PHARMACEUTICAL PATENT CHALLENGES

Company Strategies and Litigation Outcomes

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ABSTRACT
The pharmaceutical industry has experienced a large number of patent challenges in recent years. Key catalysts for this were legal and regulatory changes that awarded 180-day exclusivity rights for first-filing generic firms not only on the basis of a court victory, but also through a settlement with the patent owner. In this paper, we have assembled a unique data set on new drugs approved from 1994 to 2006, including detailed information on patent challenges and litigation outcomes. We find that the new regulatory environment induced significant behavioral changes, including racing by generic firms to challenge patents for large-selling drugs in an environment where more patents are filed by branded firms. Increased generic challenges to different types of patent claims are linked to reduced market exclusivity periods for branded drugs, based on regression analyses and litigation outcomes. Settlements that allow entry prior to patent expiry are a prevalent litigation outcome given the risks of an unfavorable court decision that can adversely affect a company's market valuation. This topic remains an important issue for further research, particularly given different public policies governing patent challenges for biosimilars and biologics compared with those for generic drugs and new chemical entities.

KEYWORDS: pharmaceuticals, Hatch-Waxman Act, patent challenges, market exclusivity, generic competition
JEL CLASSIFICATION: D22, I18, K20, L65, O30

I. Introduction

In recent years, the pharmaceutical industry has experienced a wave of patent challenges. Some have expressed concerns that the wave of paragraph IV patent challenges is resulting in significant adverse consequences for pharmaceutical innovation incentives (Higgins and Graham 2009). The number of patent challenges has increased rapidly since the late 1990s. In this regard, over 80 percent of the new molecular entities (NMEs) experiencing first generic entry in 2011–12 experienced a patent challenge, compared with an average of less than 20 percent prior to 1998 (Grabowski, Long, and Mortimer 2014).

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In this paper, we examine what is driving these increased challenges, and how they are influencing strategic behavior and the competition between branded and generic firms. Under the 1984 Hatch-Waxman Act, a generic firm can be given a 180-day exclusivity period if it is the first to file an abbreviated new drug application (ANDA) with patent challenge. For the first decade and a half after the 1984 act was passed, paragraph IV challenges were relatively infrequent and tended to occur late in the branded product's life cycle. A set of regulatory and legislative changes that occurred between 1998 and 2003 were a key catalyst for the increased number of patent challenges by generic firms. These changes awarded the first-filing firms 180-day market exclusivity not only from a court victory, but also through a settlement agreement with the patent owner (FDA 2003).

The strategies of both generic and branded firms with regard to patent challenges have evolved over time. The business model of generic firms has increasingly revolved around being an early ANDA filer with a patent challenge to obtain 180-day exclusivity rights, especially in the case of commercially successful products. In particular, generic drugs can earn large margins and market shares when there is only one or a few generics available, but these returns can quickly erode as multiple generics enter. Accordingly, it is argued that generic firms have an incentive to race to be the first ANDA filer with a patent challenge, and to challenge patents even when the probability of success is low, which some have characterized as a "prospecting" strategy.

In the case of innovators, it has been observed that they often pursue multiple patents with different expiration times (sometimes characterized as an "evergreening" strategy). In particular, separate patents can be obtained on a product's active ingredient, method(s) of use, and formulation(s). The latter forms of non–active ingredient patents are often filed later in the development process. These latter patents have been characterized as "weaker" patents by some researchers, and are more susceptible to patent challenges (Hemphill and Sampat 2011, 2012). However, they exhibit considerable heterogeneity and can provide essential core patent protection for new molecular entities (for example, when an active ingredient patent is not present or has a very short market life). This was the case of the first AIDS therapy, AZT, and other important new introductions.[1]

In this study, we consider how regulatory and legislative developments changed the incentives for patent challenges and the strategic behavior of generic and innovative firms. The next section provides background information and summarizes prior studies. The following sections present the statistical analyses including regression analyses of patent challenges and comparisons with a subset of biological entities. We also investigate the effects of litigation outcomes associated with the patent challenges of the top quintile of new drugs introduced between 1994 and 2006, a cohort that accounted for a dominant share of the new drug sales during this period.

1 AZT was an older compound initially investigated for cancer, and for which a patent claim on the active ingredient substance was unavailable (Emmons and Nimgade 1991). However, the novel discovery of its use as the initial AIDS therapy many years after it was first synthesized provided a strong method-of-use patent claim that survived legal challenge.

II. Patent Challenges and the Hatch-Waxman Act

A. THE DUAL OBJECTIVES OF THE HATCH-WAXMAN ACT

The objectives of the Hatch-Waxman Act (also known as the Drug Price Competition and Patent Restoration Act) were to encourage increased generic competition while also preserving incentives for pharmaceutical companies to develop new drugs. A key provision was the establishment of the ANDA process requiring generic drugs to demonstrate bioequivalence to the reference brand, but allowing them to rely on the brand's safety and efficacy data. These regulatory changes, combined with automatic drug substitution laws instituted by states and managed care incentives, have significantly increased generic usage. This is exemplified by the fact that generic products' share of total prescriptions in the United States increased from 18 percent in 1984 to over 80 percent in recent years (Grabowski, Long, and Mortimer 2014). As the number of generic products for a particular entity increases, generic utilization increases and prices decline toward marginal cost (Berndt and Aiken 2011). This can yield substantial savings to patients and payers.

The Hatch-Waxman Act also provided incentives for innovative firms in terms of patent term restoration provisions.[2] While the nominal life of a patent is 20 years from the date of submission, the effective patent life is significantly shorter for many core drug patents since they are typically applied for early in the lengthy drug development process. The patent provisions of the Hatch-Waxman Act are designed to restore some of this patent time lost during clinical trials and the FDA review period according to a legislatively designed formula. The patent term provisions helped offset the potential negative impacts on R&D returns associated with the 1984 act. However, the Congressional Budget Office found that the faster and more intensive generic competition after the Hatch-Waxman Act contributed to a significant decrease in the returns on R&D (CBO 1998). In a more recent paper, Branstetter, Chatterjee, and Higgins (2014) have found that therapeutic classes with high rates of generic competition have experienced significant decline in early-stage research activity, holding various other factors constant.

B. THE INCENTIVES FOR PATENT CHALLENGES

The 1984 act also created a procedure for generic firms to challenge the patents of the reference brand on the grounds of non-infringement and invalidity (a so-called paragraph IV challenge). An ANDA with a patent challenge can be submitted four years after brand approval.[3] If the brand name files suit against the generic within 45 days, there is a stay on the FDA approval of the ANDA for up to 30 months to allow for courts to rule on the generic's claims. After that time, a generic can enter "at risk" if litigation is still ongoing.

The first generic manufacturer to file a paragraph IV challenge resulting in entry prior to patent expiration is granted a 180-day exclusivity period. This generic exclusivity

2 Several studies have analyzed the special importance of patents to the innovative biopharmaceutical industry (Cohen, Nelson, and Walsh 2000; Grabowski, DiMasi, and Long 2015).

3 If an ANDA is filed without a patent challenge, the earliest that a generic can submit the ANDA application is five years after the reference brand's approval date. This is generally referred to as the data exclusivity period.

period can be very profitable to a generic manufacturer, since the generic drug typically can obtain large unit shares from the branded products with moderate discounts.[4] There also can be longer-term advantages in contracting with retail pharmacies since these providers typically do not stock multiple generic products for a particular drug product.

Patent challenges by generic firms typically focus on a patent's validity since generic products must be chemically identical to the reference brand in an ANDA filing (formulation patents can be an exception in this regard). A patent's validity can be challenged in terms of its novelty and the prior art, its obviousness, inequitable conduct in patent prosecution, and various other grounds (Voet 2014). The process including appeals can take several years and involve substantial resources in terms of attorneys, expert witnesses, and document discovery.

