Generic Drug Challenges Prior to Patent Expiration

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

December 7, 2009 Draft

Preliminary and Incomplete – Please Do Not Circulate or Cite

The Hatch-Waxman Act established the current regime for competition between brand-name and generic drugs. We examine a feature of the Act that has generated significant controversy, yet received 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. This article reports initial results from a larger empirical project investigating the determinants of Paragraph IV challenges and their effects.

We begin with a set of descriptive results about 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. During the same period, Paragraph IV challenges have increased as a share of drugs within an approval cohort. Drugs are also challenged sooner, relative to brand-name approval.

Our regression analysis shows that brand-name sales have a positive effect upon the likelihood of generic challenge and number of challengers, consistent with the view that patents that later prove to be valuable receive greater ex post scrutiny. The effect of patent protection upon Paragraph IV challenges varies by patent type. Product and composition patents, the strongest patent types, do not affect generic challenges, while the presence of weaker patents increases the likelihood of a challenge, conditional on sales and other drug features.

[*] Associate Professor of Law and Milton Handler Fellow, Columbia Law School.

[†] Assistant Professor, Department of Health Policy and Management, Mailman School of Public Health, Columbia University.

Generic Drug Challenges Prior to Patent Expiration
C. Scott Hemphill and Bhaven N. Sampat

Introduction

During the last century, new drugs have secured dramatic reductions in morbidity and mortality from disease (Murphy and Topel 2000; Lichtenberg 2007, 2009; Lichtenberg and Virabhak 2007). While the cost of discovering and testing a drug is large—some argue as high as $800 million (DiMasi et al. 2003)—the marginal cost of copying it is low. Pharmaceutical innovators in the United States rely upon two types of legal protection to protect their inventions from appropriation. The first source, patent law, is particularly important to pharmaceutical innovators, compared to other industries (Levin et al. 1987; Cohen, Nelson and Walsh 2000). In addition, a complex regulatory scheme run by the Food and Drug Administration (FDA) provides further protection against entry by so-called generic drug makers, which seek to offer a close copy of the brand-name drug (Eisenberg 2007; Thomas 2005). These protections are critical because once generic firms enter the market, prices fall, sometimes to less than 10 percent of the pre-entry price of the brand-name drug.

The Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, established the current regime for competition between brand-name and generic drugs. The Act has had a transformative effect on generic drug competition and utilization. When the Act was passed, generic drugs accounted for less than 20 percent of prescriptions (Frank 2007). Twenty-five years later, they account for 70 percent, compared to just 20 percent of expenditures (Engelberg et al. 2009). The savings from increased generic utilization has been large—more than $700

billion during the period from 1999 to 2008, according to an estimate commissioned by the Generic Pharmaceutical Association (IMS Health 2009).

Part of the increase in generic drug entry is due to a regulatory mechanism for generic drug makers to challenge brand-name drug makers' patents, prior to their expiration, in order to secure early FDA approval and market entry. The Act provides a means for a generic firm to assert that any applicable brand-name patents are invalid or not infringed. Such assertions, called "Paragraph IV challenges," frequently result in patent litigation between the brand-name and generic firms. The result of this challenge, in many cases, is early entry by the generic firm. Thus, Paragraph IV challenges are an important route to generic entry and lower drug prices.

Paragraph IV challenges are well-recognized as an important source of generic competition (FTC 2002; Grabowski 2004; Hemphill 2006). For this very reason, these challenges are the most controversial feature of the Hatch-Waxman regime (Engelberg 1999; Graham and Higgins 2009). Some commentators argue that Paragraph IV challenges are necessary to clear away patents, increasingly asserted by brand-name pharmaceutical firms, that are of questionable validity (Engelberg 1999). Given that the Patent Office lacks the capability to make a thorough evaluation of the validity of every patent (Lemley and Sampat 2009), these challenges serve a useful role in distinguishing valid, infringed patents from those that do not in fact block the marketing of a competing generic drug.

On the other hand, Grabowski (2004) and others argue that the strategy of generic drug makers—to challenge many brand-name products, in the hope of winning as to a few of them—increases uncertainty and reduces innovation incentives for brand-name

firms. Gal and Shari (2007) report a widespread suspicion that generic firms are "legal sharks that take advantage of loopholes." Graham and Higgins (2009) suggest that these challenges have a significant negative impact on effective patent life and research incentives.

Paragraph IV challenges have also been the setting for a controversial practice by brand-name firms. When a generic firm secures early entry, in many cases the brand-name firm launches an "authorized generic" product in competition with the generic firm (FTC 2009). Recent work suggests that authorized generic drugs increase price competition, and thereby provide static welfare benefits to consumers, but little is known about whether the resulting reduction in generic-firm profits might have a significant dynamic effect, by reducing the incentive to challenge weak patents in the first place.

While the source of much debate, these issues have been subject to little systematic empirical work. Understanding the determinants of Paragraph IV challenges, their impact, and the outcome of litigation is crucial for assessing whether the current regime needs amendment, whether it should be extended to other arenas (e.g., biotechnology drugs, see Engelberg et al. 2009), and whether the U.S. regime should be emulated in other nations (Ollier 2007). This paper begins to fill that gap, by providing an account of which drugs attract Paragraph IV challenges, and how and why that pattern has changed over time.

In this paper, we bring novel data to bear on these issues. We examine a new dataset of drugs approved by the FDA between 1995 and 2002, and study how the type of drug, its sales, and the extent of patent protection, among other factors, affect the probability of a Paragraph IV challenge. We also relate the timing and intensity of these

challenges to the same variables. Ours is the first paper, to our knowledge, to examine the likelihood and intensity of Paragraph IV challenges as a function of brand-name drug attributes, and the first to assess how the size and composition of patent portfolios, including different types of issued patents, relate to the likelihood of a Paragraph IV challenge.

This paper proceeds in five parts. Part I reviews previous studies of generic drug entry and patent policy that inform our inquiry. Part II provides a further introduction to the Hatch-Waxman regime, focusing upon the institutional details of Paragraph IV challenges. Part III presents new descriptive results, tracing the growth of patent portfolios for brand-name drugs and the contemporaneous increase in Paragraph IV challenges. Part IV describes the data we use in our regression analysis, explains our empirical approach, and reports the results. Part V concludes by discussing these results, their implications for several ongoing debates, and directions for future research.

I. Previous Studies

Our study connects prior analyses of generic drug entry with economic studies examining the role of patents. Generic drug entry has received significant theoretical and empirical attention. Health economists have focused upon the importance of entry for defining the availability of low generic drug prices, and scholars of industrial organization have examined determinants of generic entry.

Much of this previous work focuses upon post-expiration entry, rather than the pre-expiration entry by Paragraph IV challenge that we study here. For example, Scott Morton (1996) studies how generic entry is determined by generic-firm specialization

over time as to particular dosage forms, therapeutic classes, or molecules. One conclusion is that entry increases with market size, but less than linearly, as predicted by Bresnahan and Reiss (1987). Reiffen and Ward (2005) provide structural estimates of the price decrease that accompanies post-expiration generic entry. The data used in these studies pertains to entry only up through the 1990s. Pre-expiration entry became much more important in the late 1990s, after a legal change that made Paragraph IV challenges more financially attractive.[1] Our work builds upon these and other studies by focusing upon this later period, and by shifting the focus from post-expiration entry to pre-expiration entry.

Additional work has assessed the effect of Paragraph IV challenges upon the duration of patent protection. Grabowski and Kyle (2007) study a sample of drugs that were subjected to generic competition between 1995 and 2005, to evaluate changes over time in the effective exclusivity period for approved drugs, thus effectively testing the theoretical proposition of Grabowski (2004) that Paragraph IV challenges have the effect of reducing the duration of exclusivity. They conclude that this period indeed has decreased over time, and that the fact of a Paragraph IV challenge is one cause of the decrease. Our focus is different, as we seek to understand what gives rise to the Paragraph IV challenge in the first place. Our strategy is also different in that we examine cohorts of approved brand-name drugs, rather than only those drugs that have experienced generic competition. (Grabowski and Kyle (2007) also perform a forward-looking analysis for certain drugs introduced between 1980 and 1989.) Doing so avoids a censoring problem from considering only those drugs that have already experienced

[1] Prior to this change, a generic firm had to win the patent infringement suit in order to enjoy a valuable bounty, a 180-day exclusivity period discussed in detail below. Afterward, to simplify somewhat, it needed merely to avoid losing the suit in order to enjoy the exclusivity upon securing FDA approval.

generic competition, and permits us to observe the difference between drugs that have received Paragraph IV challenges and those that have not.

Paragraph IV challenges have also received attention in the context of authorized generic products. Berndt et al. (2007a) provide a theoretical argument that authorized generics are most likely to suppress Paragraph IV challenges for drugs with small sales, on the view that the incentives for challenges are smallest for such drugs. We provide large-sample evidence that this is indeed the case. Reiffen and Ward (2007) use the estimates of Reiffen and Ward (2005), and other earlier studies, to predict the effect of a second "branded generic" product, but as in their earlier piece, the authors focus upon post-expiration entry, and do not use data from Paragraph IV challenges.

Closest to the present project is Berndt et al. (2007b), a study providing empirical evidence that neither the number of drugs receiving first Paragraph IV challenges nor the intensity of challenges has fallen during the period over which authorized generic products have increased. The study employs a mix of data, including a proprietary survey furnished by an industry group, the Pharmaceutical Research and Manufacturers of America. This study briefly considers the effect of sales on the intensity of Paragraph IV challenge (though not whether a challenge occurs), providing a count of such drugs within their proprietary sample at different sales levels, both with and without an authorized generic product. We use an expanded set of drugs, make use of new data, and analyze the results in a regression setting.

In addition to extending and expanding on this previous work, our study is the first to assess the relationship between brand-name patents and Paragraph IV challenges or generic 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 uncertainty as to whether they cover the product of an alleged infringer. This uncertainty is also a natural consequence of the light scrutiny that patents receive during the application process (Lemley 2001), due in part to differences in the strictness of different patent examiners (Lemley and Sampat 2009; Cockburn et al. 2002). 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 litigation relative to its alternatives. 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. Thus, 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 on. One condition of effective ex post review, then, is that the likelihood of intensive review should increase with the value of the patented invention.

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. In pharmaceuticals, the interaction between patents and regulation, discussed below in Part II, means that even a single weak patent can hold up FDA approval for several years. 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, the theoretical effect of a portfolio is to increase the likelihood that an incumbent can shut down a potential entrant, thereby permitting it to exclude producers of 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). 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.

