-AI patents.Though the tables suppress eligibility year indicators, these variables do provide insights on challenge dynamics across types of drugs. To illustrate this, we estimated model 2 separately for NCEs and non-NCEs. Figure 6 plots the predicted values from these models (at the means of all other variables). For NCEs, the hazard of challenge shows a sharp decrease after year one, and is generally decreasing over time. By contrast, for non-NCEs the hazard remains more or less constant. This may reflect differential learning dynamics. For NCEs, potential challengers must wait (in most cases, for four years) before filing a challenge, which provides an opportunity to determine the feasibility of reverse engineering and manufacturing, and observe the size of the market opportunity. Accordingly, for these drugs most of the most profitable challenges will occur early after eligibility. For non-NCEs, where there is no waiting period, this learning occurs throughout the eligibility period.

To illustrate the magnitude of the impact of non-AI patents, we also estimated a variant of Model 2 where we collapsed the patent information to two categories, indicating drugs with only an AI patent (the left out category) and drugs with any non-AI patent (alone or together with an AI patent). Figure 7 plots the predicted hazards from these models over time, separately for drugs with AI patents and for drugs with non-AI patents. Across all drugs, the hazard is generally decreasing over time. But (as would be expected from the regression results) the hazard is much larger for drugs with non-AI patents.

Returning to the main results, Model 8 unpacks the "both" category into cases where non-AI patents are redundant to the AI patent (i.e., adds no extra time), and cases where they extend nominal patent life. Non-AI patents generating extra market life have a positive and significant effect on likelihood of challenge, as does a redundant non-AI patent.[9] Model 9 shows that the amount of extra time generated by non-AI patents has a positive and significant effect. A year of extra market life generates about a percentage point increase in the hazard of challenge. Model 10 employs non-parametric indicators of the amount of extra time generated by non-AI patents, and shows that the likelihood of challenges increases monotonically with this measure. Drugs with non-AI patents generating the most extra market life have a 17 percentage point higher hazard of challenge than drugs with AI patents only.

These results suggest that sales have a strong and positive effect on the likelihood of challenge. But conditional on sales, challenges are also responsive to the presence of weak patents, particularly those generating the largest increments to nominal patent life.[10] Interestingly, the effect on challenges is stronger as the increment to nominal patent life increases. There is an argument to be made that the size of the increment should not matter. So long as the late-expiring patent affords an opportunity to receive the 180-days, the amount those patents would otherwise add to patent life is irrelevant. There are a few reasons to think this story might be incomplete, however. First, although the 180-day period provides the bulk of a generic firm's profits for many drugs, the post-exclusivity period is also of some value. Second, having to wait longer before entry is risky, because by the later date, competition may have intensified, either from a

[9] The difference between the coefficients is not statistically significant (p=0.67).

[10] These models constrain the effect of sales to be constant across NCEs and non-NCEs. However, these sales figures measure a later moment after approval for NCEs, compared to non-NCEs, because NCE eligibility is delayed by the four-year waiting period. Results on the patent variables are very similar if we allow NCE and non-NCE sales to have different coefficients.

new patented therapy or a competing drug that has fallen victim to genericide. Longer-dated increases are riskier to sit out, which raises the relative profits of challenging them. Third, some brand-generic disputes result in settlements in which the generic firm accepts delayed entry in exchange for payment, but the scope of the arrangement is limited by the expiration date of the patent. A longer-dated increase can support a longer delay and hence a larger potential payment.

Surprisingly, the estimates from Model 8 also showed that drugs with non-AI patents that are redundant to AIs also have a significantly higher likelihood of challenge than drugs with only AI patents. (Though the magnitude is smaller than for drugs with term-extending non-AI patents, the difference between the two is not significant.) This is surprising because we would expect redundant non-AI patents either to reinforce the AI patents, thus discouraging a challenge, or else to make no difference at all. One possibility is that some of the AI patents are not in fact that strong. We coded AI patents expansively, as discussed in Section III, and some of these may in fact be highly vulnerable to challenge. Put differently, some of the AI patents—with which the "redundant" non-AI patents overlap—could themselves be weak. If the propensity to acquire such weak AI patents were correlated with the acquisition of non-AI patents, this could explain why drugs with redundant AI/non-AI protection have a higher hazard of challenge than drugs with AI patents alone.

Ideally, we would consider only those non-AI patents that extend beyond the "strong" AI patents as providing extra years of patent protection that might be vulnerable to a challenge. To check this, we supplemented our coding with a "revealed preference" measure of the strongest AI patent. As partial compensation for the time spent in the approval process, the Hatch-Waxman Act provides for "patent term extension," under which the brand-name drug maker is permitted to extend a single patent of its choosing. These patents tend to be strong patents, as it

would be poor strategy to extend a patent that did not offer relatively strong protection. Extension is a noisy measure of strength; not every drug has an extended patent.[11] 41 percent of our observations have an AI patent that was chosen for extension. This share is slightly higher, 52 percent, for drugs with redundant non-AIs patents. For these drugs, we recoded non-AI patents as generating extra life if they expired later than the extended AI patent (rather than *any* AI patent, as in the model 8). In practice, this reallocates non-AI patents from "redundant" to "extending" for 27 drugs.

Table 6 reports the results. Model 11 shows that drugs with redundant non-AIs do not have a statistically different hazard of challenge than those with AI patents alone. Models 12 and 13 show that, even with these new indicators of whether the non-AI patents are redundant or extending, the likelihood of challenge increases with the extent of extension. While the recoded measures used in these analyses are noisy, as noted above, these results again suggest that drugs with non-AI patents generating additional market life beyond the strong patents are the most likely to be challenged.

In all of the analyses so far, sales were introduced continuously. We relax this assumption in the analyses reported in Table 7, which reports results from models analogous to those in Table 5, but also includes indicators for sales quartiles (with the first quartile left out). The sales quartiles are calculated relative to all other drugs sold at a point in time. Model 14 suggests sales do have a non-linear effect on challenges. Relative to the bottom sales category, the predicted hazard of challenge is 1 percentage point higher for the second category, 10 percentage points higher for the third, and 26 percentage points higher for the top quartile. In addition, allowing sales to affect challenges via this more flexible functional form does not affect the patent results

[11] Roughly speaking, one patent can be extended for each NCE.

discussed above. The presence of non-AI patents is highly associated with the likelihood of challenge, and this effect is increasing with the extent of additional nominal patent life these patents generate.

Additional Analyses

These results suggest that while sales matter for challenges, so do patents. In particular, challenges are associated with low-quality patents. One threat to identification is that our results reflect omitted variable bias: the expected profitability of the drug, not captured by drug-specific sales or the time invariant therapeutic class indicators, affects both the extent of patenting and the likelihood of a challenge. To examine this, we also estimated our baseline models including the three year distributed lag of sales, in addition to contemporaneous sales. (Doing so required beginning the analyses in 2003, since sales data are not available before January 2000. This change results in a reduction of sample size of 183 drug-years, to 1624.) This approach aims to control for trends in sales, which are arguably more predictive of future profits than point-in-time sales figures.