The expected profitability of patent challenge strategies was enhanced by important court rulings in 1998 that led to a change in the rules on 180-day exclusivity. Prior to July 1998, the FDA granted generic drug exclusivity only to those firms that won a court victory based on a ruling of non-infringement or patent invalidity. After the 1998 MOVA court decision overturned this interpretation of the 1984 act, FDA regulations were changed to also grant generic exclusivity to first filers on the basis of a negotiated settlement allowing earlier entry and also in those cases where the patent owners do not file suit against the ANDA filer with respect to the patent claims at issue (FDA 2003). As the FDA noted, in the 14 years from 1984 to 1998, only three ANDA applicants qualified for 180-day exclusivity. In the first five years after 1998, more than 60 ANDAs for a specific drug/dose strength received the exclusivity (FDA 2003).[5]

A key issue that emerged in the wake of the 1998 MOVA decision was that of shared exclusivity with respect to patent challenges for ANDA applications filed at the same time, usually exactly four years after approval of the new drug application (NDA). After a long period of legal and regulatory uncertainty, the FDA ruled in July 2003 that these firms would share exclusivity on a "patent-specific" basis (FDA 2003). These rules on shared exclusivity were superseded by the December 2003 Medicare Modernization Act (MMA) amendments to the Hatch-Waxman Act, which provided for "product-based" 180-day exclusivity. For ANDAs submitted after December 2003, exclusivity attaches to first-to-file challenger(s) to an Orange Book–listed patent rather than on a patent-by-patent basis.

As discussed below, we hypothesize that the MMA provisions significantly increased the incentives for a first-filing generic firm to broadly challenge the portfolio of the reference brand's listed patents. Otherwise a first-filing firm essentially could be foreclosed from sharing in the 180-day exclusivity period if earlier expiring patent(s) are successfully challenged by a rival first-filing firm. The MMA also added various provisions aimed at closing loopholes that could delay generic entry, including the late listing of additional

4 During the 180-day exclusivity period, however, branded firms often compete with an authorized generic product, either through contracting or in-house supply (Berndt and Newhouse 2012).

5 FDA grants generic drug exclusivity on the basis of individual dosage strengths and formulations of an approved reference drug product, so generics filing first ANDA patent challenges on specific formulations or strengths can be awarded separate 180-day exclusivity periods on that basis.

patents by branded firms as well as forfeiture penalties for generic firms for failure to exercise the 180-day exclusivity period in a timely fashion (Schacht and Thomas 2012).

C. ACADEMIC RESEARCH ON PATENT CHALLENGES AND DRUG INNOVATION

A number of studies have examined the price and other competitive effects of generic entry emanating from the 1984 act.[6] Analyses of the specific role of patent challenges, and particularly their impacts on innovation incentives, are more limited.[7] Grabowski and Kyle (2007) performed the first empirical study of the relation between patent challenges and market exclusivity periods (MEPs). Market exclusivity periods were defined as time between the FDA approval of a new drug entity and the entry of the initial generic referencing this product. They found the average market life was 13.5 years for NMEs that first experienced generic competition in the 1995 to 2005 period. Average MEPs declined only moderately over time, but a downward trend in MEPs was observed in the case of the very largest drug entities that are the target of more patent challenges. Based on a regression analysis, they also found that drugs with a patent challenge, other things being equal, had lower MEPs by approximately one and a half years.

In a more recent study of the role of patent challenges and their effects on market exclusivity periods, Hemphill and Sampat (2012) investigated NMEs experiencing first generic competition in the 2001–10 period. Hemphill and Sampat's (2012) paper was the first to categorize patents by type (active ingredient versus non–active ingredient patents) and conduct analyses at both the NME and the patent levels. They found that the most prevalent behavior was for generic firms to challenge late-expiring non-AI patents challenges with long nominal patent terms. They also found an increased likelihood of challenges to AI patents for large-selling drugs, but no evidence of a statistically significant negative effect on their MEPs. In a subsequent analysis that considered litigation outcomes for drugs that were first eligible for patent challenges between 2000 and 2008, Hemphill and Sampat (2013) found that branded firms won the vast majority of AI patent challenges that ended in a court decision. However, they also found that roughly a third of the AI patent challenges resulted in a settlement, which presumably allowed somewhat early entry by the generic first-filing challenger in several cases.[8] This issue is investigated in our analysis of settlement outcomes in Section VII.

Panattoni (2011) has examined the impact of district court decisions on the stock market values of branded drug pharmaceutical firms using an event study analysis. Her event study analysis found that paragraph IV court outcomes were roughly split between brand

6 See, for example, the discussions of this subject in Berndt and Newhouse (2012) and Berndt and Aiken (2011).

7 For a recent analysis of the static welfare benefits from patent challenges associated with increased generic competition, see Branstetter, Chatterjee, and Higgins (2011). As noted above, the authors also have a companion NBER paper (2014) investigating the effects of generic entry on early-stage R&D activities.

8 For non-AI patents, Hemphill and Sampat found that generics won roughly two-thirds of the cases ending in a court decision, but the majority were settled by the parties. Our outcomes analysis in Section VII distinguishes between method-of-use and formulation patents. These two types of non-AI patents have very different outcome patterns.

and generic firms. She also found that they have substantial value consequences in terms of positive and negative abnormal shocks to a company's market valuations for both brand and generic firms. Panattoni's study provides insights on why brand and generic firms may have considerable incentives to settle patent challenge cases and avoid the uncertainty and potential losses in profits associated with these court decisions.[9]

At this point, the existing literature provides various insights on the effects of patent challenges but leaves open a number of issues for research. First, these studies have not specifically analyzed the changes in firm behavior emanating from the regulatory and legislative changes to the Hatch-Waxman Act, after MOVA and the MMA and their broader competitive effects. The increased likelihood of patent challenges to AI as well as non-AI patents, racing behavior, and other dynamic changes are key issues that we investigate in the present analysis. We also focus on the role and outcomes of settlements together with court decisions, examining patents in terms of active ingredient, method-of-use, and formulation claims.

D. HYPOTHESIS

We wish to investigate the following hypotheses in the current analysis in light of the various developments discussed above.

(1) The proportion of new drug introductions subject to patent challenges will increase and the time to patent challenge will decrease in the wake of the legal and regulatory changes to the Hatch-Waxman Act that occurred between 1998 and 2003.
(2) For commercially significant products, there is an increased likelihood of racing behavior by generic firms to obtain the 180-day exclusivity period awarded to a first-filing firm, particularly under the post-MMA awards on an NME-specific basis. These also increased incentives for generic firms to challenge AI patents as well as method-of-use and formulation patents for NMEs approved for these commercially significant NMEs.
(3) AI patents have the highest likelihood of being upheld in court litigation, followed by method-of-use patents, with formulation patents having the greatest likelihood of a successful generic challenge on the grounds of non-infringement or patent invalidity. Settlements will reflect these expected litigation outcomes, but brand and generic companies may elect to settle patent litigation, even with favorable perceived odds of winning in court, in order to avoid the risk of an adverse legal decision with significant negative market valuation impacts.

9 Another strand of the literature involves so-called "pay for delay" or "reverse payment" settlements that involve cash payments and/or in-kind benefits from the patent holder to potential generic entrants. These represent a minority of patent challenge settlement agreements, but have been the subject of various antitrust litigation cases and a recent Supreme Court ruling (Drake, Starr, and McGuire 2015). An investigation of the effects of reverse payment settlement agreements is beyond the scope of the present analysis. However, in our outcomes analysis we consider whether any of the settlements involving a product's active ingredient or core patent are characterized by reverse payments.

(4) The increased likelihood of patent challenges and settlements for more recent new drug introductions, and for patents broadly including core patents and claims involving an NME's active ingredient, will act to shorten market exclusivity times for branded products.

With respect to the first hypothesis, the existing empirical literature provides support for more and earlier patent challenges over time, but this has not been specifically analyzed with respect to the 1998 to 2003 regulatory changes. Correspondingly, there have not been empirical analyses (that we are aware of outside of some legal presentations) with respect to the second hypothesis that focuses on how these regulatory changes have contributed to racing behavior and the increased likelihood of challenging strong AI patents.[10] With respect to the hypothesis on patent challenge outcomes, Panattoni (2011) has done the most detailed analysis on the consequences of court decisions involving patent challenges for market valuations, but her analysis is not disaggregated by type of patent, nor does it consider settlement outcomes. Hemphill and Sampat (2013) provide an analysis of outcomes of patent challenges differentiated by AI versus non-AI patents, but do not investigate the consequences regarding the exclusivity times for the branded firms' NMEs.