II. How Paragraph IV Challenges Work

Paragraph IV 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 so-called 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 patented drug on the market, a generic firm may seek to market a competing version of the same drug by filing an Abbreviated New Drug Application, or ANDA, with the FDA. An ANDA includes a number of demonstrations, the most important of which is "bioequivalence," essentially a showing that the rate and absorption of the active ingredient in the generic drug is the same as the brand-name drug.[2] New safety and efficacy studies are not required. ANDA preparation is much less expensive than NDA preparation, requiring an outlay on the order of $1 million (FDA 2003a).

For some, but not all, drugs, the generic firm seeks entry prior to the expiration of applicable patents. The set of applicable patents is listed by the brand-name firm in an FDA document, "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the Orange Book. The Orange Book lists the therapeutic equivalents, patent protection, and regulatory exclusivity for each brand-name drug. The generic firm, faced with this array of patent protection, may choose instead not to challenge any patents, in which case the FDA delays ANDA approval until patent expiration.

A generic firm seeking pre-expiration entry files an ANDA containing a Paragraph IV certification ("ANDA-IV"), asserting that applicable patents are invalid or not infringed by the proposed generic product.[3] The filing of an ANDA-IV is an act of patent infringement. In response to the ANDA-IV, the brand-name firm may file a patent

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

[3] There are three alternative certifications, called "Paragraphs" (although they are actually subclauses) I, II, and III. See 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV).

infringement suit to establish validity and infringement. This pattern—launch, challenge, sue—is frequent for major drugs. For example, at least 9 out of the 10 best-selling drugs of 2000, and 12 of the top 14 drugs of 2005, had Paragraph IV challenges (Hemphill 2006, 2009). That said, ANDA-IVs are a small fraction of all ANDAs—just 6 percent of ANDAs filed between 1984 and 2000 (FTC 2002)—though that figure has likely risen since 2000. Litigation raises the financial stakes to a generic firm considerably, to upwards of $10 million (Goodman 2004).

Paragraph IV challenges are games of simultaneous entry. When generic firms learn of a brand-name drug approval, they each incur nonrecoverable expenditures to figure out how to make the drug, assess the market, and discern the strength of the brand-name patent portfolio, particularly whether and how it can be evaded. Each generic firm is largely in the dark about the similar, parallel efforts of other firms. Even after the FDA has accepted an ANDA-IV for filing, the identity of the filer is not disclosed. The FDA does disclose the fact that at least one ANDA-IV has been filed, as well as the date of the first filing.

ANDA-IV-based patent litigation has two special features. First, once an ANDA-IV is filed, and provided that the brand-name firm files a timely patent suit in response, a statutory stay blocks FDA approval for the first several years of the suit's pendency.[4] Second, the first generic firm to file an ANDA-IV 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 is intended as a bounty to generic firms that incur the costs of patent challenges.

[4] The stay takes effect provided that the brand-name firm files suit within 45 days of receiving notice of the Paragraph IV certification. The stay normally lasts for 30 months, measured from the brand-name firm's receipt of notice of the ANDA-IV.

There are several types of brand-name drugs that are subject to Paragraph IV challenges. Some drugs contain a novel active ingredient, called "new chemical entities" or "new molecular entities" (NMEs). Some have argued that these are the most innovative drugs (NIHCM 2002). Other drugs are essentially improved versions or variants that contain a previously approved active ingredient. For example, the drug may be offered in a different dosage form (e.g., tablets rather than capsules), 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). NMEs receive special regulatory protection, in that the FDA may not accept an ANDA-IV for filing during the first four years after approval of the brand-name drug maker's NDA.[5] For other drugs, an ANDA-IV may be filed immediately after NDA approval, though the ANDA-IV may not be approved during the first three years after NDA approval.

This difference in regulatory protection alters the competitive dynamic by changing the amount of time a generic firm has to mount a challenge. For non-NME drugs, once the drug is approved, generic firms are immediately in a race to be the first to file an ANDA-IV. If one firm beats the others by a day or more, the losers forfeit any chance at the 180-day exclusivity.[6] For NMEs, by contrast, generic drug makers have four years after NDA approval to perfect their ANDAs before filing. There is much less

[5] 21 U.S.C. § 355(j)(5)(F)(ii) (Supp. III 2003). If a generic firm files an ANDA-IV between four and five years after NDA approval, the automatic stay is lengthened beyond 30 months, so that it expires seven-and-a-half years after NDA approval. § 355(j)(5)(F)(ii).

[6] This statement must be qualified, because the filing of an additional brand-name patent in the Orange Book in some cases provided generic firms with 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.

need to race. One consequence is that for some NMEs, multiple generic firms file on the first day on which it is possible to do so. In 2003, the FDA concluded that multiple first-filers that file on the same day share in the exclusivity entitlement (FDA 2003b), and this view was codified by statute later that year.[7] The FDA's limited disclosure policy has the consequence that once the FDA discloses the date of first filing, the generic firm learns that it is among the first filers, but it does not know how many other first-filers there are, or their identities, unless and until the brand-name drug maker sues them.

III. The Rise in Patent Portfolios and Paragraph IV Challenges

Our dataset 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 2012 new brand-name drugs approved between 1985 and 2008, collected from an FDA database (FDA 2009a). A drug is one or more active ingredients 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, approval date, and drug type (e.g., NME) as classified by the FDA. 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, using information from current and past editions of the Orange Book (FDA 1995-2009). The Orange Book contains a comprehensive but not perfectly exhaustive account of a drug's

[7] § 355(j)(5)(B)(vi)(I) (sharing exclusivity among first applicants); § 355(j)(5)(B)(iv)(II)(bb) (defining first applicant).

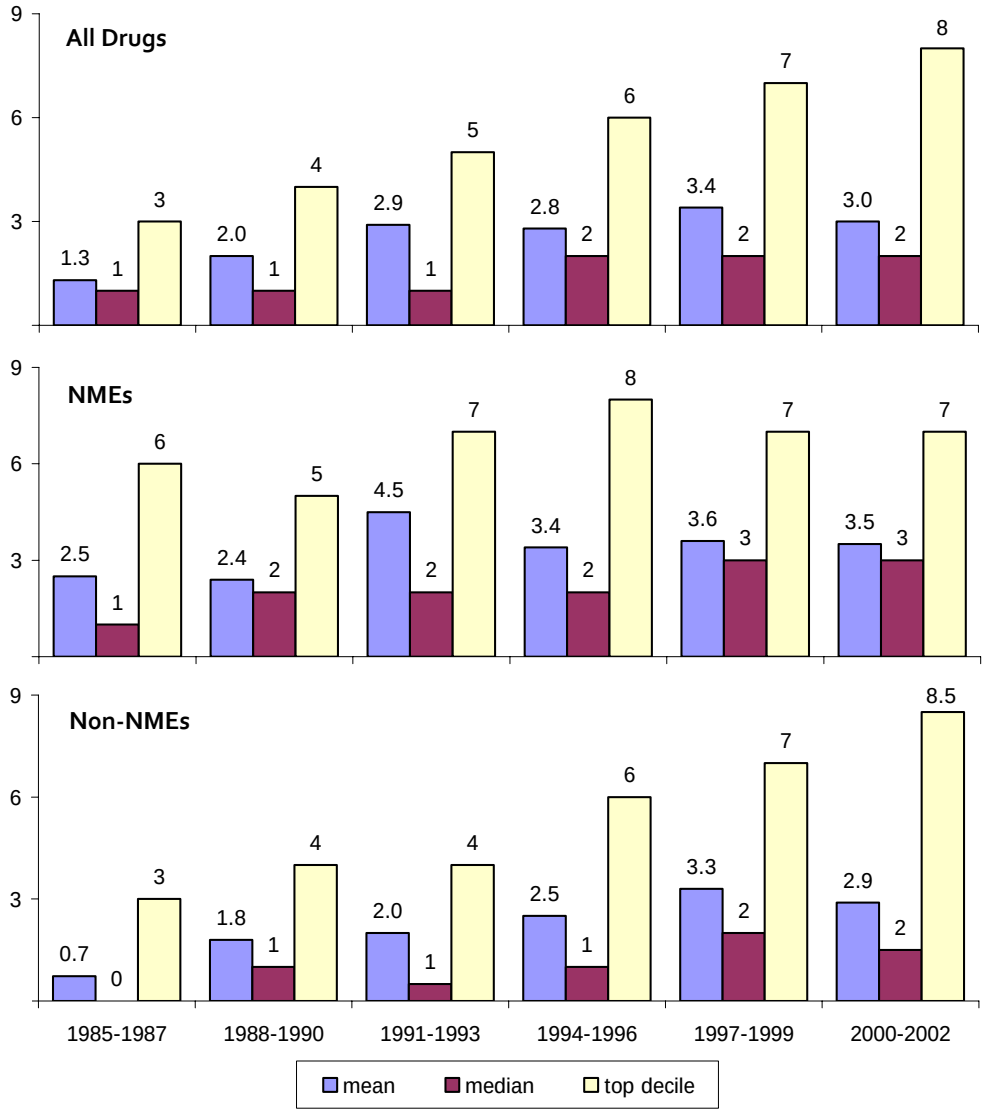
patent protection. A brand-name drug maker is required to list any patent containing at least one claim that covers the drug's active ingredient, its formulation, or any "method of use" that pertains to an approved indication (e.g., inhibiting cholesterol biosynthesis). If the patent is not listed, the generic firm filing an ANDA need not make any certification as to it, and the patent poses no bar to FDA approval, nor can it provide the basis for the automatic stay. 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 our initial assessment suggests that these instances are rare.

Our first analyses examine how the ratio of patents to products has changed over time. Our measure is the number of unique patents for an approved drug that are listed in any version of the Orange Book. We collect the drugs into a series of six three-year approval cohorts starting in 1985 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.

Figure 1 shows trends over time in the number of patents per drug. Drugs in the first cohort, approved between 1985 and 1987, had an average of 1.3 patents per drug. By the final (2000 to 2002) cohort, the mean more than doubles to three patents per drug. The median increases too. The right tail of the distribution is even more striking. As Figure 1 shows, the top decile of the distribution increases steadily from three patents per drug to eight patents per drug. In other words, the top ten percent of patent portfolio builders, among drug approvals in the first several years of the Act, had three or more

patents per drug, while the top portfolio builders fifteen years later had portfolios more than double that size.