Table 8 shows the results. In each of the models, the coefficients on sales and lagged sales are haphazard, reflecting collinearity between the measures. (Wald tests show that the sales measures are jointly significant all each of the models.) More importantly, the direction, magnitude, and significance of estimates on all of the patent variables are unchanged.

As another proxy for expectation of sales, we also re-estimated the baseline models, adding a measure of expected market size. Specifically, we use total sales for all other drugs in a therapy class, three years forward, to proxy for expected sales. This measure reflects a "rational expectations" assumption, that firms anticipate the future size of the market (and thus expected

profits), and make decisions to challenge and file patents in response. In constructing this measure for market size, we focus on all other drugs in the market, since the size of the market for a given drug would be directly affected by a successful challenge (for example, if generic entry means wider utilization), which would introduce a different source of reverse causality to our analysis.

Table 9 shows the results. Since we use sales data in a class three years after a given observation year, we had to drop the 636 observations from 2008 and 2009 from these analyses, leaving 1171 observations. In each of the models, future sales (conditional on current sales) has a positive but statistically insignificant impact on the likelihood of challenge. This could reflect that the therapeutic class indicators were adequate controls for future sales, that future sales don't matter for challenges. It could also be that this proxy for future market size is not a good one. Subject to this caveat, our main patent results are robust to introduction of this control.[12]

VI. Discussion and Conclusion

In the quarter century since the passage of the Hatch-Waxman Act, the practice of listing questionable patents on the Orange Book has grown rapidly. There has been a concomitant increase in Paragraph IV challenges. The interplay of these two trends—and the patterns of litigation, settlement, and entry that result—determine the effective patent life for new drugs. In effect, the policies and rules governing these activities determine how we balance dynamic

[12] The analyses above focused on omitted variable bias—specifically, that profit expectations drive both challenges and patenting decisions. A related threat to validity is that we have it backwards. Rather than patenting practices causing challenges, the anticipation of a challenge leads to increased patenting. As a check on this hypothesis, in unreported analyses we focused on orally administered drugs, which are easier to imitate, and thus more vulnerable to challenge. We found no evidence that these drugs acquired more non-AI patents or that they were more likely to acquire late patents. These results are available on request.

efficiency (research and development incentives) and static efficiency (price competition) in pharmaceuticals.

We provide the first comprehensive evidence that allegations of attempted evergreening are real, and that such efforts have grown over time, using data on all (non-injectable) drugs approved since the Hatch-Waxman Act was passed, and all Orange Book patents on those drugs. We observe a rise in low-quality patents over the period between 1985 and 2002, and an increase in nominal patent life over the same period. How does this relate to the finding of Grabowski and Kyle (2007) that the effective patent term stayed constant or—for the highest sales drugs—decreased slightly, for a set of drugs subjected to generic entry between 1995 and 2002? The two results are not at odds, because the present study measures *nominal* patent life, rather than effective patent term. That is, we observe the outer bounds of brand-name firms' effort to protect their drugs, whereas Grabowski and Kyle measured the final result—entry.[13] The difference between nominal patent life and effective patent term reflects Paragraph IV challenges. The rise of these challenges may explain why, in the face of increasing nominal patent life, effective patent term has not increased concurrently.[14]

In our econometric analyses of drugs first eligible for challenge between 2000 and 2008, we find a strong association between patent portfolios and generic challenges. One striking result from our regressions is the importance of weak patents for the likelihood of a Paragraph IV challenge. Non-AI patents have a strong positive relationship with challenges, especially those generating extra market life. Conditional on sales, drugs with more questionable patents, a larger

[13] Grabowski and Kyle also find some evidence that patent challenges reduce effective patent terms, though this result is statistically insignificant at conventional levels. As noted in the text, our focus is different—challenges, not entry—and the evidence we present here neither confirms or raises doubts about that finding.

[14] Paragraph IV challenges may have the effect of cutting back nominal patent life to the baseline set by stronger, earlier-expiring patents. This line of thinking—that increases over the past decades in nominal patent life generated by evergreening have been reined in by Paragraph IV challenges—is the subject of ongoing work.

number of late patents, and greater nominal patent life generated by late patents are much more likely to draw challenges. While these results are based on our own characterization of patents, we also show that drugs with "low quality" patents using standard patent indicators—citations and family size—are also more likely to be challenged. These findings suggest that the characterization of challenges as frivolous attacks that reduce patent life (and perhaps, as a result, research and development incentives) is too simple. We strongly reject the null hypothesis that the composition and quality of a drug's patent portfolio don't matter. The finding that patent quality matters for challenges is surprising, in light of the conventional wisdom that challenges are only about sales.

In addition to demonstrating that nominal patent life and low quality patents have been increasing over time, and that patent portfolio characteristics matter for generic challenges, another surprising result from our analysis is the non-importance of patent thickets in pharmaceuticals. In contrast to other industries, additional patents don't discourage attempts to enter. Indeed, they sometimes encourage challenges.

What about welfare? Assume that some challenges are successful and reduce time to generic entry, by eliminating low-quality patents. There is a broad question about whether, absent the incremental market life provided by dubious patents, brand-name firms would have sufficient incentives to invest in socially valuable research. From the perspective of the dominant rationale for patent protection—patents as an incentive to invent—the exclusivity period should be just large enough to cover firms' risk adjusted investment in research. Despite decades of economic theory and empirical work, however, the optimal patent term remains elusive, and we

do not answer the question here.[15] Accordingly, even if challenges were saving purchasers significant sums or improving access to drugs, we cannot say definitively whether reining in the patent term via challenges would be good or bad, since we do not know the dynamic effect upon innovation.

We can make more limited statements, however, about the social value of generic patent challenges. Our results suggest that patent challenges target drugs whose portfolios include weak, late expiring patents. Under the assumption that weaker patents are less likely to be related to socially valuable research and development, challenges might be an important means to curtail patents that have high social costs (by sustaining high prices) but bring little innovative benefit. From a legal perspective, these challenges provide a thorough-going second look at patents of doubtful merit. In light of PTO examiners' lack of capability and incentive to provide a thorough look in the first place—and that, judged ex ante, this "rational ignorance" may be rational—observers have proposed ex post bounties as a way to improve patent quality (Miller 2004; Thomas 2001). Our work suggests that—in pharmaceuticals at least, the one industry where bounties actually exist—the bounties are focused where we want them to be, on high value drugs, in which at least part of the patent portfolio contains low-quality patents.

At the same time, there are significant transaction costs associated with this system. Challenges are expensive, litigation even more so, and the complexities of the Hatch-Waxman Act provide manifold opportunities to game the system. The issuance and Orange Book listing of doubtful patents is just one source of waste that is induced by the scheme. There is evidence that drug makers "game" the post-challenge process (Bulow 2004; Hemphill 2006, 2009). If we find large-sample evidence that this behavior is widespread, the assessment may be quite different.

[15] The optimal period would also take into account numerous complexities, including whether the loss of an existing source of profits makes a firm more or less innovative (Arrow 1962), which further cloud the analysis of welfare analysis.