III. Data

A. SMALL MOLECULE DRUG SAMPLE

We have assembled a comprehensive data set of new molecular entities (NMEs) approved by the FDA from 1994 to 2006 to analyze the hypotheses presented above on the determinants and outcomes of patent challenges. Our sample of NMEs is based on year of approval rather than the year of initial generic competition employed in prior studies. This arguably provides a better framework to analyze the regulatory changes discussed above. NMEs approved beginning in 1999 were the first cohort to experience the full effects of the changes, given they were first subject to ANDAs with a patent challenge in 2003 under the new rules involving patent challenge codified by the MMA. We have a number of NMEs that span the pre- and post-MMA periods, and this is a focus of our statistical analysis.

Our sample is initially constructed from data in FDA files on all new molecular entities approved between 1994 and 2006. We excluded from this sample new biologics, over-the-counter and diagnostic drugs, as well as NMEs that were discontinued for medical or economic reasons (such as Vioxx). For each of the remaining NMEs, we collected

10 The rationale for increased incentives for a generic firm to challenge a reference product's AI patents under the 2003 MMA provisions was recognized by legal experts (Berman 2007). In particular, consider the scenario where two firms share exclusivity as same-day first filers, but only one challenges the branded firm's early expiring AI patent. If that firm is successful in its challenges to the AI patents through a court win or settlement, the other first-filing firm risks losing shared exclusivity because there is only one 180-day exclusivity period per NME that would be triggered by the first firm's entry. With the prior patent-based exclusivity system, a first-filing firm could still retain limited 180-day exclusivity associated with a non-AI patent in this scenario vis-à-vis the later entrant, but would still be delayed due to the initial entrant successfully challenging the AI patent.

information on the patents listed in the FDA's Orange Book. After April 2003, patents listed in the Orange Book are categorized by patent type, in particular whether a specific patent involves AI substance, formulation, and method-of-use claims. Prior to April 2003, the only information provided on the FDA site was on method-of-use claims. We further classified patents listed prior to April 2003 into the three FDA categories utilized after 2003. In particular, we determined whether each of these patents specifically contained AI and formulation claims in addition to any method-of-use claims, using information from various sources. Further details are provided in the Online Appendix (see http://www.mitpressjournals.org/doi/suppl/10.1162/ajhe_a_00066).

This approach produced a sample of 214 NMEs approved between 1994 and 2006. For these 214 NMEs there are 716 Orange Book–listed patents at issue.[11] Many patents have AI claims combined with method-of-use and/or drug product formulation claims. In the analysis that follows, we employ a hierarchical ordering approach reflecting the views of legal experts on patent claims, namely AI patents being the strongest in terms of the scope of patent claims and drug product claims being the most limited in this regard (Voet 2014). This hierarchical ordering, therefore, is as follows:

(1) AI patent: All patents with an AI claim, either separately or in combination with method-of-use and/or drug product claims.
(2) Method-of-use patent: All patents with only a method-of-use claim, or a method-of-use plus a drug product claim.
(3) Drug product patent: All patents with only a drug product formulation claim.

Based on this classification approach, an NME in our drug product sample has, on average, 1.13 AI patents (most often in combination with non-AI claims), 1.34 method-of-use patents (also including supplementary drug product claims), and 0.87 drug product–only patents (for an average of 3.34 patents per NME).

Under the provisions of the Hatch-Waxman Act, firms may select one of the listed patents in the Orange Book for a particular NME and apply for a patent term extension. The term of the extension is based on patent time lost during the clinical testing and regulatory review periods.[12] Most often, firms will then apply for patent term extension on their key active ingredient patent, since this provides the broadest scope of patent protection and frequently expires earlier than any non-AI patents. If an active ingredient patent is unavailable, or has a very short patent term remaining on approval of the NME, firms can elect patent term extension on a key method-of-use patent, or in more limited circumstances for a drug product or formulation patent. In the analysis that follows, we designate patents granted a patent term extension by the US Patent and Trademark Office as an

11 We focus on patents listed in the Orange Book at the time of launch and for the first five years after FDA approval in this compilation. We include late-listed patents only if they are subject to a patent challenge. Patents that are listed after an ANDA is filed are not subject to a 30-month stay on generic entry.

12 Patent restoration is equal to one-half of the effective patent time lost during clinical trials, plus the full time lost during FDA review, subject to five years' maximum extension and no patents can be extended beyond 14 years from the date of NDA approval.

NME's "core" patent.[13] This set of patents is a particular focus of interest with respect to patent challenges over time.

In addition to this patent information, we have assembled data on a drug product's peak US sales to investigate the effects of market size on patent challenges. An additional feature of our analysis involves the outcomes of patent challenges for the top quintile of NMEs ranked by their peak sales over the period 1994–2006. As discussed, the potential impact on R&D incentives from an economic standpoint can be particularly significant for the top quintile of new drug approvals. These drugs, 43 NMEs in our sample, have peak sales ranging from $800 million to several billion dollars. They account for over 70 percent of the sales distribution of 1994 to 2006 NMEs (based on peak sales in 2010 dollars) and have been a primary target of patent challenges by generic firms.

B. COMPARATIVE ANALYSIS OF PATENT LITIGATION FOR NDA-APPROVED BIOLOGICS

Our empirical analysis is focused on changing trends and outcomes with respect to patent challenges for small molecule pharmaceuticals. Many other medical therapies and products have experienced increased patent litigation over time. Consequently, we wanted to perform comparative analyses regarding the extent of patent litigation for other pharmaceutical products that have not been subject to the same incentives to engage in patent challenges as small molecule drugs. The most natural comparators are large molecule biologics. They are subject to pre-market FDA approvals, require physician prescriptions, and share common reimbursement systems to small molecule chemical entities. However, no abbreviated pathway or counterpart to generic drugs existed in the case of biologics until the 2010 Biosimilar Price Competition and Innovation Act (BPCIA) established one for biosimilars.

The BPCIA established a different pathway for so-called biosimilars compared with generics, and different rules for patent challenges and regulatory exclusivity periods than for small molecule drugs.[14] While it is too early to assess how these different regulatory approaches for small and large molecule drugs will affect market competition, there is a set of biological entities that provide an interesting comparative group. These biologics were approved as new drug applications (NDAs) under the Hatch-Waxman statute rather than as biological licensing applications (BLAs) under the Public Service Act. While they constitute a limited set of products, they include some important recombinant biologic drug classes (e.g., human insulins and human growth hormones and specialty orphan

13 A small minority of NMEs in our sample do not have any patents receiving a patent term extension. As noted in Section II, patent extensions are capped at 14 years of effective patent life, including the extensions. Some of the products in our sample have an active ingredient patent in excess of 14 years even before any extension, and are therefore ineligible for a patent extension on these AI patents. These patents are also treated as core patents in the current analyses. In our sample of 214 NMEs, 188 of the NMEs have a core patent assignment based on these dual criteria.

14 Biosimilars are drugs that are manufactured from large-scale cultures of living cells that are similar—but not structurally identical—to the originator's biological entity or reference product (Grabowski, Guha, and Salgado 2014).

drug products like Cerezyme). Many of these biologics had prior chemical entity versions synthesized from animal sources.

Biologic drugs approved as NDAs are subject to patent challenges and some of the other aspects of the Hatch-Waxman statute. They also are eligible to utilize an abbreviated pathway to gain FDA approval rather than a full NDA or BLA submission. This pathway, legally denoted as a 505(b)(2) application, allows a product to rely on the reference brand's safety and efficacy data, usually supplemented by some small-scale clinical trials to demonstrate comparable outcomes.[15] Companies using this abbreviated pathway usually compete as therapeutically similar therapies rather than as bioequivalent or interchangeable products. Omnitrope, a human growth hormone, used the 505(b)(2) pathway and gained approval in 2006 as a biosimilar referenced to Genotropin, but without a rating of bioequivalence to Genotropin.[16]

Like small molecule drugs, biologics approved as NDAs are subject to patent challenges with the challenger relying on much of the originator's safety and efficacy data in an abbreviated FDA application. At the same time, we expect less economic incentive to challenge patents compared with generic drugs, given the absence of first-filer exclusivity or the likelihood of interchangeability with the reference brand. They essentially have to compete more "brand to brand" rather than "generic to brand," engaging in marketing to providers and competing on quality as well as price. This was the case for Omnitrope (Grabowski, Guha, and Salgado 2014).