FIGURE 1
NUMBER OF PATENTS PER DRUG BY APPROVAL COHORT



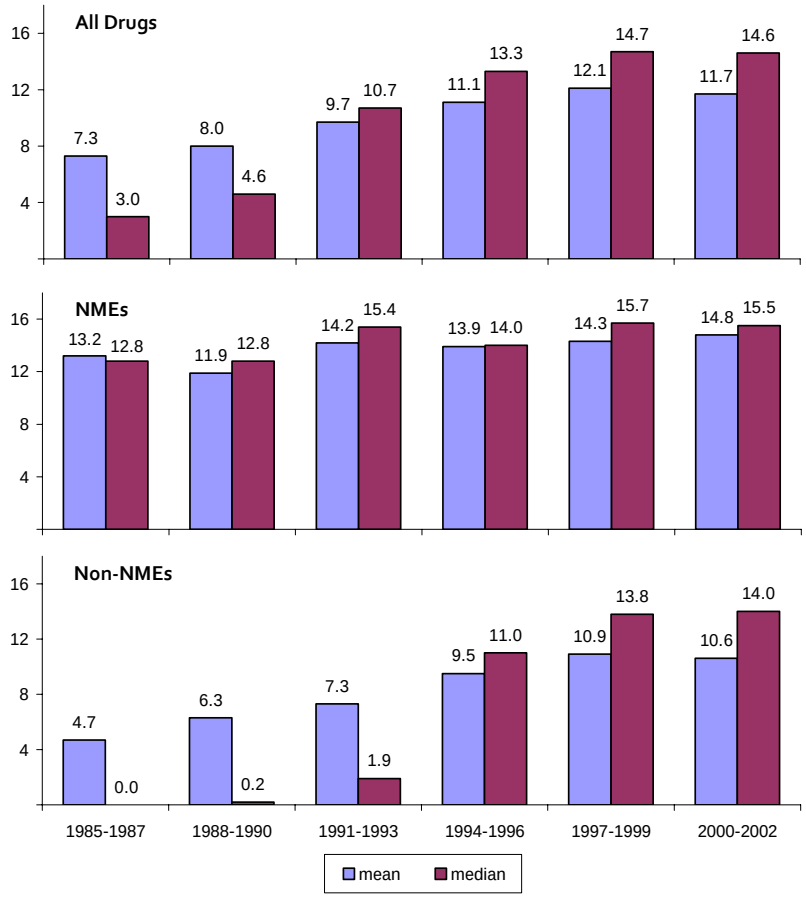
This trend plays out differently for different types of drug. Figure 1 depicts the mean, median, and top decile of patents per drug for NME and non-NME drugs. For each cohort, NMEs tend to have more patents on average. The median and top decile are larger

too, except for the final cohort, for which non-NME drugs have more patents per drug in the top decile (8.5 versus 7). Breaking out the trends by drug type also reveals a dramatic increase in top-decile patenting for non-NME drugs, from 3 patents per drug in the first cohort to more than 8 in the final cohort. These trends are also reflected in the full distribution, reported in Appendix 1.

The patents within a portfolio, although they all pertain to the same drug, do not all expire at the same time. Some expire many years later, providing a substantial temporal extension in a brand-name drug maker's exclusivity, at least in theory. Brand-name firms and other market participants often use the date of the last-expiring patent in their announcements and discussions of when a drug goes off-patent. We call the lag between a drug's approval date and the date of its last-expiring patent (in any version of the Orange Book) the "nominal" patent life for that drug.

Figure 2 shows the increase in nominal patent life over time, again grouped by approval cohort. NMEs have seen an increase in mean nominal patent life of almost two years, from 13.2 years to 14.8 years. The increase for non-NME drugs has been much more dramatic, a more than doubling from 4.7 years to 10.6 years. This dramatic increase is due in part to a large number of non-NME drugs in the first several approval cohorts that have no Orange Book-listed patents. The large number of zeroes is reflected in the median patent life for non-NME drugs in the first three cohorts, and in the full distribution reported in Appendix 2.

FIGURE 2
MEAN AND MEDIAN YEARS OF NOMINAL PATENT LIFE BY APPROVAL COHORT



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 active ingredient are 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.

Some active ingredient patents are less "basic" than this initial account suggests. In some instances, the active ingredient is an "enantiomer"—a kind of chemical variant—of an existing molecule, and the generic firm can argue that the new drug is obvious and hence unpatentable in light of the prior art.[8] The case of Paxil, a blockbuster antidepressant, presents a second exception. Here, the basic active ingredient patent had expired. The primary remaining patent covered a particular "polymorph," or crystalline structure, of the active ingredient. A generic entrant might therefore try to market a distinct, noninfringing polymorph that is nevertheless bioequivalent to the brand-name drug, or, alternatively, argue that the patent was itself invalid.

In comparison to active ingredient 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.

For a generic drug maker, the presence of weak patents in a brand-name drug maker's portfolio, in addition to a strong active ingredient patent, has an obvious effect: it makes it less likely that the generic firm will win as to every patent, as well as more costly to fight them all. But it does not follow that the likelihood of a Paragraph IV

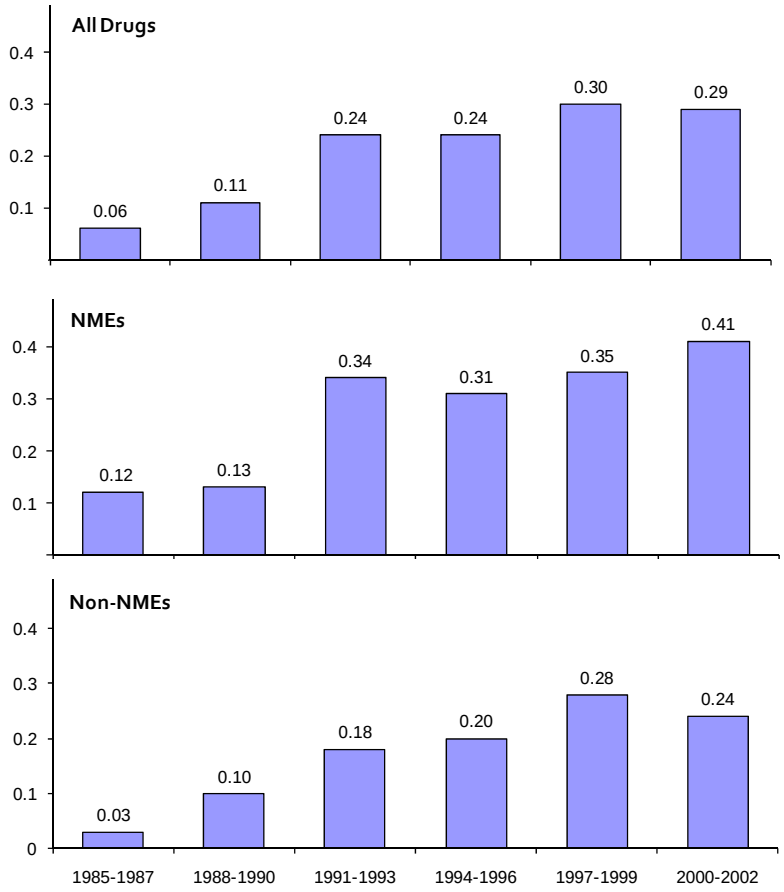
[8] Enantiomers are two compounds that are mirror images of one another, like left and right hands: similar but not identical, in that they are not superimposable. In some cases, a drug will be discovered at first as a mixture of left- and right-hand versions. But only the left-hand enantiomer is really doing the therapeutic work; the right-hand version has no effect or may even be harmful. Later, the left-hand enantiomer is separated, purified, and marketed separately as a new drug. The question is whether that purification of a single enantiomer is a nonobvious advance over the prior art, given the earlier disclosure of the mixture and knowledge about how to accomplish the separation and purification of a single enantiomer.

challenge is necessarily reduced. A weak patent could attract a challenger rather than deterring it. That is because the generic firm can earn the 180-day exclusivity period by challenging only the weak patent, while filing a certification that concedes the strong patent's validity and breadth. This is an attractive strategy when the strong, basic patent is expiring soon, and the weaker patent later. Had there been only a strong patent, the first-filing generic firm might not have filed a challenge, but the addition of another patent attracts a challenge. In that instance, the accumulation of patents in a portfolio is less like a fortress and more like a linked chain, only as strong as its weakest link.

To explore the importance of portfolio building, we collected information about individual patents listed in the Orange Book using the Patent Focus database maintained by IMS Health, the leading commercial provider of drug data. Patent Focus sorts individual patents into one or more categories: product, composition, process, method of use, or drug delivery system. We aggregated these patents into two categories. "Flagship" patents are product or composition patents. These patents claim the active ingredient or drug formulation, and are widely thought to be the primary means of protection. Non-flagship patents account for the rest.

In recent years, the use of non-flagship patents has increased dramatically, and may account for the increase in nominal patent term. Figure 3 traces out the trend, grouped by cohort. In the first cohort of NMEs, just 12 percent have a non-flagship patent listed in the Orange Book. By the time of the 2000 to 2002 cohort, more than two-fifths of approved NMEs have at least one non-flagship patent. Non-NMEs have seen similar growth. As discussed below, these patents have a significant effect upon the likelihood of a Paragraph IV challenge.