The discussion above assumes that low quality patents do little for innovation incentives. If patent standards are not well aligned with innovation (Eisenberg 2007; Roin 2009), then this assumption is problematic. A related possibility is that the exclusivity period generated by strong patents is insufficient to generate enough profits, in which case the option to evergreen and thereby obtain longer patents terms might be necessary to induce drug development. While we cannot speak to this—again, we do not know the "right" patent term—we are skeptical that the issuance and listing of invalid patents is a promising path toward the first best. (In related work, we examine the effects of challenges on the timing of entry (Hemphill and Sampat 2011.)

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Appendix

This Appendix describes our data collection in greater detail.

Drug approvals. We collected data for every non-injection prescription drug approved by the FDA. We omitted over-the-counter (OTC) drugs, following FTC 2009, which have a quite different consumer purchase process. Drugs that were initially approved as prescription drugs, and only later had a further OTC approval, are included. We also omitted injection drugs, again following FTC 2009, as these have a distinctive method of administration and sales (i.e. hospitals).

Patents listed in the Orange Book: We collected patent data for each brand-name drug from the FDA's compendium of Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. The Orange Book also lists, for each brand-name drug, any unexpired regulatory exclusivity and approved therapeutically equivalent generic drugs. For early editions, we collected the data by hand, augmented by the results of a FOIA request to the FDA. For data from 2000 to the present, we rely on archival electronic versions of the Orange Book.

The Orange Book contains a comprehensive, though not perfectly exhaustive, account of patent protection relevant to each drug. For patents issued before NDA approval, a brand-name drug maker is required to list any patent containing at least one claim that covers the drug's AI, its formulation, or any method of use pertaining to an approved indication. For patents issued after NDA approval, listing is not required, but there is a strong incentive to do so. If the patent is not listed, the generic firm filing an ANDA need not certify that the patent is invalid or not infringed as a condition for FDA approval. Nor can the unlisted patent provide a basis for an automatic stay of approval, ordinarily enjoyed by brand-name drug makers that file a timely

patent suit in response to an ANDA containing a patent challenge. The drug maker is prohibited from including other types of patents in the Orange Book, such as methods for manufacturing the drug. Some brand-name drug makers, however, tend to err on the side of inclusion. Brand-name drug makers are free to assert unlisted patents against generic drug makers, but these instances are rare.

Our coding strategy separates patents into two categories, AI and non-AI. The AI category includes both basic compound patents and other patents that are not so basic. For example, some AI patents claim a variant of an existing molecule, permitting the generic firm to argue that the new drug is obvious and hence unpatentable in light of the prior art.[16] In other instances, the basic AI patent may have expired already, and the relevant AI patent may only cover a particular form of the drug, such as a particular crystalline structure. In that case, the generic entrant might try to market a distinct, noninfringing form that is nevertheless bioequivalent to the brand-name drug, or, alternatively, argue that the patent is invalid. Finally, the coding sweeps in a few patents claiming aspects of the drug, such as particular salt forms of previously patented substances, that are not AI claims at all.

ANDAs with Paragraph IV certifications: We limit our examination to ANDAs containing a Paragraph IV certification. There are three alternative certifications, in which the generic drug maker asserts that there are no Orange Book-listed patents, that any such patents have expired, or that the generic drug maker is content to wait until the expiration of the last listed patent. See 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV). Only Paragraph IV certifications provide

[16] An example is enantiomers, which are compounds that are non-superimposable mirror images of one another, like left and right hands. Sometimes, a drug will be discovered and marketed first as a mixture of multiple enantiomers. But only one enantiomer is really doing the therapeutic work, and later it may be purified and marketed separately as a new drug. The question is whether the single enantiomer can receive separate protection, given the earlier disclosure of the mixture and knowledge about how to accomplish the separation and purification of a single enantiomer.

for generic entry prior to patent expiration, or potential eligibility for the 180-day exclusivity period. The exclusivity period is available only to the first ANDA filer, though, as noted in the text, if multiple ANDAs are filed on the same day, they share in the exclusivity.[17]

Determining the date of first Paragraph IV challenge. We determine the date of first Paragraph IV challenge for all drugs that become eligible for challenge in January 2000 or later. The FDA reports the date of first challenge only for first challenges starting in March 2004; before that date, the FDA reports only that at least one challenge occurred. We have filled in the gaps for drugs that were first challenged between January 2000 and March 2004. For challenges between August 2000 and March 2004, we determined the date by comparing archived versions of the Paragraph IV List, and augmented these results with reports about new challenges written by equity analysts at financial firms. For challenges between January 2000 and August 2000, we inferred that the challenge occurred during that period from the facts that the drug became eligible for challenge in 2000 or later, and was not challenged during the range for which we have more detailed data (August 2000 to present). A similar approach allows us to determine whether a drug was challenged within the one-year window or three-year window, as described in Part III.

Determining the date of challenge eligibility. In our regression analyses, we examine drugs that first became eligible for challenge between 2000 and 2008. A key distinction is between NCEs and non-NCEs. NCEs are drugs for which no "active moiety"—roughly speaking, an active ingredient—has been approved by the FDA. NCEs receive special regulatory

[17] The FDA reached this conclusion in 2003 (FDA 2003b), and this view was codified by statute later that year. § 355(j)(5)(B)(vi)(I) (sharing exclusivity among first applicants); § 355(j)(5)(B)(iv)(II)(bb) (defining first applicant). There is a second route to shared exclusivity. In some cases, the filing of an additional patent in the Orange Book gave generic firms a fresh opportunity to share in the exclusivity period. Under "patent-by-patent" exclusivity, multiple generic firms, each first to a file a Paragraph IV certification for a different patent, could potentially share in the exclusivity. This interpretation, which applies to a substantial number of drugs, was ended by a statutory change in December 2003.

protection under the Hatch-Waxman Act: no ANDA containing a Paragraph IV certification may be filed during the first four years after drug approval. (The relevant data exclusivity is sometimes referred to as "five-year exclusivity," but the period is shorter in the case of a Paragraph IV certification. 21 U.S.C. § 355(j)(5)(F)(ii).) For example, Razadyne tablets were first approved by the FDA in February 2001. This was the first approval for the drug's active ingredient, galantamine hydrobromide, so Razadyne tablets are first available for challenge in February 2005. Thus, our dataset includes NCEs approved between 1996 and 2004. An NCE approved in 1996 is eligible for challenge in 2000. An NCE approved in 2005 or later is not eligible for challenge until 2009 or later, and is omitted from our data.