Based on FDA records, there were 24 biologic entities that were approved through the NDA process over the comparable 1994–2008 period utilized for our small molecule drug sample. In addition, there were 86 listed patents for these compounds obtained primarily from the FDA's Orange Book, supplemented by company documents and litigation-based websites. The extent of patent challenges and litigation for these products and patents was compared with that for our small molecule drug sample. The results are reported in Section V.B.

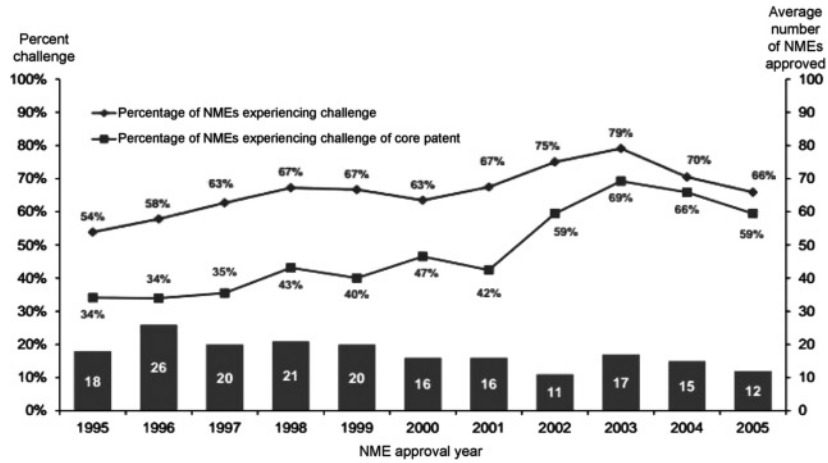
IV. Descriptive Statistics and Trends

In this section, we consider various descriptive statistics and time trends with respect to patent challenges for our sample of 214 NMEs. In Figure 1 we plot the percentage of NMEs experiencing paragraph IV challenges by NME approval year. A three-year moving average is employed to smooth out year-to-year fluctuations. As shown, there is a strong upward trend in the percentage of NMEs experiencing a paragraph IV patent challenge to at least one of their listed patents. There is an increase from 54 percent for the 1995 cohort of NMEs experiencing a challenge to a peak of 79 percent for the 2003 cohort. Similarly, the percentage of NMEs that have their core patents challenged increases from 34 percent in the 1995 cohort to a maximum of 69 percent in the 2003 cohort. Some right

15 According to the FDA, a 505(b)(2) application is an abbreviated filing that relies on existing safety and efficacy data, supplemented by a sponsor's own data when necessary, for modified drug formulations with comparable outcomes to their reference drug products.

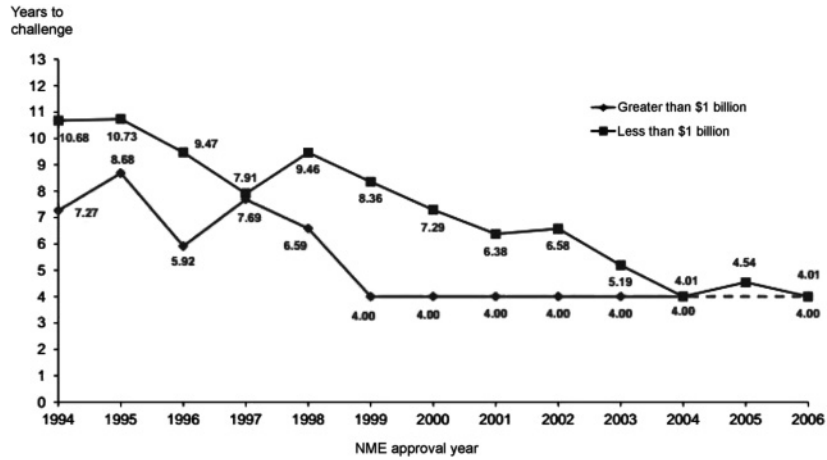
16 For an economic analysis of the Omnitrope case examples, see Grabowski, Guha, and Salgado (2014).

FIGURE 1. Percentage of NMEs experiencing paragraph IV challenges and number of NMEs approved: Three-year moving averages (1995–2005)



Data sources: IMS; Orange Book 1994–2011; FDA (NME data; paragraph IV patent certifications). Company reports and litigation based data sources.

FIGURE 2. Median years from approval to paragraph IV challenge (1994–2006)



Data sources: IMS; Orange Book 1994–2011; FDA (NME data; paragraph IV patent certifications). Company reports and litigation based data sources.

censoring occurs in the percentage of NMEs experiencing patent challenges in the last few NME approval years in Figure 1.

In Figure 2 we consider the median number of years from NME approval to a paragraph IV challenge for those NMEs experiencing a challenge. This is plotted over time by

NME approval year. This graph provides supportive evidence concerning the racing behavior hypothesis discussed in the previous section for large-selling NMEs. The median time to patent challenge for the largest-selling drug cohort with sales in excess of $1 billion was generally around seven years for 1994 to 1998 approvals, but this median value declined to exactly four years for 1999 to 2006 approvals. Four years is the earliest possible time for an ANDA-based patent challenge. The median time in years from approval to paragraph IV challenge for NMEs with sales less than $1 billion also exhibits a strong downward trend. Median time averaged just below 10 years in the 1994 to 1998 NME cohorts, with a decline to just over five years for the 2003 cohort. We also performed a logistic regression specification to examine the likelihood that a particular NME experiences a challenge in the fourth year after approval. The results, shown in Table A1 in the Online Appendix, provide further support for the racing behavior hypothesis.[17]

Table 1 provides drug-level summary statistics on the characteristics of patent challenges and market exclusivity periods. For the data on the overall sample shown in the first column, 64 percent of NMEs experience a challenge to at least one of their patents. In addition, 47 percent of the NMEs experience a challenge to an AI patent and 46 percent to the NME's core patent. Peak annual US sales for the 214 NMEs average $658 million with a range from $1.9 million to $9.5 billion in value. The final three rows in Table 1 show the nominal and effective patent life in years for our sample of NMEs. The mean nominal patent life, measured from date of approval to last expiring patent, is 16.2 years for the full sample of NMEs, while the effective market life is 13.3 years.[18] The effective market life is 13.4 years for the top quintile of drugs in a subsample for which we have researched outcomes in detail in the analysis presented in Section VII below.

Table 1 also provides summary statistics on patent challenges grouped by years. Specifically, we compare summary statistics on those NMEs approved in the 1994 to 1998 period (the pre-MMA cohort, given the four-year patent challenge waiting period) with those approved in the 1999 to 2006 period (the post-MMA cohort). This table supplements information on time trends presented in Figures 1 and 2. In particular, this table shows that the number of NMEs with an AI patent challenge increased from 34 percent in the pre-MMA cohort to 57 percent in the post-MMA cohort, with a similar upward trend in core patent challenges. The count of both AI patents and non-AI patents also increased significantly over these two periods, from 1.00 to 1.23 AI patents per NME, and from 1.81 to 2.53 non-AI patents per NME.[19] Perhaps the most interesting finding in Table 1 is a statistically significant decline in the average effective life for the top quintile drugs from

17 In particular, large-selling NMEs are more likely to experience a paragraph IV challenge exactly four years after approval (statistically significant at the 1 percent level) and post-MMA and recent approvals are more likely to experience a challenge at the earliest possible date of four years (all significant at the 1 percent level).

18 As noted in the footnotes in Table 1, we omit NMEs for which the outcomes of patent litigation are not available in calculating effective market life, and also omit the lowest quintile of NMEs, given few generic entrants or challenges for very small NMEs.