FIGURE 3
SHARE OF DRUGS WITH A NON-FLAGSHIP PATENT BY APPROVAL COHORT

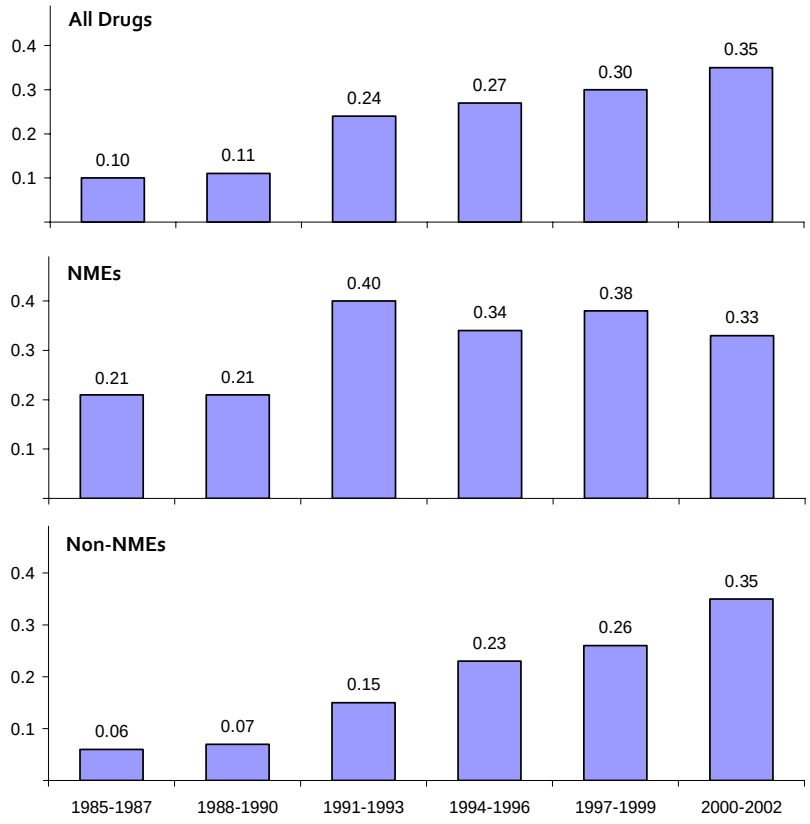


Paragraph IV Challenges

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 have attracted challenges as of August 2009 using a list of such drugs, which we call the "Paragraph IV List," maintained by the FDA (FDA 2009b). Comparing the Paragraph IV List to the set of approved brand-name drugs yields a set of 492 drugs (out of 2012) that have been subjected to Paragraph IV challenge by August 2009.

Overall, the fraction of drugs challenged has grown over time. We report the trends, grouped by approval cohort, in Figure 4. Overall, the fraction of drugs has increased from 10 percent of drugs approved in the first cohort to 35 percent in the last cohort. As a general matter, a larger share overall of NMEs (29 percent) than non-NMEs (21 percent) have been subjected to Paragraph IV challenges, a difference reflected in Figure 4. The most striking change, however, has been the rise in challenges against non-NMEs, from just 6 percent of non-NMEs approved in the first cohort, to more than a third (35 percent) of those approved in the last cohort.

FIGURE 4
SHARE OF DRUGS WITH PARAGRAPH IV CHALLENGE BY APPROVAL COHORT



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 challenge for first challenges that occurred in March 2004 or later, but does not report dates for earlier first challenges. We extended this data using two methods. First, from mid-2000 until March 2004, the FDA posted a list, updated monthly, of drugs receiving a first Paragraph IV challenge, though not the date of first challenges. By comparing archived versions of the list, we were able to identify the date of first challenge for some drugs. Second, we augmented these results with reports written by equity analysts at financial firms that track generic challenges. As a result, we are able to report information about first challenges from August 2000 through July 2009. As Table 1 reports, during this nine-year period, the number of drugs receiving first challenges has more than doubled.

TABLE 1
FREQUENCY OF FIRST PARAGRAPH IV CHALLENGE BY CHALLENGE YEAR

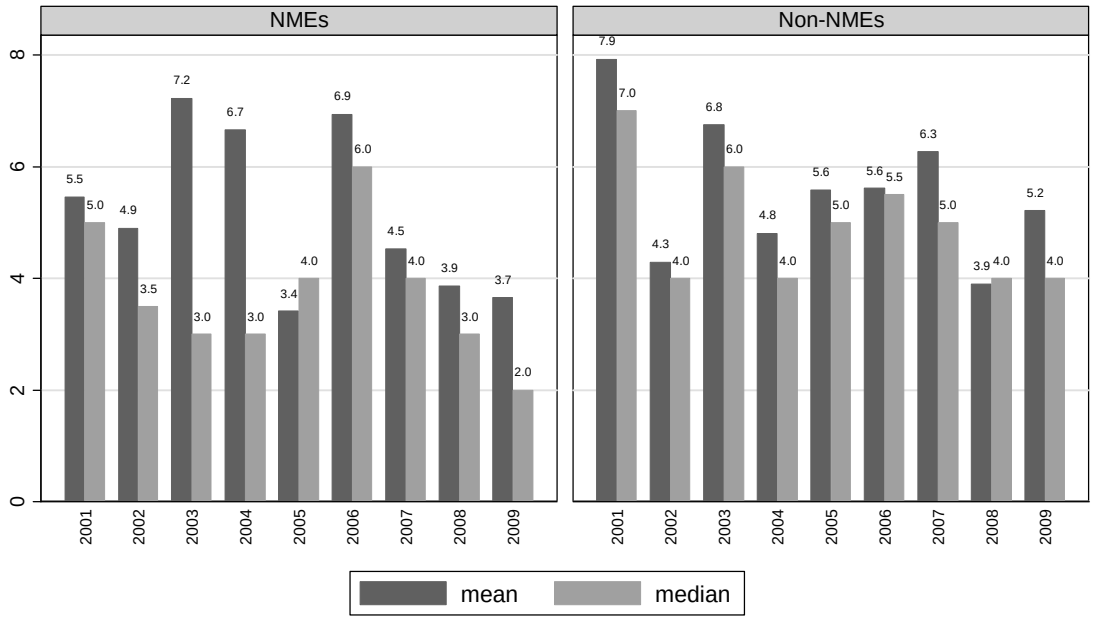
	Frequency	Percent	Cumulative
1985-2000	111	22.56	22.56
2001	26	5.28	27.85
2002	27	5.49	33.33
2003	38	7.72	41.06
2004	37	7.52	48.58
2005	42	8.54	57.11
2006	42	8.54	65.65
2007	50	10.16	75.81
2008	57	11.59	87.40
2009	62	12.60	100.00
Total	492	100.00	

Year extends from August to July; hence 2001 is August 2000 to July 2001.

Combining the year of Paragraph IV challenge with the year of brand-name NDA approval, we determine the average "time to challenge": the amount of time from the point a drug is available for challenge until it is challenged. For NMEs, a drug is

available for challenge four years after its approval. For other drug types, a challenge may be filed immediately after NDA approval, though in practice the generic drug maker needs time, at least a few months, to devise and implement a Paragraph IV strategy. Figure 5 depicts the mean and median lag between the year a drug is eligible to be challenged and actual challenge, reported by year of challenge.[9] Overall, this period is decreasing, meaning that drugs that are challenged are having the challenge occur earlier in their lifecycle. For NMEs, the mean lag has fallen from 5.5 years to 3.7 years. For non-NME drugs, the lag has fallen further, from 7.9 years to 5.2 years.[10]

FIGURE 5
TIME TO CHALLENGE BY CHALLENGE YEAR



[9] We report results by challenge cohort instead of approval cohort because we have data about the timing of challenges only for the most recent nine years, resulting in a left censoring problem: the first several approval cohorts are missing data where the challenge was relatively quick.

[10] For a subset of drugs for which PhRMA provided information about Paragraph IV challenges, Berndt et al. (2007b) report an increase in the number of "early" challenges to NMEs in more recent challenge cohorts. "Early" is defined as challenges occurring within six years of approval—that is, in the first two years during which challenges could be filed. Our data show that these early challenges continued to increase after 2005, when the Berndt et al. (2007) dataset stops, both in levels and also as a share of all challenges. Over the period from 2000 to 2005, about 35 percent of challenges to NMEs in our data occur within six years. This share increased to over half (53 percent) by 2009.

IV. Regression Analysis

Our baseline regression model relates whether a brand-name drug receives a Paragraph IV challenge to the patent protection, sales, and type of the brand-name drug. In subsequent regressions, we use several alternative measures of sales and sponsoring firm fixed effects. We also explore specifications in which the challenge is limited to a seven-year window after approval. Finally, we examine whether the *intensity* of challenge—the number of Paragraph IV challenges—varies with these drug characteristics.

Data

To determine which drugs have attracted Paragraph IV challenges, we use the FDA's Paragraph IV List, as discussed in Part III. The indicator variable *PIV* equals 1 for drugs that receive a challenge. We count the drug as receiving a challenge if it does so as to at least one strength. (A few drugs receive challenges for some but not all strengths.)

We start with the set of 721 brand-name drugs approved between 1995 and 2002. The range of years is dictated by available sales data, as discussed below. For each drug, we collected information about applicable patent protection in the manner discussed above, including the patent if it appeared in any annual edition of the Orange Book. 176 out of 721 drugs had no Orange Book-listed patents, and were therefore dropped from the dataset, as they could not result in Paragraph IV challenges. The remaining 545 drugs have an average of 4.2 patents each, with a median of 3 patents. We do not observe which patents, among Orange Book-listed patents, are subjected to Paragraph IV challenge.

To measure the strength of patent protection, we created several variables using the Patent Focus data. *PRODUCT* and *COMPOSITION* count the number of product and composition patents. *NONFLAG* counts "non-flagship" patents as defined in Part III—that is, Patent Focus-coded patents that are neither product nor composition patents. Patent Focus codes slightly more than four-fifths of the patents in our sample. *UNCODED* counts patents listed in the Orange Book that are left uncoded by Patent Focus.

Annual sales data for each drug, from 1996 to 2007, is drawn from the Medical Expenditure Panel Survey (MEPS), a large ongoing survey focused on the health expenditures of the U.S. population, used widely by health economists to make national-level projections of drug sales (Lichtenberg and Philipson 2002). Our main sales measure is average annual sales during the five years after launch. Thus, we can construct such a measure for drugs approved between 1995 and 2002. Slightly more than a quarter of the drugs in our sample (152) had no sales recorded in MEPS. We drop drugs with zero sales in MEPS, resulting in a set of 393 drugs. This decision is unobjectionable for those drugs that really had zero or near-zero sales, and thus were not at risk for a challenge. In a few other cases, however, the missing data is due to several "blind spots" in the MEPS data collection protocol, rather than truly zero sales.[11] 199 drugs out of 393, or 51 percent,

[11] For example, MEPS data contains enough personal information that, for a drug with small enough consumption, the individual patient might be identifiable if the drug name were reported. To preserve confidentiality, MEPS omits mention of these sales. Moreover, since MEPS is a survey of prescribed medicines, it fails to identify drugs administered in an in-patient setting (such as chemotherapy drugs) or sold over the counter. 22 of the 152 dropped drugs in fact had Paragraph IV challenges, suggesting that dropping these drugs does have an effect on our analysis.

have been subjected to Paragraph IV challenges, substantially larger than the fraction of Paragraph IV challenges in the overall population of drugs.[12]

For the 393 drugs with MEPS sales, average five-year sales shows a rightward skew: the mean is $177 million and median is $45 million. In some specifications, we take the log of sales, *LOGSALES*, as our sales measure. In others, we use indicator variables *SALESCAT2* through *SALESCAT5* for drugs in each quintile of sales (other than the first).[13] The top category includes "blockbuster" drugs with average annual sales over $1 billion.[14]

To assess the role of drug type, we code an indicator variable, *NME*, equal to one if the drug is a new molecular entity. 139 out of 393 drugs, or 35 percent, are NMEs. Since the drugs in our sample were approved at different times, we also include indicator variables *NDAYEAR96* to *NDAYEAR02* for approval years. Approval year 1995 is the left out category.