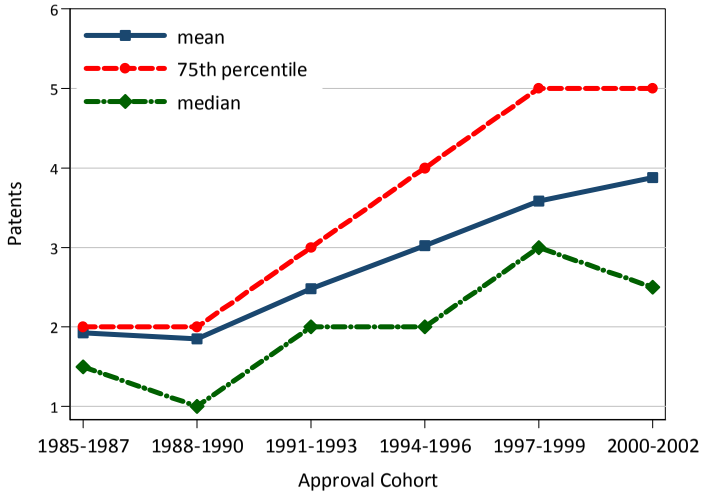
Most non-NCE drugs are eligible for challenge as soon as the drug is approved.[18] An exception is drugs that contain an active ingredient giving rise to NCE protection, which also receive whatever is left of the four years of protection. For example, an extended-release formulation of galantamine hydrobromide, Razadyne ER, was approved in December 2004. That drug, like Razadyne tablets, became eligible for challenge starting in February 2005.

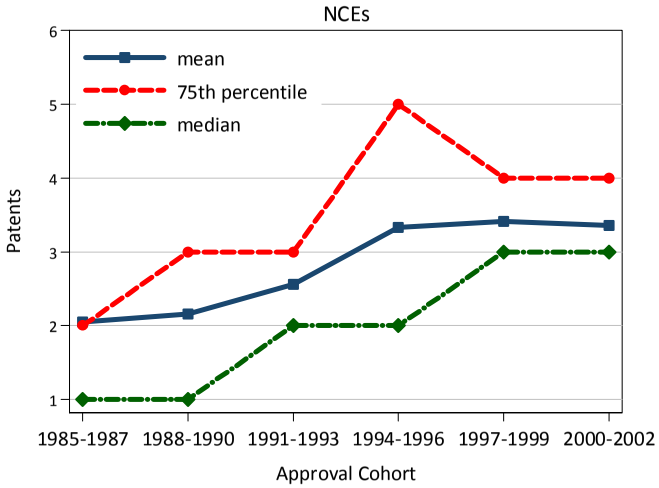
Delayed eligibility is also the result, under a highly unusual formula, for certain antibiotics. Prior to 1997, the FDA approved antibiotics under a special regime that did not include patent listing or Paragraph IV challenges. A statutory change in that year subjected antibiotics to the regular procedure on a going forward basis, but exempted "old antibiotics," that is, drugs containing an active ingredient that had been applied for under the old regime. The exemption extended to new, later-approved drugs with old antibiotic ingredients. In October 2008, these old antibiotics were subjected to the Orange Book listing requirements and made

[18] For certain non-NCE drugs, an ANDA cannot be approved for three years after NDA approval, but this restriction does not limit the filing of an ANDA.

subject to Paragraph IV challenges (FDA 2008). As a result, 35 antibiotics had listed patents, of which four attracted a Paragraph IV challenge.

Figure 1: Patents Per Drug





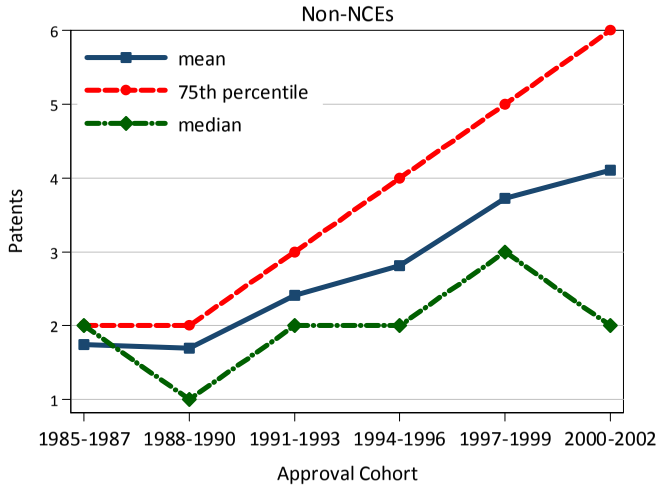


Figure 2: Share of Drugs with Non-AI Patent

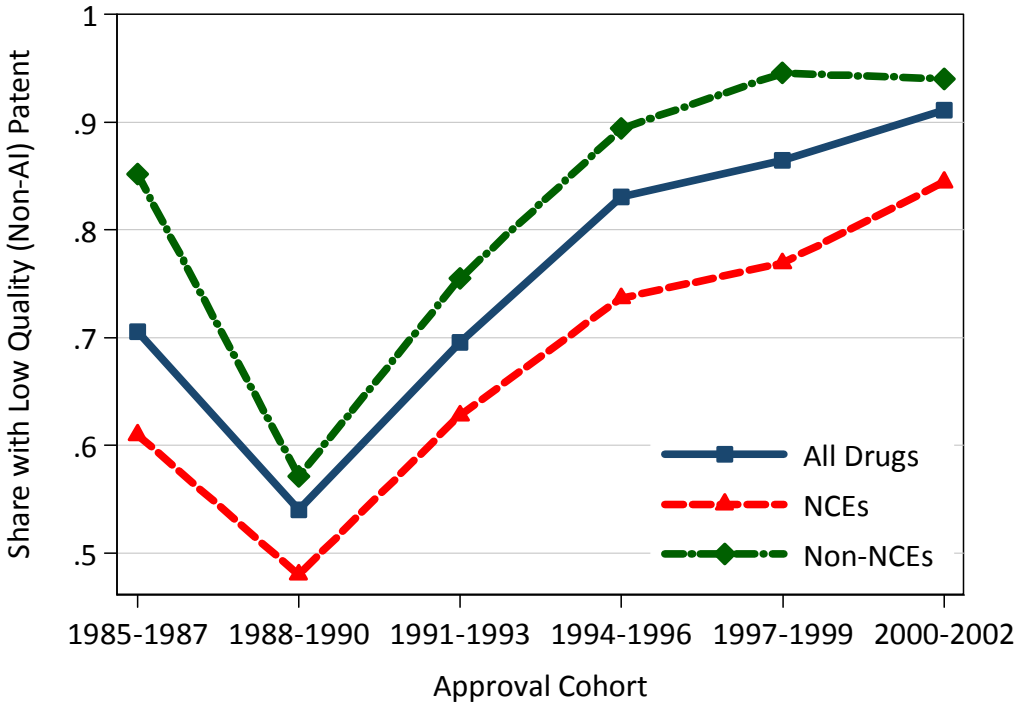
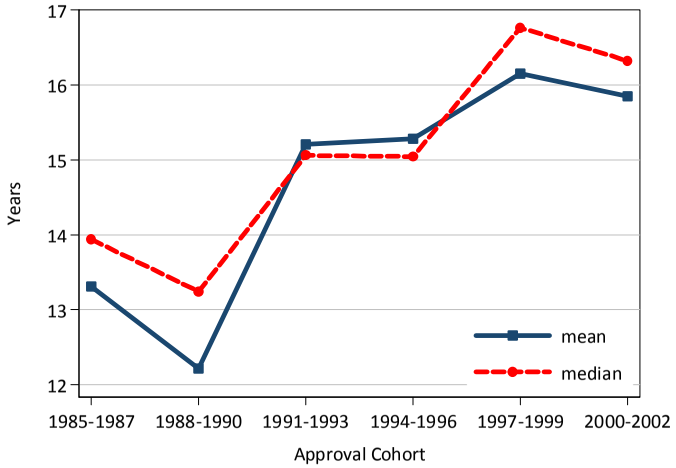
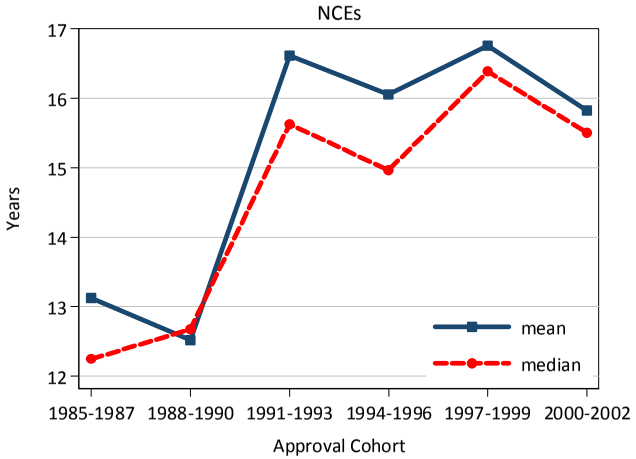