19 This upward trend in the number of listed patents by NMEs has been observed in other studies (Hemphill and Sampat 2012). This trend in increased patents can be viewed as a reason for increased patent challenges by generics, or a defensive response by branded firms to more challenges. We also performed

TABLE 1. NME-level summary statistics

	Full sample					NME approval year: 1994–98					NME approval year: 1999–2006				
	Mean	Std. dev.	Min.	Max.	*N*	Mean	Std. dev.	Min.	Max.	*N*	Mean	Std. dev.	Min.	Max.	*N*
NME challenged	0.64	0.48	0	1	214	0.59	0.49	0	1.00	93	0.69	0.47	0	1	121
AI patent challenged	0.47	0.50	0	1	168	0.34	0.48	0	1.00	74	0.57	0.50	0	1	94
Core patent challenged	0.46	0.50	0	1	188	0.34	0.48	0	1.00	83	0.55	0.50	0	1	105
Count of AI patents	1.13	0.88	0	6	214	1.00	0.66	0	3.00	93	1.23	1.01	0	6	121
Count of non-AI patents[1]	2.21	2.55	0	13	214	1.81	2.31	0	11.00	93	2.53	2.68	0	13	121
Annual sales ($ millions)	658	1,205	1.86	9,549	214	819	1,530	1.86	9,549	93	534	864	2.00	5,192	121
Nominal patent term (in years)	16.2	3.98	1.70	28.14	214	16.3	3.98	5.01	25.42	93	16.1	3.99	1.70	28.14	121
Effective market life (in years)[2]	13.3	3.45	5.74	22.02	155	14.1	3.28	6.62	21.99	64	12.7	3.47	5.74	22.02	91
Effective market life for top quintile NMEs (in years)[3]	13.4	2.44	8.17	21.59	40	14.5	2.10	11.69	21.59	21	12.2	2.24	8.17	15.79	19

Data sources: IMS; Orange Book 1994–2011; FDA (NME data; paragraph IV patent certifications); company reports and litigation based data sources.
Notes: Late-listed patents that first appear in the Orange Book more than five years after NME approval and are not challenged are excluded from the analysis. [1]There are on average 1.34 method-of-use patents and 0.87 drug product patents for each NME. [2]Effective market life is calculated as the time between approval and the earlier of (1) the date of patent expiration or (2) the date of generic entry. NMEs that were challenged but for which litigation outcome information is not available have been excluded from the calculation. Additionally, the lowest quintile of NMEs by sales are excluded, given few generic entrants or patent challenges in this quintile. [3]Effective market life is calculated as the time between approval and the earlier of (1) the date of patent expiration or (2) the date of generic entry. Litigation outcomes research was performed for these NMEs. Two drugs with entry at risk and one with ongoing litigation are excluded from this calculation.

TABLE 2. Likelihood of core or active ingredient patent challenged: Logistic regression at the NME level

	Core patent		Active ingredient patent	
Variable	(1)	(2)	(3)	(4)
Approval date	0.038[a]		0.030[a]	
	(0.012)		(0.011)	
Post-MMA		0.291[a]		0.215[a]
		(0.078)		(0.083)
ln (maximum yearly sales)	0.172[a]	0.177[a]	0.188[a]	0.190[a]
	(0.030)	(0.030)	(0.032)	(0.032)
# observations	188	188	168	168

Data sources: IMS; Orange Book 1994–2011; FDA (NME data; paragraph IV patent certifications); company reports and litigation based data sources.
Notes: Standard errors are shown in parentheses. The first sample of core patents consists of NMEs approved in 1994 or later that received a patent extension from the US PTO; the second sample consists of NMEs with an active ingredient patent. Coefficients display the marginal effect calculated at the mean of each independent variable. For categorical independent variables, coefficients display the marginal effect of changing the variable from 0 to 1. [a]$p < 0.01$, [b]$p < 0.05$, [c]$p < 0.10$.

14.5 years to 12.2 years over the two periods. This decline in effective market life, which is statistically significant at the 1 percent level, is discussed further in the outcome analysis section (Section VII).[20]

V. Statistical Analyses of Patent Challenges

In this section, we utilize a logistic regression framework to examine the factors influencing the likelihood of patent challenges. We focus on challenges to an NME's core and AI patents. We also do some comparative analyses to the set of biologic entities approved as NDAs under the regulatory framework of the Hatch-Waxman Act.

A. REGRESSION ANALYSES OF PATENT CHALLENGES TO CORE AND AI PATENTS

In Table 2 we consider the likelihood that an AI or core patent will be challenged as a function of NME approval time and peak sales. The coefficients for these logistic

some descriptive regressions that indicate the increase of AI and non-AI patents are statistically significant across these two periods (see Table A3 in the Online Appendix).

20 In addition, we examined summary statistics for NMEs grouped by their peak sales, with details provided in Table A2 of the Online Appendix. As expected, there is an increased likelihood of a patent challenge, including an AI or core patent challenge, as product peak sales increase. This is consistent with the logistic regressions discussed in Section V.

regressions display the marginal effects calculated at the mean of each independent variable. The independent variables include the year of an NME's approval and whether the approval is pre- or post-MMA. A drug's peak sales is also included as an explanatory variable.

Table 2 provides support for the hypothesis that an NME's core patent has a greater likelihood of being challenged in the case of large-selling drugs and for post-MMA approvals. In particular, post-MMA approvals are 29 percent more likely to have a patent challenge to their core patent and 21 percent more likely to have a challenge to their AI patent (statistically significant at the 1 percent level). Approval date is also statistically significant at the 1 percent level and indicates a 3 to 4 percent increase in the likelihood of a patent challenge per year for core and AI patents. The estimated coefficient for the natural log of maximum yearly sales is statistically significant in all the specifications at the 1 percent level. Similar findings are observed in the case of challenges to an AI patent for those NMEs with an AI patent. Given the fact that an NME's core patent is frequently an active ingredient patent, the similarity of the results for these two cases is not surprising.

In Table 3 we utilize patent-level data to investigate hypotheses on the likelihood of a challenge to a specific NME patent depending on whether the patent is a core or an AI patent. Utilizing a logistic regression framework, the dependent variable is an indicator value that takes the value of one if there is a challenge to the specific patent at issue and zero otherwise. The independent variables include the variables based on year of an NME's approval, whether an NME is pre- or post-MMA, and the natural log of its maximum yearly sales as in Table 2. We also include an indicator variable that takes the value of one if a patent is a core patent (columns 1 and 2), or if it is an AI patent (columns 3 and 4). We also include interactive term variables between these core and AI patent variables and the approval year and peak yearly sales variables. The standard errors are clustered at the NME level.

The logistic regression in Table 3 indicates that a core patent is less likely to be challenged than a noncore one (statistically significant at the 1 percent level). Similar results are observed in the case of challenges to the AI patent and non-AI patents. However, the interactive terms indicate that NMEs approved in the post-MMA period have a higher likelihood of a patent challenge to a product's core and AI patents (statistically significant at the 1 percent level). The marginal changes in probability displayed in Table 3 for these variables are economically as well as statistically significant. These results confirm the findings on increased challenges to an NME's AI and core patents based on the NME-level regressions in Table 2.

B. PATENT CHALLENGES FOR NDA-APPROVED BIOLOGICS

As discussed in Section III, there is a small set of biologic drugs that were approved as NDAs through the Hatch-Waxman Act. Based on FDA approval data, we found 24 biologic drugs were approved through this pathway covering the period 1994 to 2008 with 86 patents listed in the FDA's Orange Book and related sources. On average, there are 3.5 patents listed for the 24 biologic drugs in the sample, which is comparable with the value for the small molecule drugs sample shown in Table 1.