Aside from whether a Paragraph IV challenge occurred, the *intensity* of challenge is also a variable of interest, since drug prices fall with multiple generic entrants. Unfortunately, no publicly available data reports the number of challengers.[15] We construct our own measure using information from paragraphfour.com, a private database that compiles detailed information from litigation and media reports about the number and identity of challengers. Eighty-two percent of the drugs in our sample that received Paragraph IV challenges (164 out of 199) also had information in paragraphfour.com.

[12] We hope to employ more complete sales data in future work.

[13] The quintile cutoff points are $7, $28, $76, and $185 million.

[14] For example, Advair, Allegra, Celebrex, Claritin, Diovan, Lexapro, Lipitor, Nexium, Prevacid, Protonix, Singulair, Vioxx, Zoloft, and Zyprexa.

[15] The FDA does not make this information available, and the FDA's Paragraph IV List indicates only that there is at least one Paragraph IV filer.

Using information from this database, we constructed a variable, *N_TOTAL*, that counts the total number of challengers. Table 2 shows descriptive statistics for each of the variables in our final dataset.

TABLE 2
DESCRIPTIVE SUMMARY OF VARIABLES

	Mean	Std. dev.	Min	Max	*N*
Paragraph IV Challenge	0.52	0.51	0	1	393
Patents					
Product	1.16	1.64	0	17	393
Composition	1.04	1.69	0	12	393
Non-Flagship	0.97	2.03	0	20	393
Uncoded	1.11	1.87	0	14	393
Average Sales ($m)	177.34	399.10	0.02	3305.49	393
New Molecular Entity	0.35	0.48	0	1	393
Number of Challenges	2.701	2.44	1	13	164

Number of Challenges is conditional on a challenge, further limited to those drugs for which information about challenges can be obtained.

Baseline Model

Model 1.1 is a linear probability model relating the existence of a Paragraph IV challenge to sales, patent protection, drug type, and approval year:[16]

$$PIV_i = \alpha + \beta LOGSALES_i + \gamma_1 PRODUCT_i + \gamma_2 COMPOSITION_i + \gamma_3 NONFLAG_i + \gamma_4 UNCODED_i + \delta_1 NDAYEAR96_i + \ldots + \delta_7 NDAYEAR02_i + \lambda NME_i + \varepsilon$$

The results from the baseline model are reported in Table 3, with robust standard errors in parentheses. Sales have an economically meaningful and statistically significant impact on the likelihood of challenge. Somewhat surprisingly, drug type has no effect. The

[16] Below we report OLS models, for ease of interpretation. We also estimated probit models of the likelihood of challenge and negative binominal models of the intensity of challenge. These models yielded qualitatively similar results.

number of product and composition patents have no economically or statistically significant impact, nor does the number of "uncoded" patents for which Patent Focus provides no information. However, the number of non-flagship patents does have a strong effect. A one standard deviation increase in the number of non-flagship patents (about two patents) results in a 7 percentage point increase in likelihood of challenge, after controlling for sales.

Model 1.2 examines the effect of sales and non-flagship patents with categories for each. Sales are divided by quintile, and the non-flagship patents are divided into three categories: one patent, two patents, and three or more patents. Drugs in the second quintile of sales have a 13 percentage point higher likelihood of challenge (significant at the 10 percent level) than those in the first quintile (the left out category). Drugs in the third and fourth quintiles have a 26 percentage point higher likelihood of challenge than the first quintile, and drugs in the top quintile have a 40 percentage point higher likelihood of challenge. In levels, for the left out approval year category (1995), drugs in the top quintile had a 63 percent probability of resulting in a challenge.

Having one non-flagship patent increases the likelihood of challenge by 16 percentage points, relative to having none. Having two non-flagship patents increases the likelihood by 20 percentage points, relative to having none. These estimates are conditional on sales. Interestingly, the coefficient on the indicator for three or more non-flagship patents is smaller and statistically insignificant, suggesting the possibility that a stockpile of low-quality patents might deter challenges. However, further investigation of this effect (not reported) suggests that the effect of non-flagship patents varies

haphazardly beyond three patents, with no clear patterns in direction, magnitude, or significance.

TABLE 3
PROBABILITY OF CHALLENGE, FIVE-YEAR SALES

	(1.1)	(1.2)	(1.3)
Sales			
Log (sales)	0.0936***		0.0870***
	(0.0162)		(0.0235)
Second quintile		0.130*	
		(0.0757)	
Third quintile		0.258***	
		(0.0804)	
Fourth quintile		0.259***	
		(0.0788)	
Top quintile		0.400***	
		(0.0800)	
Patents			
Product	–0.00891	–0.00633	–0.0127
	(0.0171)	(0.0183)	(0.0215)
Composition	–0.00864	–0.00259	0.00524
	(0.0159)	(0.0164)	(0.0221)
Non-Flagship	0.0355***		0.0417***
	(0.00915)		(0.0124)
Uncoded	–0.0133	–0.00663	–0.0206
	(0.0137)	(0.0141)	(0.0176)
One NFP		0.163**	
		(0.0674)	
Two NFPs		0.202**	
		(0.0893)	
More Than Two NFPs		0.120	
		(0.0802)	
New Molecular Entity	0.0215	0.00624	0.0710
	(0.0516)	(0.0524)	(0.0643)
Constant	0.265***	0.233**	0.179
	(0.0886)	(0.0955)	(0.109)
Firm Fixed Effects	No	No	Yes
Observations	393	393	393

The dependent variable, *PIV*, is an indicator equal to 1 if the drug received a Paragraph IV challenge. Robust standard errors are in parentheses. All regressions include (unreported) approval year fixed effects. Asterisks indicate statistical significance at the ***1%, **5%, and *10% levels.

Model 1.3 includes dummy variables for each brand-name firm. In these fixed effects models, the effects of sales and patents are identified based on within-firm variation in the independent variables. (For example: How much more likely are Pfizer's drugs with large sales to be challenged than Pfizer's drugs with small sales, holding other factors constant? How much more likely are challenges to Glaxo's drugs with many non-flagship patents than Glaxo's drugs with few patents?) As in Model 1.1, sales and non-flagship patents remain strong predictors of the likelihood of challenge, even within firms. The observed result that non-flagship patents matter is thus unlikely to reflect any unobservable firm-specific factors.

Using five-year sales raises a potential problem of reverse causality, because the fact of a (successful) Paragraph IV challenge within the five-year period could, in turn, reduce brand-name sales. (This is only a risk as to non-NME drugs. For NMEs, the challenge cannot be initiated until four years after brand-name product approval, and even if a challenge is filed immediately, it is unlikely to be resolved within a year.) Model 2 repeats the analyses of Model 1, but now the sales measure is sales in year 1 rather than the five-year average.

The results, reported in Table 4, are broadly similar to the results in Model 1. Sales and non-flagship patents remain economically and statistically significant. Other patent types and drug type are not. The sales coefficient is reduced in size—in logs by about two-thirds, and in quintiles by one-third to one-half. This may reflect attenuation bias, since single-year MEPS sales estimates are likely to be noisier than those averaged over five years. Another possibility is that the impact of sales in Model 1 in part does reflect the impact of challenge on sales. Overall, the results suggest that even with a

measure not subject to this concern—one-year sales—the impact of sales is large, with the top quintile of sales having a 19 percentage point higher likelihood of challenge, all else equal. Moreover, the impact of non-flagship patents in these models is similar to that reported for Model 1.

TABLE 4
PROBABILITY OF CHALLENGE, ONE-YEAR SALES

	(2.1)	(2.2)	(2.3)
Sales			
Log (sales)	0.0387***		0.0393**
	(0.0125)		(0.0177)
Second quintile		–0.00129	
		(0.0796)	
Third quintile		0.0913	
		(0.0768)	
Fourth quintile		0.177**	
		(0.0782)	
Top quintile		0.185**	
		(0.0789)	
Patents			
Product	0.00286	0.00278	–0.00266
	(0.0178)	(0.0184)	(0.0217)
Composition	–0.00391	0.00113	0.0105
	(0.0166)	(0.0170)	(0.0224)
Non-Flagship	0.0416***		0.0457***
	(0.00966)		(0.0128)
Uncoded	–0.0144	–0.00619	–0.0240
	(0.0140)	(0.0145)	(0.0175)
One NFP		0.163**	
		(0.0702)	
Two NFPs		0.215**	
		(0.0864)	
More Than Two NFPs		0.160**	
		(0.0809)	
New Molecular Entity	0.0288	0.0109	0.0785
	(0.0534)	(0.0537)	(0.0655)
Constant	0.336***	0.307***	0.239**
	(0.0917)	(0.0971)	(0.111)
Firm Fixed Effects	No	No	Yes
Observations	393	393	393

The dependent variable, *PIV*, is an indicator equal to 1 if the drug received a Paragraph IV challenge. Robust standard errors are in parentheses. All regressions include (unreported) approval year fixed effects. Asterisks indicate statistical significance at the ***1%, **5%, and *10% levels.

Challenge Windows

Some drugs receive their first Paragraph IV challenge only after a lengthy delay. Because the drugs in our sample were approved at different times over an eight-year period, they are exposed to the hazard of a Paragraph IV challenge for different lengths of time. To guard against truncation bias, in the next set of models we impose a seven-year window on the time to bring a challenge. Thus our dependent variable in these models is whether a drug was challenged at some point during the seven years after approval.[17] These results are reported in Table 5. Models 3.1 and 3.2 use the five-year and one-year sales measures, respectively. Sales and non-flagship patents are statistically significant and have similar magnitudes as in earlier specifications. In these models, the product patent variable is also statistically and qualitatively significant, and negative. A one standard deviation increase in the number of product patents, about 1.64 patents, is associated with a more than 6 percentage point drop in the likelihood of challenge. This is consistent with strong product patents discouraging challenges. Models 3.3 and 3.4 repeat Models 3.1 and 3.2 but add brand-name firm fixed effects. While magnitudes in these models are generally similar to those from the previous two models, the estimates are less precise. However, the estimated effects of non-flagship patents and sales are statistically significant at the 1 percent level.