Figure 3: Years of Nominal Patent Life





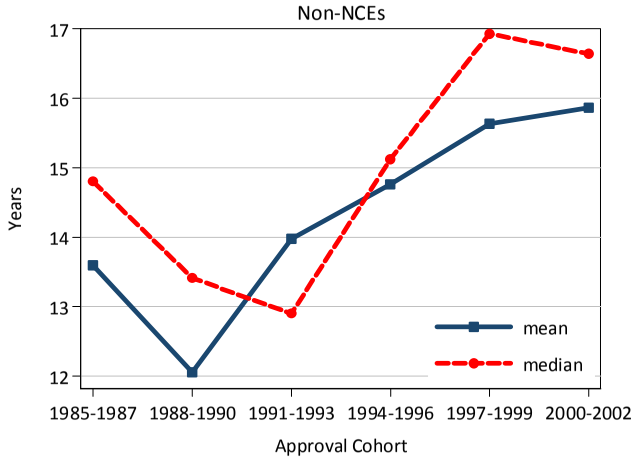


Figure 4: Share of Drugs with Paragraph IV Challenge

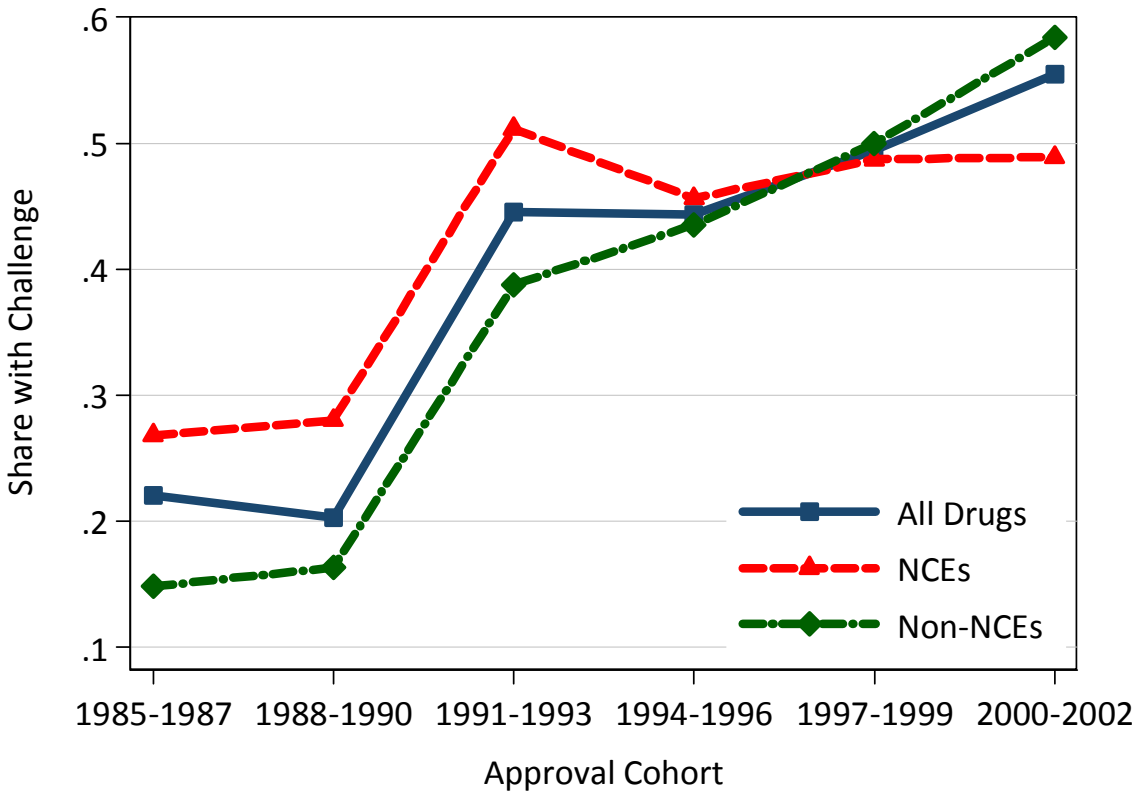
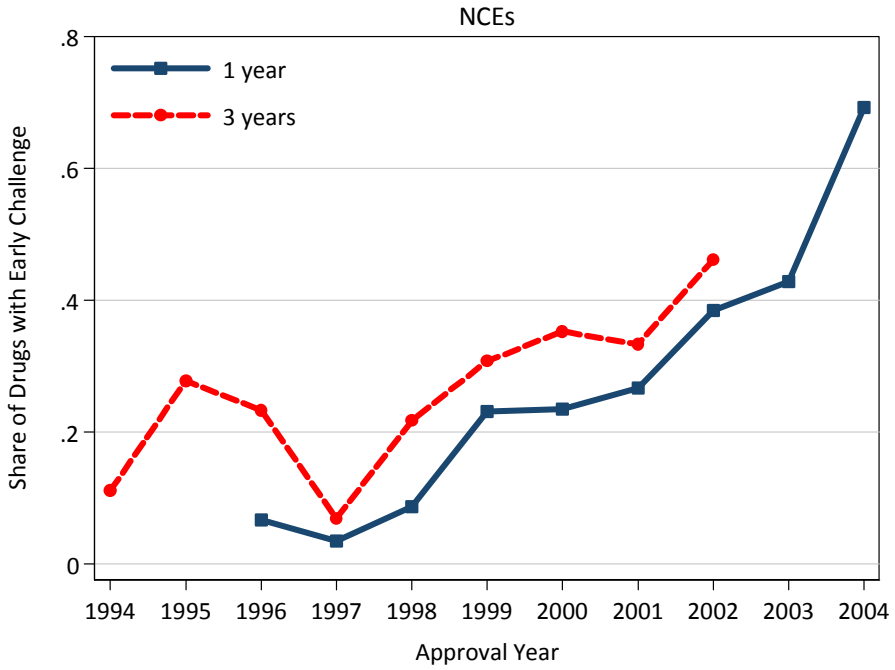