TABLE 3. Likelihood of core vs noncore and active ingredient vs non–active ingredient patent challenges: Logistic regression at the patent level

	Core vs noncore		Active ingredient vs non–active ingredient	
Variable	(1)	(2)	(3)	(4)
Approval date	0.015		0.016	
	(0.010)		(0.010)	
Post-MMA		0.031		0.011
		(0.084)		(0.089)
ln (maximum yearly sales)	0.126[a]	0.121[a]	0.136[a]	0.130[a]
	(0.027)	(0.026)	(0.030)	(0.028)
Core patent flag	−0.138[b]	−0.318[a]		
	(0.054)	(0.079)		
Core patent flag × post-MMA		0.255[a]		
		(0.086)		
Core patent flag × maximum yearly sales	0.039	0.059[c]		
	(0.031)	(0.033)		
AI patent flag			−0.207[a]	−0.405[a]
			(0.057)	(0.082)
AI patent flag × post-MMA				0.279[a]
				(0.089)
AI patent flag × maximum yearly sales			0.009	0.029
			(0.034)	(0.035)
# observations	716	716	716	716

Data sources: IMS; Orange Book 1994–2011; FDA (NME data; paragraph IV patent certifications); company reports and litigation based data sources.

Notes: Sample consists of NMEs approved in 1994 or later. Standard errors are clustered at the NME level and are shown in parentheses. Coefficients display the marginal effect calculated at the mean of each independent variable; for categorical independent variables, coefficients display the marginal effect of changing the variable from 0 to 1. [a]$p < 0.01$, [b]$p < 0.05$, [c]$p < 0.10$.

These NDA approval biologics exhibit a very different experience with respect to patent challenges and litigation compared with the small molecule drugs approved over the same period. In particular, the data obtained from court and company documents indicate biologic drug patents were subject to much less patent litigation and fewer challenges. As shown in Table A4 in the Online Appendix, we found that only 7 of the 24 biologic entities were subject to litigation. In terms of the 86 listed patents for these 24 biologic drugs, 12 patents were subject to litigation and only 3 of these involved an active ingredient patent. By contrast, more than half of the NMEs and more than half of their listed patents in our small molecule sample were subject to patent challenges. We should note that for this biologic sample we included not only patent litigation ensuing from a

paragraph IV patent challenge, but also challenges to the patents from other branded firms not using this procedure.[21]

The striking differences in patent litigation for NDA-approved biologics compared with small molecule drugs indicate that our findings are not simply reflective of a general trend toward increased patent litigation for pharmaceuticals more broadly. The combination of low-cost entry, bioequivalence to the reference brand, and high potential economic rewards for being a first-filer of a paragraph IV patent challenge appear to lead to powerful incentives for patent challenges that are unique in nature. At the same time, these findings are subject to various qualifications and should not be generalized to other classes of biologics. There are significant differences in the complexity of various biologic products, such as the leading monoclonal antibody entities, and many of these complex biologic products have large and varied patent estates. The abbreviated pathway for biosimilars referenced to biologic entities created by the BPCIA will be governed by very different regulatory rules and patent challenge processes (Grabowski, Long, and Mortimer 2014). It remains to be seen how patent litigation will evolve as biosimilar entities emerge for these newer and more complex biologics. This topic remains an important issue for further research.

VI. The Impact of Patent Challenges on Market Exclusivity Periods

In this section, we examine how increased patent challenges have affected the time to generic entry and market exclusivity periods using a least squares regression analysis. The key independent variables measure whether there is a patent challenge to at least one of our NME's patents as well as a challenge to an NME's core patent or AI patent. Other variables in the regression analysis include the natural log of an NME's peak sales, the number of active and non–active ingredient patents, and the NME's approval date or whether it is a pre- or post-MMA approval. The sample includes only the top four quintiles of NMEs, omitting the lowest quintile of NMEs because there are few economic incentives for generic entry when brand sales are very low in value.[22]

The regression estimates presented in Table 4 indicate that the effect of patent challenges on time to generic entry is both economically and statistically significant. In the first two columns, the effect of a challenge to at least one of an NME's patents is displayed. The coefficient on the patent challenge variable indicates a reduction of approximately two years in the time to generic entry (statistically significant at the 1 percent level). NMEs

21 Two of the NMEs experienced litigation on five patents that were done as paragraph IV challenges, whereas the other seven challenged patents involved more general litigation and challenges by branded rival firms with competing or potentially competing products.

22 The majority of 1994–2006 NMEs included in our sample regressions already have generic competition. In these cases we utilize the time from FDA approval to initial generic entry. For those without generic entry yet, we utilize the expected date of generic entry based on court and company documents. A small number of NME observations are omitted from regression equation estimates where litigation regarding patent challenges is ongoing at the district court level, and where settlements have occurred but remain confidential.

TABLE 4. Determinants of time to generic entry

Variable	(1)	(2)	(3)	(4)	(5)	(6)
Approval date	−0.094		−0.125		−0.170[b]	
	(0.083)		(0.088)		(0.080)	
Post-MMA		−1.396[b]		−1.465[b]		−1.787[a]
		(0.553)		(0.582)		(0.547)
ln (maximum yearly sales)	0.219	0.149	0.244	0.171	0.152	0.068
	(0.240)	(0.237)	(0.244)	(0.242)	(0.224)	(0.222)
# active ingredient patents	0.394	0.439	0.237	0.298	0.370	0.441
	(0.312)	(0.305)	(0.371)	(0.363)	(0.310)	(0.304)
# non–active ingredient patents	0.206[c]	0.207[c]	0.190[c]	0.193[c]	0.091	0.096
	(0.114)	(0.112)	(0.113)	(0.110)	(0.104)	(0.101)
Challenge flag	−2.185[a]	−2.087[a]				
	(0.730)	(0.719)				
Active ingredient patent challenge flag			−1.635[b]	−1.526[c]		
			(0.809)	(0.794)		
Core patent challenge flag					−1.391[b]	−1.167[b]
					(0.564)	(0.558)
Constant	13.52[b]	11.82[b]	14.17[b]	11.24[b]	17.38[a]	12.99[a]
	(6.059)	(4.595)	(6.359)	(4.757)	(5.904)	(4.345)
# observations	156	156	129	129	141	141

Data sources: IMS; Orange Book 1994–2011; FDA (NME data; paragraph IV patent certifications); company reports and litigation based data sources.

Notes: Time to generic entry and changes in approval date are measured in years. Standard errors are shown in parentheses. For NMEs for which a generic has not yet entered the market, the patent expiration date is assumed to be the expected date of entry based on available information from court and company documents. Sample consists of the top four quintiles of NMEs approved in 1994 or later. Sample excludes NMEs with ongoing litigation at the district court level and those for which settlement information on expected date of generic entry remains confidential.

[a] $p < 0.01$, [b] $p < 0.05$, [c] $p < 0.10$.

introduced in the post-MMA period also have a statistically significant decline in the market exclusivity period of just under one and a half years (significant at the 5 percent level). None of the other variables are statistically significant except for the number of non–active ingredient patents. The estimated coefficient indicates that an additional patent results in a few months' increase in the time to generic entry (statistically significant at the 10 percent level).

The next four columns in Table 4 display the effects of a challenge to an NME's AI or core patent, respectively. The samples are correspondingly restricted to NMEs that contain an AI or core patent. The AI and core patent challenge variables are also statistically significant, but with smaller estimated values compared with a challenge to any NME patent. In particular, specific challenges to an AI or core patent result in an estimated

reduction in market exclusivity times of between one and one and a half years (generally statistically significant at the 5 percent level). Otherwise, the results are similar in character to the regression with the general patent challenge flag. The post-MMA variables display a statistically significant decline in the time to generic entry as before, and the number of non–active ingredient patents is the only other statistically significant variable (at the 10 percent level).

It is plausible that the challenge flag variable would have greater magnitude and significance in the estimated equations in Table 4 than the patent challenge variables associated with core or AI patents. Based on the estimated equations, challenges to an NME's AI or core patents have about half the negative impact on time to generic entry than patent challenges more generally. At the same time, these results are subject to the qualification that it is difficult statistically to separate the effects of challenges to AI or non-AI patents since most challenges occur together, particularly in the post-MMA period. To further consider the role of patent challenges on market exclusivity periods and time to generic entry, we look at the litigation outcomes of different types of challenges to the top quintile of NMEs in our sample that account for a large share of sales across the NME approvals.