[17] Once we collect more fine-grained data on the timing of challenges, sales, and patents, we plan to estimate duration models that explicitly deal with censoring, and also allow us to take advantage of the time variation in our regressors.

TABLE 5
PROBABILITY OF CHALLENGE WITHIN A SEVEN-YEAR WINDOW

	(3.1)	(3.2)	(3.3)	(3.4)
Log (5-year average sales)	0.0914***		0.0794***	
	(0.0160)		(0.0229)	
Log (1-year sales)		0.0468***		0.0480***
		(0.0122)		(0.0164)
Patents				
Product	–0.0390***	–0.0301*	–0.0323*	–0.0258
	(0.0149)	(0.0158)	(0.0186)	(0.0189)
Composition	–0.00781	–0.00446	0.0147	0.0176
	(0.0144)	(0.0152)	(0.0218)	(0.0222)
Non-Flagship	0.0343***	0.0400***	0.0379***	0.0414***
	(0.0131)	(0.0144)	(0.0139)	(0.0418)
Uncoded	0.00437	0.00362	–0.00230	–0.00504
	(0.0142)	(0.0147)	(0.0159)	(0.0160)
New Molecular Entity	–0.0410	–0.0302	0.0133	0.0236
	(0.0468)	(0.0490)	(0.0574)	(0.0580)
Constant	0.0191	0.0637	–0.0359	–0.0163
	(0.0753)	(0.0799)	(0.0865)	(0.0858)
Firm Fixed Effects	No	No	Yes	Yes
Observations	393	393	393	393

The dependent variable is an indicator equal to 1 if the drug received a Paragraph IV challenge within seven years after approval. Robust standard errors are in parentheses. All regressions include (unreported) approval year fixed effects. Asterisks indicate statistical significance at the ***1%, **5%, and *10% levels.

Intensity of Challenge

Our final set of models considers the intensity of challenge. The setup is analogous to Model 3, except that now our dependent variable is *N_TOTAL*, the count of Paragraph IV challengers for which we have information from paragraphfour.com. Here, we limit our sample to the 164 drugs (out of 199) for which paragraphfour.com reports detailed information. Our analysis is therefore conditional on having at least one challenge.

Table 6 reports the results. In the five-year sales model, sales and non-flagship patents are again positive and statistically significant. Thus the number of challengers,

conditional on having been challenged, is increasing in sales. In the one-year sales model, non-flagship patents remain significant, but sales no longer are. When firm-level fixed effects are added, the magnitude of the sales and non-flagship patent variables are similar to those in the baseline models, but only the five-year sales variable is statistically significant (Model 4.3). This could reflect lack of statistical power to estimate the impacts of these variables precisely within firms, or that these variables don't actually explain differences in intensity of challenge across a firm's drugs. We hope to collect more comprehensive data on the intensity of challenge to distinguish between these two possibilities.

TABLE 6
INTENSITY OF CHALLENGE

	(4.1)	(4.2)	(4.3)	(4.4)
Log (5-year average sales)	0.423***		0.399**	
	(0.118)		(0.198)	
Log (1-year sales)		0.140		0.211
		(0.0964)		(0.146)
Patents				
Product	0.006	0.054	0.002	0.037
	(0.127)	(0.137)	(0.161)	(0.167)
Composition	0.0167	0.0745	0.121	0.156
	(0.116)	(0.117)	(0.206)	(0.207)
Non-Flagship	0.272**	0.301**	0.204	0.211
	(0.120)	(0.118)	(0.150)	(0.148)
Uncoded	0.178	0.180	0.070	0.076
	(0.122)	(0.124)	(0.192)	(0.197)
New Molecular Entity	0.674	0.744	0.627	0.602
	(0.450)	(0.463)	(0.645)	(0.649)
Constant	1.823*	2.331**	2.016*	2.330*
	(0.928)	(1.032)	(1.173)	(1.224)
Firm Fixed Effects	No	No	Yes	Yes
Observations	164	164	164	164

The dependent variable, *N_TOTAL*, equals the number of Paragraph IV challenges. Robust standard errors are in parentheses. All regressions include (unreported) approval year fixed effects. Asterisks indicate statistical significance at the ***1%, **5%, and *10% levels.

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

Understanding which drugs get challenged, and why, is an important first step toward assessing the welfare implications of the Hatch-Waxman regime. Our results suggest that both the likelihood and intensity of Paragraph IV challenges are strongly responsive to drug sales. We also find that, conditional on sales, drugs with a larger number of questionable patents are much more likely to draw challenges. This latter finding suggests 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, present at least implicitly in the existing literature, that the composition and quality of a drug's patent portfolio don't matter.

Specifically, the most striking result from our initial regressions is the importance of non-flagship patents for the likelihood of a Paragraph IV challenge. This result may reflect the fact that a weak patent provides a new opportunity for a generic drug maker to secure the 180-day exclusivity period. In the language of Part III, the portfolio may be more like a linked chain, rather than a fortress. That is not to say that adding a weak patent is a bad strategy for a brand-name firm. After all, a later filer does not have access

to the 180-day period, and so its incentives to challenge would not be increased by the addition of a weak patent.

Moreover, the prospect of increased challenges by first filers need not discourage the brand-name firm from seeking weak patents, for a reason discussed in Hemphill (2009). The brand-name firm may see a benefit from the weak patent, even if it is challenged and results in an award of exclusivity to the generic firm. Suppose, for example, that the brand-name firm has a strong patent that expires at the end of year 1 and a weak patent that expires at the end of year 2. The generic firm has no plausible challenge to bring against the strong patent, and a very powerful argument that the weak patent is invalid. If the brand-name firm had only the strong patent, entry by multiple generic firms would occur at the end of year 1. By winning a challenge against the weak patent, by contrast, the generic firm secures entry at the end of year 1, this time with exclusivity. Exclusive entry prevents other generic firms from entering the market for 180 days. Prices remain high during exclusivity, compared to entry by multiple generic firms. In this instance, generic exclusivity is a benefit to the brand-name firm, rather than a detriment.

One natural next step in evaluating the role of non-flagship patents is to examine the subset of drugs for which non-flagship patents were issued and added to the Orange Book subsequent to NDA approval. The question to test is whether the later addition of a non-flagship patent has a discernable effect on the likelihood of challenge. A second test exploits the fact that a later-filing generic firm does not have access to the 180-day exclusivity period. Thus, the addition of weak patents should have a differential effect

upon first filers, whose incentive to challenge is increased, and later filers, whose incentive to challenge should decrease.

We recognize that patents are not randomly assigned to drugs, complicating the task of assessing the causal impact of patents. For example, it is possible that there are omitted variables that are correlated with both patent protection and the likelihood of challenges; if so, our coefficients would be biased. The literature on generic entry (e.g., Scott Morton 1996) suggests the main draw is sales, which our models include. Nonetheless, in future work we plan to introduce a richer set of covariates, including measures of competition in therapeutic class, raw material availability and, we hope, sales variables with less measurement error than those derived from MEPS. It is also possible that the expectation of Paragraph IV challenges causes branded firms to accumulate non-flagship patents, as we suggested above.[18] In future work, we plan to examine the timing of listing of non-flagship patents, and interactions between patent types, which may help in understanding these issues. We are also exploring potential instruments for the number of non-flagship patents on a drug, including the average patent propensity of the brand-name firm (across all of its drugs).[19]

Subject to these caveats, our finding that the likelihood of challenge is increasing in brand-name sales has several implications. For example, we find that not only the probability but also the number of challengers increases sharply with sales. As Berndt et

[18] Not all drugs can accumulate the same number of non-flagship patents however: chemistry and biology put limits on the number of salts, delivery mechanisms, etc. that are possible for any given drug.

[19] In future analyses where we will explicitly consider timing of patent listings and challenges, we may also be able to make use of variation in the timing of patent grants, and thus patent listings on the Orange Book. In a recent paper on patents and markets for ideas, Gans, Hsu, and Stern (2009) use variation in the grant lag to assess the causal impact of patent arrival on hazard of licensing. Previous research (Cockburn et al. 2004) suggests the grant lag is strongly related to the identity of the specific examiner who evaluates a patent. The assignment of patent applications to examiners is random within art units (Lemley and Sampat 2009).

al. (2007) suggest, the number of challengers affects the dynamic effects of authorized generics on incentives to challenge. Suppose (having read this paper?) generics know that lucrative drugs attract more challenges, and thus that the probability that any given firm's challenge will be first (or, for an NME, that the firm will be the only first challenger) is low. Then, the expected value of such a challenge is low. But the data suggest they still occur. If challengers on large drugs are undeterred by this, it is unlikely that the prospect of one more competitor (an authorized generic product) during the exclusivity period matters much. Moreover, for large drugs, even if one challenger were deterred by this prospect, it is unlikely all would be. As Reiffen and Ward (2007) suggest, the extent potential authorized generics have a deterrent effect, it is likely to be limited to challenges to less lucrative drugs.

The role of large sales in encouraging Paragraph IV challenges also provides qualified support for the idea that ex-post review is an effective way to test probabilistic patents. As discussed in Part I, such "rational ignorance" is cost-effective provided that most patents have little economic importance, and the set of important patents cannot be identified early on. Instead, we should focus evaluation resources on those few patents that turn out to be valuable. The Paragraph IV challenge process is perhaps the most vigorous example of that ex post analysis, subjecting patent protection for economically important drugs to intensive ex post scrutiny.[20]

[20] There is a broader 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. Answering that question is beyond the scope of this paper, though, if true, that suggests that patentability standards are a poor fit for the incentives needed to generate valuable innovation in pharmaceuticals (Eisenberg 2007). Moreover, it is unclear whether the ability to assert dubious patents—or the equilibrium implied by the listing, challenge, and litigation process described in this paper—is a move towards the first-best outcome. More information on which patents are challenged, and how the outcomes of challenges vary with this, may help us say more about this question.

Whether this scrutiny is effective, however, depends upon what happens after the challenge is filed. In ongoing work, we are examining the dynamics of litigation, settlement, and entry that follow these challenges. If these processes resulted in low-cost and rapid invalidation of dubious patents (and early generic entry on the associated drugs), this might suggest the Hatch-Waxman regime is working as intended, and ex post analysis is making up for "rational ignorance" ex ante. However, as Farrell and Shapiro (2008) emphasize, weak patents can be an instrument for anticompetitive licensing. There is evidence, moreover, that some 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 is quite different. Accordingly, while the results reported in this paper provide new insights into the determinants of challenges, more work is needed before we can make strong claims about their welfare impact.