Figure 5: Share of Drugs with Early Paragraph IV Challenge



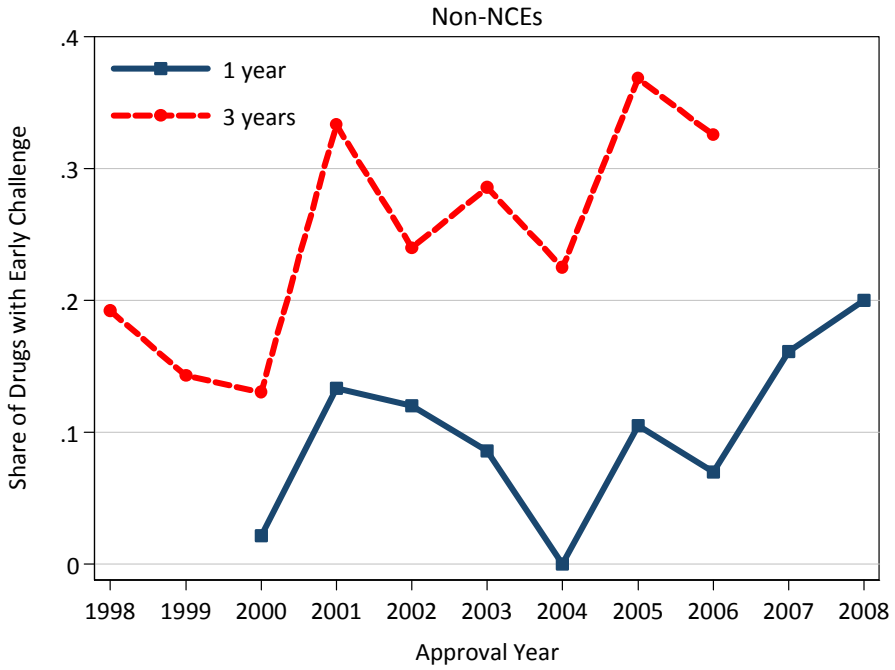


Figure 6: Predicted Values of Hazard of Challenge by Drug Type

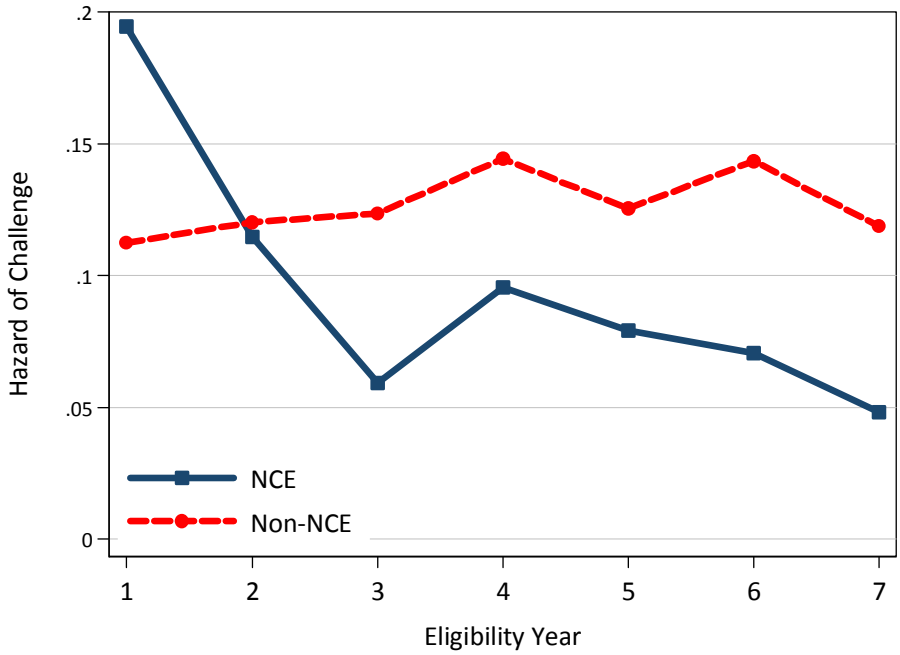


Figure 7: Predicted Values of Hazard of Challenge by Patent Portfolio

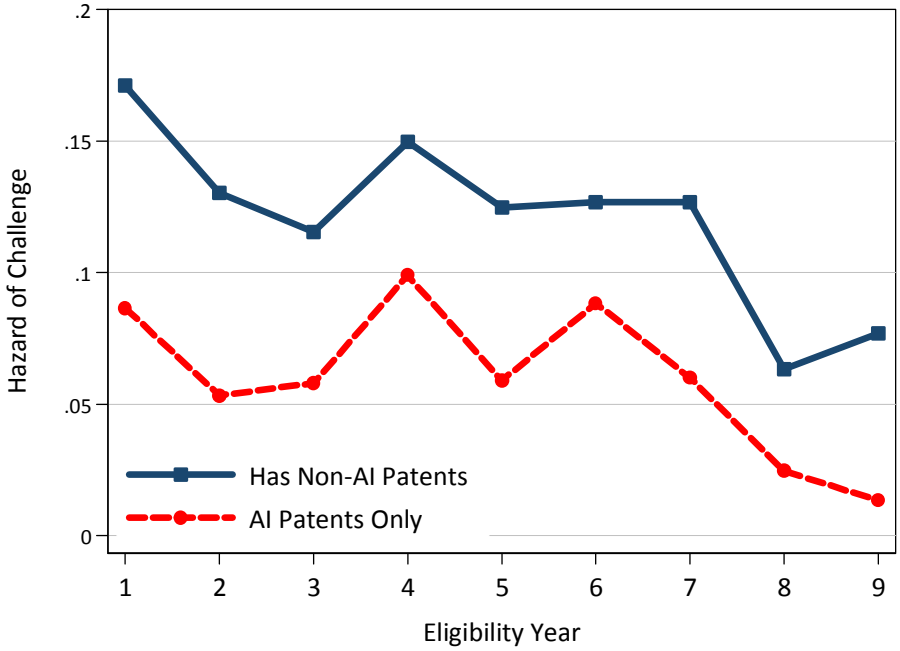


Table 1

Description of Variables

Paragraph IV challenge	=1 if a generic drug maker, in year *t*, officially asserts to FDA its plan to launch a competing therapeutically equivalent drug, and that one or more brand-name patents are invalid or not infringed
Sales	Sales of drug in year *t* (annualized $ billions)
Oral dosage form	=1 if drug offered in a tablet, capsule, or liquid form
New chemical entity	=1 if drug contains a novel active ingredient (see Appendix for details); exempt from challenge during the first four years after approval
Therapeutic class dummies	Indicators for primary use of drug (e.g., cardiovascular)
Observation year dummies	Indicators for observation year (2001 through 2009)
Eligibility year dummies	Indicators for years since drug's initial eligibility for challenge (1 through 9)
Future sales	Sales of all other drugs in therapeutic class in year *t*+3
<u>Patent type</u>	
AI only	=1 if all patents pertain to the drug's active ingredient (AI); excludes patents on enantiomers or other isomers or polymorphs and other crystal forms
Non-AI only	=1 if no patents pertain to the drug's AI
Both types	=1 if at least one patent pertains to the AI, and at least one does not
<u>Effect of non-AI patents</u>	
Extra time from non-AI	=1 if both types of patent, and last non-AI patent expires later than last AI patent
Extra years from non-AI	Years of difference between expiration of last-expiring non-AI patent and last-expiring AI patent (=0 if no additional life)
<u>Other patent measures</u>	
First quartile citations	Number of patents containing at least one patent in the first quartile of forward citations, among patents issued in that year
First quartile family size	Number of patents containing at least one patent in the first quartile, among patents issued in that year, of number of jurisdictions in which patent was applied for
Early patents	Number of patents with application filed prior to drug approval
Late patents	Number of patents with application filed after drug approval