VII. Litigation Outcomes for the Top Quintile of NMEs

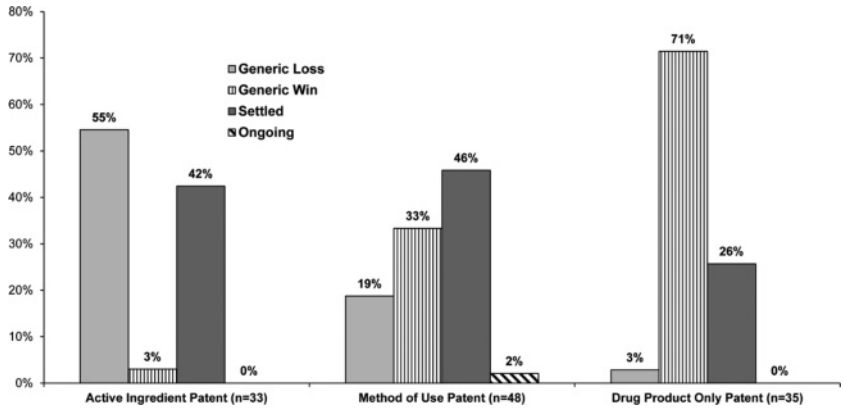
The top quintile of NMEs ranked by sales provides a particularly interesting subset of drugs to evaluate in terms of litigation outcomes. As discussed, a number of studies have pointed to the skewed nature of the sales distribution in the case of biopharmaceutical drugs (Berndt et al. 2015; Grabowski, Vernon, and DiMasi 2002). In this regard, the top quintile of NMEs in our sample accounts for over 70 percent of total peak sales obtained by all the 1994 to 2006 approvals. These are critical NMEs to a pharmaceutical company's return on R&D as well as primary targets for generic firms to obtain 180-day exclusivity rights. The regression analyses undertaken in the last section indicate that these top-selling drug products have a high likelihood of experiencing a patent challenge, and these challenges generally extend to the NME's AI and core patents as well as its non-AI or method-of-use and drug product–only patents.

There is also an essentially complete record of litigation outcomes for the top quintile of NMEs in terms of actual and expected dates of generic entry. In this regard, settlement agreements allowing early generic entry from patent challenges for top-selling drugs are usually published as material information in company SEC filings. In addition, given that patent challenges are typically filed as early as possible after an NME is approved, enough time has elapsed even for the most recent NME approvals in our sample to assess court litigation including appeals.[23]

Our basic hypothesis on litigated outcomes, enumerated in Section V above, is that AI patents have the highest likelihood of being upheld in court litigation, followed by method-of-use patents with drug product formulation patents being the most likely for generic firms to be able to successfully overturn in terms of invalidity or non-infringement,

23 As noted in Figure 3, only one NME in our sample (Alimta) has an ongoing generic appeal at the Federal Circuit on one of its patents, and this does not substantially affect the results.

FIGURE 3. Litigation outcomes by patent type: Top quintile NMEs (1994–2006)



Data sources: IMS; Orange Book 1994–2011; FDA (NME data; paragraph IV patent certifications). Notes: [1]The top quintile of NMEs contains 43 NMEs. NMEs with no challenged patents (Arimidex and Coreg) are excluded. The final sample for this figure consists of 116 patents, covering 41 NMEs. [2]Patents can have multiple designations. Patents with an active ingredient designation are first classified as active ingredient patents. Patents with a method-of-use designation but not an active ingredient designation are classified as method-of-use patents. Patents with only a drug product designation are classified as drug product patents. [3]The generic win classification includes patents that were challenged, but not defended by the brand manufacturer. [4]Ongoing litigation involves a method-of-use patent for Alimta currently on appeal at the Federal Circuit by generic firm challenger.

although this depends on the specific patent claims at issue.[24] While innovative firms have a greater likelihood of prevailing in the case of AI patents, we hypothesize that they may elect to settle challenges by offering somewhat earlier entry to the generic firm(s) filing patent suits to avoid the risk of a low-probability adverse legal decision, particularly for those top quintile products that have a disproportionate impact on company earnings. Similarly, a first-filing generic firm may also elect to settle a patent dispute even where they enjoy favorable odds of success in the case of a top-selling product that is important to future earnings growth.

To investigate this issue, we have reviewed various court and legal documents to determine litigation outcomes for the top quintile of NMEs in our sample, ranked by their peak sales. In Figure 3 we present litigation outcomes by patent types for this sample. In particular, the values in this figure are associated with the following outcomes: for those cases terminating in a court decision (including appeals), the first two categories denote

24 In this regard, the panels at the US Patent and Trademark Office adjudicating patent challenges in the form of an Inter Partes Review (IPR) recently upheld formulation patents in the case of two drug entities, Tygacil and Oracea. The IPR bodies have built up a reputation for upholding high standards on patent validity and infringement in cases brought before them since this pathway was established under the American Invents Act. The act became effective in October 2012.

whether there is a generic loss or win. The third category denotes litigation case outcomes involving settlement between the generic and branded firm. As shown in Figure 3, branded firms have won a majority of court decisions on AI patents. In particular, the breakdown of outcomes on AI challenges across the categories is 55 percent wins by branded firms, 3 percent wins by generic firms, and 42 percent resulting in settlements between the brand and generic firms. For method-of-use patents, there are 33 percent wins for generic firms, 19 percent wins for branded firms, with 46 percent of method-of-use patent challenges resulting in settlements.[25] In the case of drug product formulation–only patents, generic firms prevail in an overwhelming percentage of the patent cases, winning 71 percent in court decisions to 3 percent for the branded firm, while 26 percent are resolved through settlements.

The court outcomes for top quintile products shown in Figure 3 are generally consistent with patent experts' opinions on the strength and scope of biopharmaceutical patents. At the same time, settlements are prevalent across all these categories of patent types. This raises the question of why this is the case. There appear to be several reasons why this occurs. First, as noted above, it can reflect risk averse behavior that can vary across companies and different patents. The perceived degree of patent protection for an NME can vary within as well as across the patent categories in Figure 3. Second, a settlement can be tailored to reflect the perceptions of the likelihood of success by the opposing parties, allowing early entry from a few months before a patent expires to much lengthier periods. Even settlement allowing entry a few months prior to a patent's future expiration date can preserve the 180-day exclusivity period for the first-filing generic firms. Third, a settlement agreement can resolve multiple patent challenges at the same time, allowing early entry for some, but not all, patents.[26]

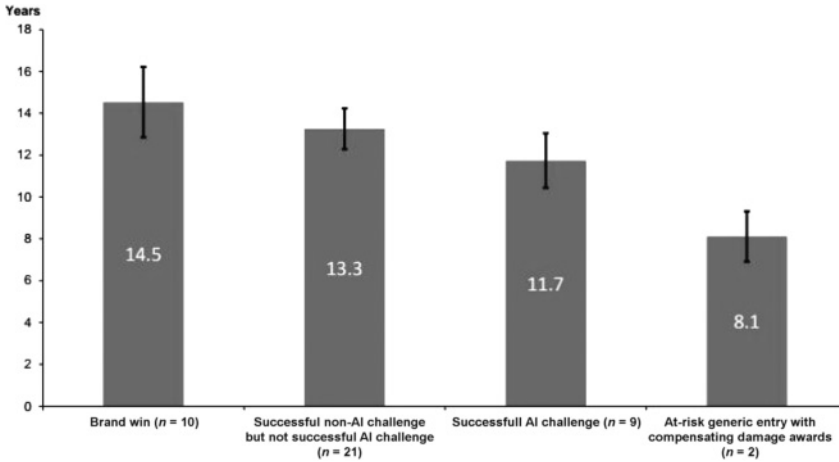
Next, we consider how these patent challenge outcomes have affected the MEPs of top quintile drug products. In Figure 4, outcomes are categorized into four different groups. A brand win means the patent owner successfully defended all the challenged patents, AI and non-AI patents, listed in the Orange Book. This group also includes two cases where firms' listed patents were not challenged. Successful patent challenges that trigger 180-day exclusivity for generic firms are categorized into two subcategories: (1) a successful challenge to an AI patent that results in entry prior to its expiry; (2) a successful non-AI challenge that results in entry prior to a patent expiry, but no successful AI challenge. Finally, there is a category of two NMEs that experienced an "at risk" entry, with respect to AI patents of these NMEs prior to a ruling on validity and infringement by a district court.