References

Berndt, Ernst R., Richard Mortimer, Ashoke Bhattacharjya, Andrew Parece and Edward Tuttle (2007a). "Authorized Generic Drugs, Price Competition and Consumers' Welfare." *Health Affairs* 26:790-799.

Berndt, Ernst R., Richard Mortimer and Andrew Parece (2007b). "Do Authorized Generic Drugs Deter Paragraph IV Certifications? Recent Evidence." *Working Paper*.

Bresnahan, Timothy F. and Peter C. Reiss. "Do Entry Conditions Vary Across Markets?" *Brookings Papers in Economic Activity*:833-871.

Bulow, Jeremy (2004). "The Gaming of Pharmaceutical Patents." Innovation Policy and the Economy (Adam B. Jaffe et al. eds.).

Cockburn, Iain M., Samuel Kortum and Scott Stern (2002). "Are All Patent Examiners Equal? Examiners, Patent Characteristics, and Litigation Outcomes." Patents in the Knowledge-Based Economy (W. M. Cohen and S. A. Merrill eds.):17-53.

DiMasi, Joseph A., Ronald W. Hansen and Henry G. Grabowski (2003). "The Price of Innovation: New Estimates of Drug Development." *Journal of Health Economics* 22:151-185.

Eisenberg, Rebecca S. (2007). "The Role of the FDA in Innovation Policy." *Michigan Telecommunications and Technology Review* 13:345-388.

Engelberg, Alfred B. (1999). "Special Patent Provisions for Pharmaceuticals: Have They Outlived Their Usefulness?" *IDEA: The Journal of Law and Technology* 39:389-428.

Engelberg, Alfred B., Aaron S. Kesselheim and Jerry Avorn (2009). "Balancing Innovation, Access and Profits: Market Exclusivity for Biologics." *New England Journal of Medicine*: http://healthcarereform.nejm.org/?p=2070.

Farrell, Joseph and Carl Shapiro (2008). "How Strong Are Weak Patents?" *American Economic Review* 98:1347-1369.

Federal Trade Commission (2002). Generic Drug Entry Prior to Patent Expiration.

Federal Trade Commission (2009). Authorized Generics: An Interim Report.

Food and Drug Administration (1985-2009). The Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations.

Food and Drug Administration (2003a). "Requirements for Submission of In Vivo Bioequivalence Data." *Federal Register* 68:640.

Food and Drug Administration (2003b). "Guidance for Industry: 180-Day Exclusivity When Multiple ANDAs Are Submitted on the Same Day."

Food and Drug Administration (2009a). Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/.

Food and Drug Administration (2009b). Paragraph IV Certifications as of November 16, 2009. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm047676.htm.

Frank, Richard G. (2007). "The Ongoing Regulation of Generic Drugs." *New England Journal of Medicine* 357:1993-1996.

Gal, Ronny and Shari Nikhil (2007). "US Generics – Predicting Para IV: Generic Companies Have the Upper Hand in Formulation Patent Cases." *Bernstein Research Report*.

Goodman, Marc et al. (2004). Quantifying the Impact from Authorized Generics. *Morgan Stanley Research Report*.

Grabowski, Henry G. (2004). "Are the Economics of Pharmaceutical R&D Changing? Productivity, Patents and Political Pressures." *PharmcoEconomics* 22 (Supp. 2):15-24.

Grabowski, Henry G. and Margaret Kyle (2007). "Generic Competition and Market Exclusivity Periods in Pharmaceuticals." *Managerial and Decision Economics* 28:491-502.

Hall, Bronwyn H. and Rosemary Ham Ziedonis (2001). "The Patent Paradox Revisited: An Empirical Study of Patenting in the U.S. Semiconductor Industry." *Rand Journal of Economics* 32:101-128.

Hemphill, C. Scott (2006). "Paying for Delay: Pharmaceutical Patent Settlement as a Regulatory Design Problem." *New York University Law Review* 81:1553-1623.

Hemphill, C. Scott (2009). "An Aggregate Approach to Antitrust: Using New Data and Rulemaking to Preserve Drug Competition." *Columbia Law Review* 109:629-688.

Higgins, Matthew J. and Stuart J.H. Graham (2009). "Balancing Innovation and Access: Patent Challenges Tip the Scales." *Science* 326:370-371.

Hsu, David, Joshua Gans and Scott Stern (2008). "The Impact of Uncertain Intellectual Property Rights on the Market for Ideas: Evidence from Patent Grant Delays." *Management Science* 54:982-997.

IMS Health (2009). Economic Analysis of Generic Pharmaceuticals 1999-2008. http://www.gphaonline.org/sites/default/files/$734%20Billion%20in%20Generic%20Savings%20GPhA.pdf.

Lemley, Mark (2001). "Rational Ignorance at the Patent Office." *Northwestern University Law Review* 95:1495-1532.

Lemley, Mark and Bhaven N. Sampat (2009). "Examiner Characteristics and the Patent Grant Rate." *Working Paper.*

Lemley, Mark and Carl Shapiro (2005). "Probabilistic Patents." *Journal of Economic Perspectives*:75-98.

Levin, Richard C., Alvin K. Klevorick, Richard R. Nelson and Sidney G. Winter (1987). "Appropriating the Returns from Industrial Research and Development." *Brookings Papers on Economic Activity (Special Issue).*

Lichtenberg, Frank R. and Tomas J. Philipson (2002). "The Dual Effects of Intellectual Property Regulations: Within- and Between-Patent Competition in the US Pharmaceuticals Industry." *Journal of Law and Economics* 45:643-672.

Lichtenberg, Frank R. (2007). "The Impact of New Drugs on U.S. Longevity and Medical Expenditure, 1990-2003."*American Economic Review* 97:438-443.

Lichtenberg, Frank R. (2009). "The Effect of New Cancer Drug Approvals on the Life Expectancy of American Cancer Patients, 1978-2004." *Economics of Innovation and New Technology* 18:407-428.

Lichtenberg, Frank R. and Suchin Virabhak (2007). "Pharmaceutical-Embodied Technical Progress, Longevity, and Quality of Life: Drugs as 'Equipment for Your Health.'" *Managerial and Decision Economics* 28:371-392.

Murphy, Kevin and Robert Topel (2000). Measuring the Gains from Medical Research: An Economic Approach.

National Institute for Health Care Management (2002). Changing Patterns of Pharmaceutical Innovation.

Ollier, Peter (2007). "U.S. Trade Deal Creates Drug Patent Controversy." *Managing Intellectual Property*: http://www.managingip.com/Article/687095/US-trade-deal-creates-drug-patent-controversy.html.

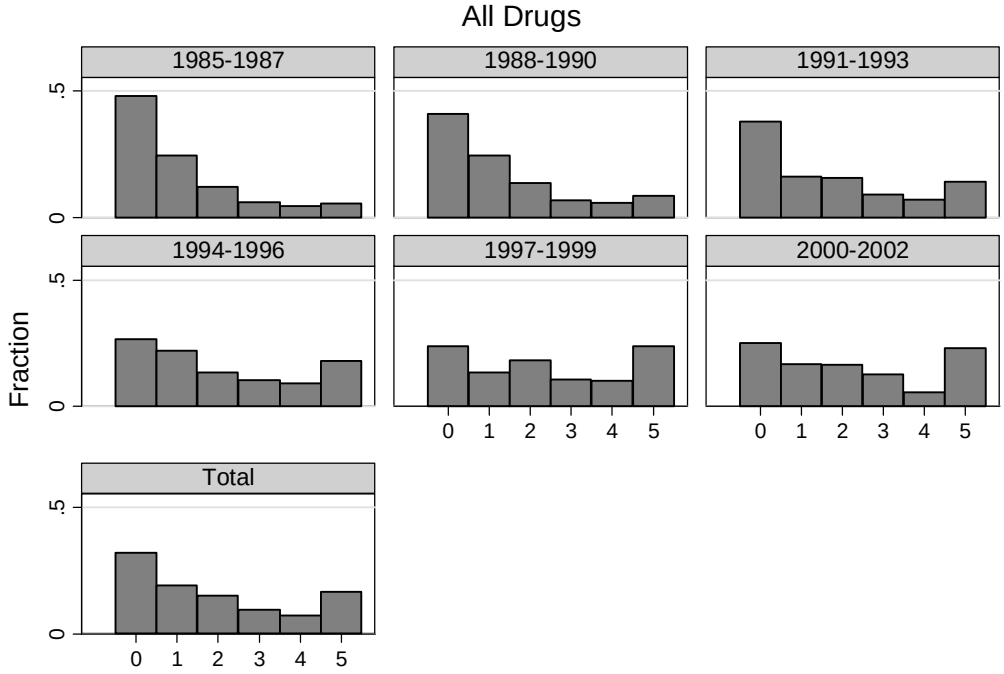
Perett, Stephen (2008). "The Modified-Release Drug Delivery Landscape." In Modified-Release Drug Delivery Technology (2nd ed., vol. 2):1-16.

Reiffen, David and Michael R. Ward (2005). "Generic Drug Industry Dynamics." *Review of Economics and Statistics* 87:37-49.

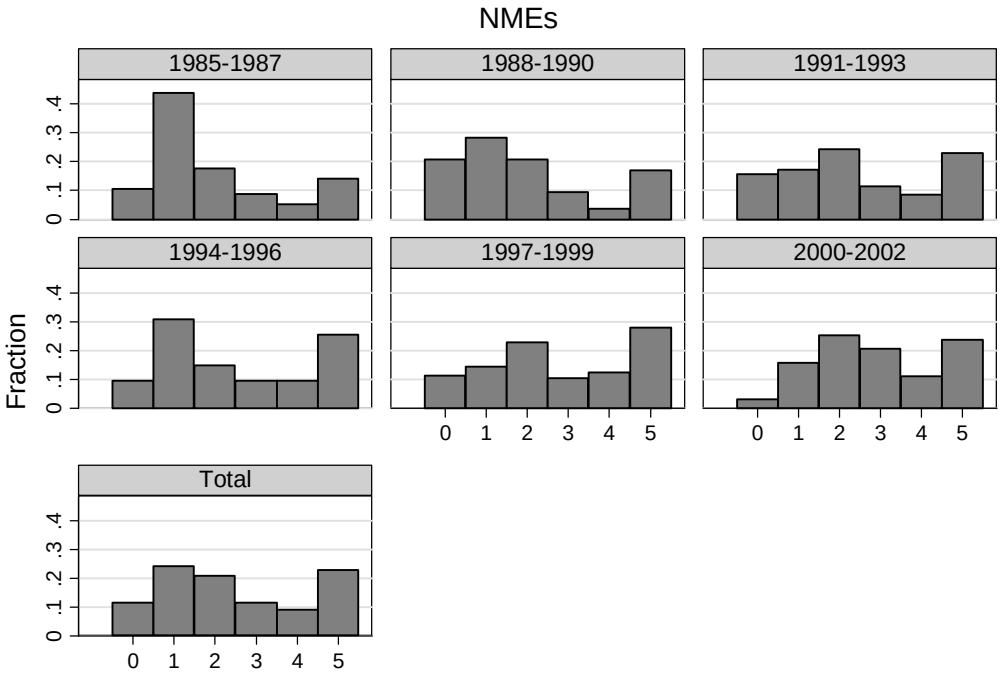
Scott Morton, Fiona (1996). "Entry Decisions in the Generic Pharmaceutical Industry." *Rand Journal of Economics* 30:421-440.