Table 2

Summary of Variables

	Mean	Std. dev.	Min	Max
Paragraph IV challenge	0.51	0.50	0	1
Oral dosage form	0.66	0.48	0	1
New chemical entity	0.35	0.48	0	1
Old antibiotics	0.07	0.26	0	1
Approval year	2001.87	3.54	1990	2008
Sales ($ billion)	0.20	0.51	0	5.99
Patents				
AI only	0.12	0.33	0	1
Non-AI only	0.47	0.50	0	1
Both AI and non-AI	0.41	0.49	0	1
No extra time from non-AI	0.08	0.28	0	1
Extra time from non-AI	0.33	0.47	0	1
Extra years from non-AI	1.86	3.46	0	17.2
Bottom citations	0.98	1.27	0	8
Bottom family size	0.79	1.43	0	9
Early patents	3.26	3.06	0	25
Late patents	0.36	1.07	0	9

$N = 479$.

Table 3

Data Structure of Duration Analysis

Period	Challenge		No challenge		Censored		Total
1	77	16.1%	362	75.6%	40	8.4%	479
2	43	12.0%	292	81.8%	22	6.2%	357
3	31	10.8%	228	79.4%	28	9.8%	287
4	32	14.2%	171	76.0%	22	9.8%	225
5	19	11.4%	131	78.4%	17	10.2%	167
6	15	12.0%	81	64.8%	29	23.2%	125
7	9	11.2%	56	70.0%	15	28.8%	80
8	3	5.4%	32	57.1%	21	37.5%	56
9	2	6.4%	0	0.0%	29	93.6%	31
Total	231		1353		223		1807

Table 4

Logit Model of Hazard of Challenge—Baseline and Standard Patent Measures

(Dependent variable: challenge = 1 if drug *i* is challenged in year *t*)

	(1)	(2)	(3)	(4)	(5)	(6)
Sales	1.214***	1.172***	1.242***	1.269***	1.178***	1.168***
	(0.302)	(0.296)	(0.300)	(0.299)	(0.301)	(0.276)
Oral dosage form	1.090***	1.118***	1.158***	1.143***	1.138***	1.074***
	(0.285)	(0.296)	(0.292)	(0.295)	(0.296)	(0.286)
NCE	–0.024	-0.003	-0.031	0.037	-0.088	-0.151
	(0.196)	(0.198)	(0.197)	(0.203)	(0.203)	(0.199)
Old antibiotics	0.485	0.522	0.567	0.565	0.331	0.120
	(0.623)	(0.621)	(0.616)	(0.607)	(0.644)	(0.635)
Patents						
Total patents		0.020				
		(0.031)				
First quartile citations			0.141**			
			(0.057)			
Other citations			-0.017			
			(0.037)			
First quartile family size				0.123**		
				(0.057)		
Other family size				-0.008		
				(0.036)		
Late patents					0.282***	
					(0.106)	
Early patents					-0.018	
					(0.034)	
Nominal patent term						0.094***
						(0.025)
Constant	–7.350***	-7.449***	-7.459***	-7.584***	-7.766***	-8.778***
	(1.367)	(1.377)	(1.381)	(1.408)	(1.376)	(1.416)
Eligibility year indicators	Yes	Yes	Yes	Yes	Yes	Yes
Obs. Year indicators	Yes	Yes	Yes	Yes	Yes	Yes
Therapeutic class f.e.	Yes	Yes	Yes	Yes	Yes	Yes
Observations	1807	1807	1807	1807	1807	1807

Standard errors clustered by drug are in parentheses. Asterisks indicate statistical significance at the *** 1%, ** 5%, and * 10% levels.

Table 5

Logit Model of Hazard of Challenge

Quality Measures Based on Patent Type (AI vs. Non-AI)

(Dependent variable: challenge = 1 if drug *i* is challenged in year *t*)

	(7)	(8)	(9)	(10)
Sales	1.207***	1.205***	1.198***	1.352***
	(0.304)	(0.303)	(0.297)	(0.282)
Oral dosage form	1.209***	1.213***	1.127***	1.093***
	(0.299)	(0.299)	(0.301)	(0.299)
NCE	0.100	0.105	0.158	0.161
	(0.205)	(0.205)	(0.209)	(0.206)
Old antibiotic	0.680	0.673	0.596	0.792
	(0.617)	(0.616)	(0.616)	(0.637)
Patents				
Total patents	-0.007	-0.008	0.005	-0.019
	(0.034)	(0.034)	(0.032)	(0.034)
Non-AI only	0.975***	0.986***	0.567**	1.230***
	(0.364)	(0.364)	(0.252)	(0.389)
Both types	1.021***			
	(0.352)			
No extra time from non-AI		0.894**		1.099**
		(0.448)		(0.468)
Extra time from non-AI		1.054***		
		(0.356)		
Extra years from non-AI			0.095***	
			(0.031)	
First quartile				0.704
				(0.563)
Second quartile				1.457***
				(0.434)
Third quartile				1.472***
				(0.412)
Top quartile				2.041***
				(0.502)
Constant	-8.344***	-8.355***	-8.006***	-8.653***
	(1.462)	(1.464)	(1.448)	(1.555)
Eligibility year indicators	Yes	Yes	Yes	Yes
Obs. Year indicators	Yes	Yes	Yes	Yes
Therapeutic class f.e.	Yes	Yes	Yes	Yes
Observations	1807	1807	1807	1807

Standard errors clustered by drug are in parentheses. Asterisks indicate statistical significance at the *** 1%, ** 5%, and * 10% levels.