Thomas, John R. (2005). Pharmaceutical Patent Law.

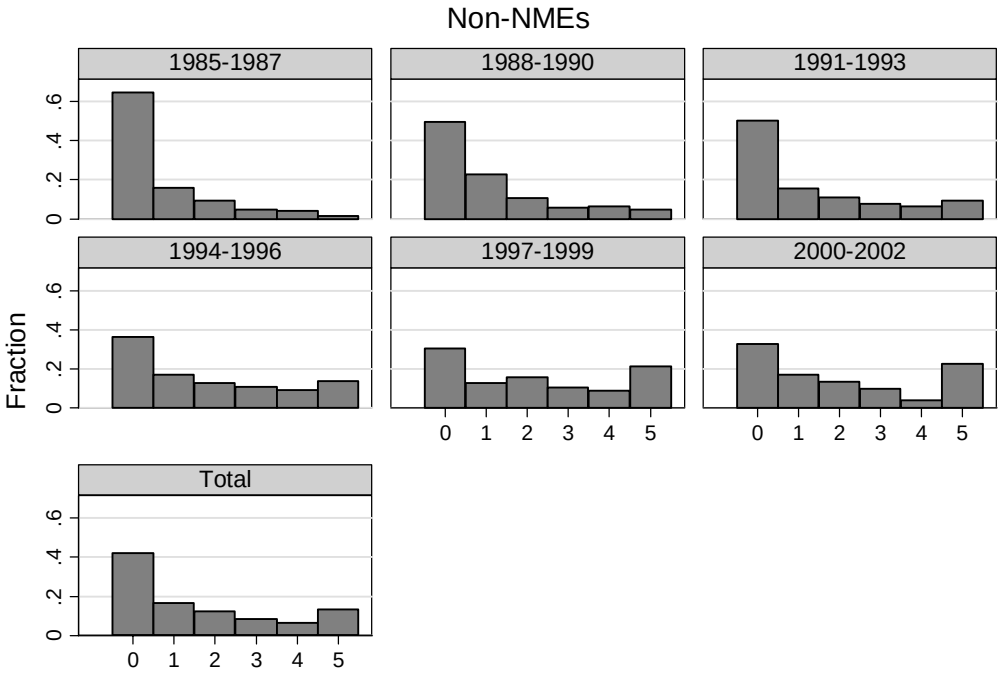
APPENDIX 1
DISTRIBUTION OF PATENTS PER DRUG BY APPROVAL COHORT



The category 5 includes drugs with 5 or more patents.



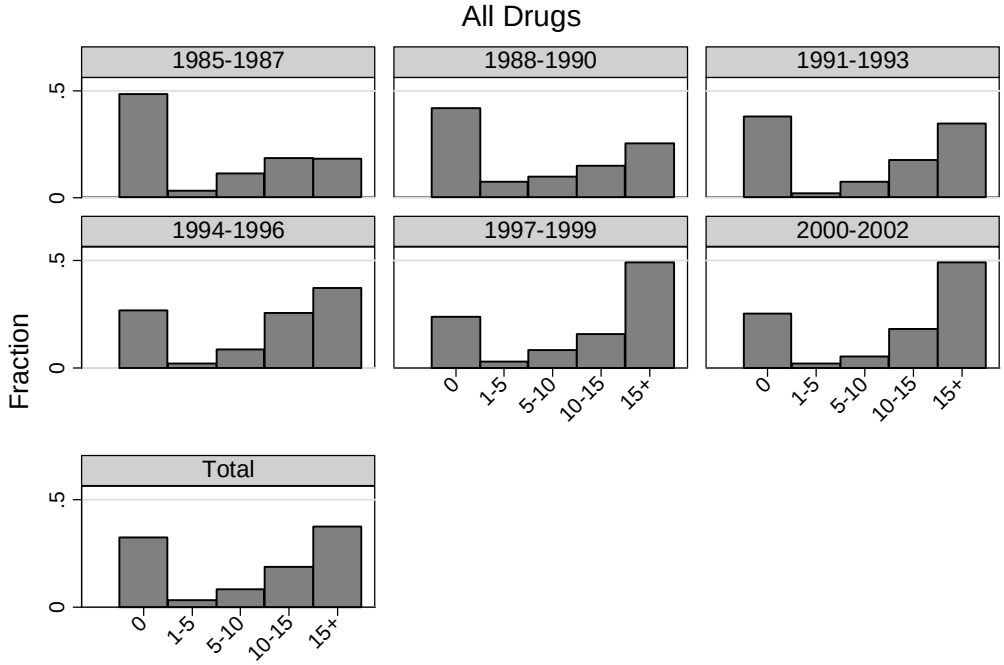
The category 5 includes drugs with 5 or more patents.

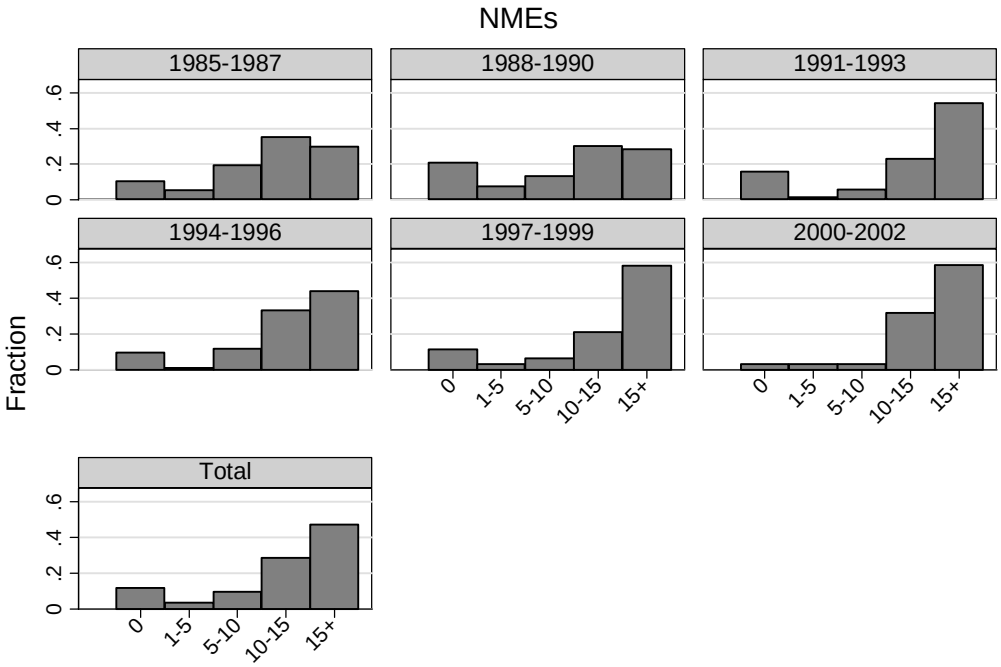


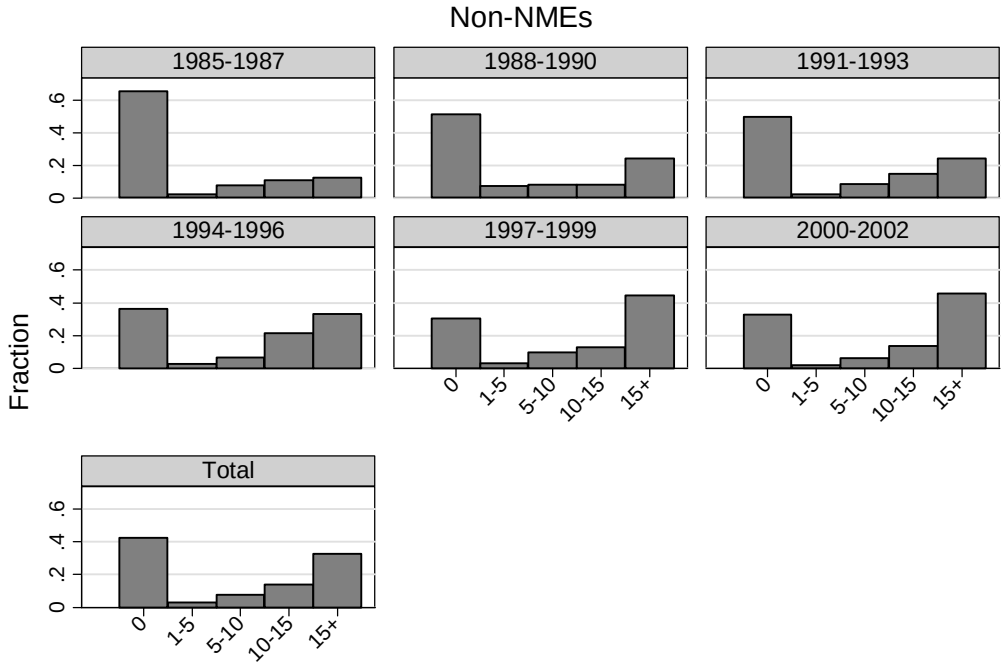
The category 5 includes drugs with 5 or more patents.

APPENDIX 2

DISTRIBUTION OF NOMINAL PATENT LIFE BY APPROVAL COHORT






Non-NMEs
1985-1987
1988-1990
1991-1993
1994-1996
1997-1999
2000-2002
Total
Fraction
0
.2
.4
.6
0
1-5
5-10
10-15
15+
Years from FDA approval to last patent expiration