Table 6

Logit Model of Hazard of Challenge

Alternative Measures of Extra Time from Non-AI Patents

(Dependent variable: challenge = 1 if drug *i* is challenged in year *t*)

	(11)	(12)	(13)
Sales	1.207***	1.204***	1.323***
	(0.302)	(0.297)	(0.281)
Oral dosage form	1.217***	1.123***	1.098***
	(0.299)	(0.301)	(0.298)
NCE	0.115	0.173	0.159
	(0.206)	(0.210)	(0.207)
Old antibiotic	0.655	0.605	0.738
	(0.613)	(0.617)	(0.630)
Patents			
Total patents	-0.011	0.002	-0.012
	(0.034)	(0.032)	(0.034)
Non-AI only	1.001***	0.607**	1.046***
	(0.363)	(0.255)	(0.364)
Both types			
No extra time from non-AI	0.625		0.607
	(0.485)		(0.486)
Extra time from non-AI	1.103***		
	(0.355)		
Extra years from non-AI		0.103***	
		(0.031)	
First quartile			0.559
			(0.518)
Second quartile			1.237***
			(0.412)
Third quartile			1.275***
			(0.388)
Top quartile			1.832***
			(0.481)
Constant	-8.359***	-8.035***	-8.480***
	(1.468)	(1.454)	(1.533)
Eligibility year indicators	Yes	Yes	Yes
Obs. Year indicators	Yes	Yes	Yes
Therapeutic class f.e.	Yes	Yes	Yes
Observations	1807	1807	1807

Standard errors clustered by drug are in parentheses. Asterisks indicate statistical significance at the *** 1%, ** 5%, and * 10% levels.

Table 7

Logit Model of Hazard of Challenge

Non-Parametric Sales

(Dependent variable: challenge = 1 if drug *i* is challenged in year *t*)

	(14)	(15)	(16)	(17)
Sales				
Second quartile	1.137**	1.138**	1.122**	1.154**
	(0.487)	(0.486)	(0.482)	(0.478)
Third quartile	3.070***	3.069***	3.064***	3.082***
	(0.488)	(0.487)	(0.480)	(0.479)
Fourth quartile	4.251***	4.251***	4.240***	4.258***
	(0.490)	(0.488)	(0.482)	(0.480)
Oral dosage form	1.694***	1.697***	1.606***	1.598***
	(0.369)	(0.369)	(0.371)	(0.372)
NCE	-0.239	-0.232	-0.211	-0.205
	(0.212)	(0.212)	(0.215)	(0.214)
Old antibiotic	0.224	0.217	0.127	0.237
	(0.774)	(0.769)	(0.766)	(0.779)
Patents				
Total patents	-0.027	-0.028	-0.018	-0.037
	(0.028)	(0.028)	(0.028)	(0.030)
Non–AI only	0.804**	0.819**	0.437*	0.810**
	(0.351)	(0.352)	(0.256)	(0.327)
Both types	0.881***			
	(0.337)			
No extra time from non-AI		0.745*		0.721*
		(0.427)		(0.415)
Extra time from non-AI		0.914***		
		(0.346)		
Extra years from non-AI			0.077**	
			(0.031)	
First quartile				0.727
				(0.487)
Second quartile				0.873**
				(0.361)
Third quartile				0.901**
				(0.359)
Top quartile				1.564***
				(0.469)
Constant	-10.444***	-10.438***	-10.030***	-10.250***
	(1.497)	(1.497)	(1.481)	(1.483)
Eligibility year indicators	Yes	Yes	Yes	Yes
Obs. Year indicators	Yes	Yes	Yes	Yes
Therapeutic class f.e.	Yes	Yes	Yes	Yes
Observations	1807	1807	1807	1807

Standard errors clustered by drug are in parentheses. Asterisks indicate statistical significance at the *** 1%, ** 5%, and * 10% levels.

Table 8

Logit Model of Hazard of Challenge

Lagged Sales

(Dependent variable: challenge = 1 if drug *i* is challenged in year *t*)

	(18)	(19)	(20)	(21)
Sales				
Current	-0.447	-0.409	-0.458	-0.461
	(0.934)	(0.940)	(0.982)	(1.005)
1 year lag	2.519	2.446	2.595	2.770
	(1.673)	(1.687)	(1.745)	(1.832)
2 year lag	-1.231	-1.199	-1.256	-1.315
	(1.345)	(1.348)	(1.345)	(1.462)
3 year lag	0.715	0.722	0.645	0.788
	(1.328)	(1.329)	(1.278)	(1.249)
Oral dosage form	1.358***	1.364***	1.287***	1.232***
	(0.325)	(0.325)	(0.328)	(0.324)
NCE	0.014	0.020	0.097	0.079
	(0.232)	(0.232)	(0.233)	(0.227)
Old antibiotic	0.550	0.538	0.479	0.636
	(0.619)	(0.619)	(0.621)	(0.641)
Patents				
Total patents	-0.022	-0.023	-0.015	-0.042
	(0.037)	(0.037)	(0.034)	(0.037)
Non–AI only	0.886**	0.901**	0.570**	1.175***
	(0.371)	(0.371)	(0.267)	(0.392)
Both types	1.055***			
	(0.356)			
No extra time from non-AI		0.892*		1.100**
		(0.455)		(0.482)
Extra time from non-AI		1.098***		
		(0.360)		
Extra years from non-AI			0.124***	
			(0.031)	
First quartile				0.712
				(0.543)
Second quartile				1.393***
				(0.450)
Third quartile				1.564***
				(0.427)
Top quartile				2.519***
				(0.507)
Constant	-4.772***	-4.775***	-4.452***	-5.029***
	(1.168)	(1.169)	(1.129)	(1.171)
Eligibility year indicators	Yes	Yes	Yes	Yes
Obs. Year indicators	Yes	Yes	Yes	Yes
Therapeutic class f.e.	Yes	Yes	Yes	Yes
Observations	1624	1624	1624	1624

Standard errors clustered by drug are in parentheses. Asterisks indicate statistical significance at the *** 1%, ** 5%, and * 10% levels.

Table 9

Logit Model of Hazard of Challenge

Future Sales

(Dependent variable: challenge = 1 if drug *i* is challenged in year *t*)

	(22)	(23)	(24)	(25)
Sales	2.049***	2.012***	2.087***	2.032***
	(0.702)	(0.712)	(0.731)	(0.719)
Future sales	0.673	0.651	0.717	0.571
	(0.530)	(0.540)	(0.547)	(0.582)
Oral dosage form	0.749*	0.748*	0.601	0.558
	(0.383)	(0.382)	(0.388)	(0.385)
NCE	0.281	0.306	0.364	0.394
	(0.262)	(0.263)	(0.267)	(0.265)
Patents				
Total patents	-0.007	-0.008	0.009	-0.020
	(0.049)	(0.050)	(0.046)	(0.050)
Non–AI only	0.937*	0.975*	0.466	1.185**
	(0.510)	(0.513)	(0.348)	(0.537)
Both types	1.151**			
	(0.508)			
No extra time from non-AI		0.821		0.983
		(0.737)		(0.741)
Extra time from non-AI		1.227**		
		(0.512)		
Extra years from non-AI			0.095**	
			(0.042)	
First quartile				0.848
				(0.758)
Second quartile				1.641***
				(0.567)
Third quartile				1.638***
				(0.568)
Top quartile				1.937***
				(0.664)
Constant	-6.864***	-6.929***	-6.365***	-7.194***
	(1.185)	(1.194)	(1.146)	(1.269)
Eligibility year indicators	Yes	Yes	Yes	Yes
Obs. Year indicators	Yes	Yes	Yes	Yes
Therapeutic class f.e.	Yes	Yes	Yes	Yes
Observations	1171	1171	1171	1171

Standard errors clustered by drug are in parentheses. Asterisks indicate statistical significance at the *** 1%, ** 5%, and * 10% levels.