A key finding in Figure 4 is that for NMEs with a successful AI challenge by generic firms, the average market exclusivity is 11.7 years. This compares with an average effective

25 As noted, one NME representing 2 percent of method-of-use patent challenges is still under appeal at the Federal Circuit, with a decision expected in 2016.

26 In the case of the 14 AI patents that were subject to settlements as shown in Figure 3, half involved settlements resulting in entry prior to the patent's expiration. The others were part of a broader settlement involving AI and/or non-AI patents where early entry occurred on some of the other patents involved in the settlement agreement.

FIGURE 4. Mean market exclusivity by litigation outcome on AI patents: Top quintile NMEs (1994–2006) ($n = 42$)



Data sources: IMS; Orange Book 1994–2011; FDA (NME data; paragraph IV patent certifications); company reports and litigation based data sources.
Notes: [1]The top quintile of NMEs contains 43 NMEs. One NME with ongoing litigation (Alimta) is excluded from the market exclusivity calculations. [2]For NMEs that do not have an AI patent, core patents are substituted. [3]A classification of a challenge as successful requires at least one of the following: a court ruling in favor of the generic manufacturer, a settlement, or a challenge that is not defended by the drug manufacturer. [4]Error bars indicate the 95% confidence intervals for mean market exclusivity.

patent life of just under 14.5 years for brand wins and 13.3 years for those with a successful non-AI challenge but no successful AI challenge. The two NMEs in which there were entries at risk by generic firms experienced the shortest exclusivity period (8.1 years average). However, juries subsequently ruled that the patents for these NMEs were valid and awarded monetary damages.

The analysis presented in Figure 4 shows that the NMEs that experience a successful AI patent challenge have two years less of market exclusivity on average than those NMEs that do not (11.7 years compared with an average of 13.7 years for the 31 NMEs in Figure 4 without a successful AI challenge). These NMEs with a successful AI challenge lost an average of 1.1 years of AI patent life and otherwise would have had just under 13 years of market exclusivity in the absence of these successful patent challenges. Some important points to note regarding the distribution of lost AI patent time is that there is considerable variance, with a skewed distribution ranging from a few months to over four years in value. The skewness is reflected in the fact that the mean patent loss is over a year, while the median value is four months.[27] Second, seven of the nine of the NMEs with lost AI patent

27 None of the seven settlements with respect to the NMEs with successful AI challenges involved so-called "pay for delay" settlements that triggered an antitrust suit by the Federal Trade Commission. One of the drugs, Lamictal, experienced civil antitrust suits from the indirect and direct purchasers revolving

time involve post-MMA approvals, and most of the lost AI patent time is concentrated in this period.

A significant finding with respect to the top quintile of drugs is a declining trend in their average MEP over time (Table 1). The effective market life for top quintile drugs declined from an average of 14.5 years for the NMEs introduced in the 1994 to 1998 period to 12.2 years for those NMEs approved in the post-MMA period, and this decline is statistically significant at the 1 percent level (t-value = 3.37). This decline can be attributed in considerable part to a decline in AI patent expiry times between the pre- and post-MMA periods. The AI patent time (before any lost time as a result of generic challenges) declined by just over a year, and lost AI patent through challenges resulted in an additional half-year loss. Declining market exclusivity times were also accompanied by fewer annual top quintile drugs, with 4.4 NMEs per year in the pre-MMA period to 2.6 NMEs per year in the post-MMA period.

Our findings on the reduction in the number of blockbuster products and shortened market exclusivity periods over time are consistent with the results of some other recent studies. A study by Berndt et al. (2015) finds that the 1995–99 cohort had a "golden age" in terms of high lifetime economic profits from R&D investments, but successive cohorts have experienced steady and sharply declining economic profits. Returns on R&D are influenced by a number of economic and policy actions, including the probability of success of products now in the R&D pipeline, the costs of development, and the revenues and market exclusivity periods of new drugs after launch. Whether this observed decline is an economic cyclical phenomenon or a secular decline remains an important issue for further research.

VIII. Conclusion

Our results indicate that the regulatory changes emanating from the 1998 Mova court decision and the 2003 MMA have had important consequences for the biopharmaceutical industry. While earlier studies indicated that patent challenges were focused on non-AI patents with long nominal terms (Hemphill and Sampat 2012), we find that patent challenges for NMEs approved post-MMA increasingly extend to the ostensibly stronger AI and core patents. In the case of the very largest-selling products, the vast majority of NMEs are subject to a broad set of challenges to their whole patent portfolio, frequently at the earliest possible date of four years after approval. Our regression analysis indicates that patent challenges are resulting in shorter average effective market exclusivity periods for these NMEs, but there is considerable variability across drug products.

A novel feature of the present study is a detailed analysis of court decisions and settlement outcomes on patent challenges for the top quintile of NME products, ranked by US sales. We found branded firms have a strong record in winning court decisions involving an active ingredient patent, while generics win more often in the case of non-AI patents,

around an agreement by the branded firm with the generic first filer not to launch an authorized generic during the first-filer's 180-day exclusivity period. Litigation concerning this issue is ongoing in a number of court venues (Silber 2015).

particularly patents involving drug product formulation patent claims. We also found that many patent challenges are settled prior to a final court outcome. Taking account of both court decisions and settlements, a majority of successful patent challenges are associated with non-AI patents. A significant trend observed for the top quintile products is a decline in average MEPs over time, even given the presence of more total listed patents by branded firms.

Patent challenges that result in earlier generic competition than would otherwise be the case can lead to substantial static welfare benefits in the form of lower prices to consumers. But an environment of prevalent patent challenges also can increase uncertainty about expected returns to R&D, especially where R&D investments are lengthy, costly, and risky (DiMasi, Grabowski, and Hansen 2016). A number of studies have found large welfare benefits from new drug therapies across a wide spectrum of diseases and disabilities (Cutler and McClellan 2001; Murphy and Topel 2003). It is also important to note that empirical analyses of approved NMEs cannot evaluate the potential negative impacts with respect to promising drug therapies that are not developed because of insufficient or uncertain exclusivity periods.[28]

In recent years, policy makers have enacted new laws to increase R&D incentives in particular therapeutic areas and circumstances of perceived market failure. In the GAIN Act of 2012, for example, Congress extended the data exclusivity period by an extra five years in recognition of a growing threat of antibiotic resistance to existing therapies and a relative paucity of new antibiotic approvals over the past decade (Grabowski, DiMasi, and Long 2015). Under the 21st Century Cures Initiative, the House Energy and Commerce Committee has recently advanced a series of legislative proposals containing various incentives to encourage biomedical research and cures, including increased market exclusivity in particular circumstances of high disease burden and unmet needs.

Biologics, which account for an increasing share of new drug therapies, have been regulated historically under the Public Health Services Act rather than the Hatch-Waxman Act (with some notable exceptions discussed earlier). As discussed, the 2010 BPCIA established an abbreviated approval pathway for biosimilars that are referenced to large molecule biological entities. One notable feature of the BPCIA is that Congress established a longer regulatory exclusivity period for new biological entities (12 years compared with 5 years for new chemical entities). Congress also did not create a 180-day exclusivity period for the first-filing biosimilar application challenging the patents of the reference product. Rather, for biological entities, the FDA's acceptance of a biosimilar application triggers the exchange of information on patents between the parties, and then litigation, if any, can proceed in accordance with specific timelines (Grabowski, DiMasi, and Long 2015).

The different regulatory exclusivity provisions of the BPCIA and the Hatch-Waxman Act for new drug introductions have raised concerns regarding the potential implication of different R&D incentives for small molecule and large molecule investment projects. In

28 In this regard, a recent study has raised concerns on whether current market exclusivity periods provide adequate incentives for large and risky investments in specific therapeutic areas such as oncology drugs that require long-term survival data for FDA approval versus those that can rely on surrogate input (Budish, Roin, and Williams 2015).

this regard, Goldman et al. (2011) modeled the effects of extending regulatory exclusivity for all small molecule new drugs to the 12-year period that exists for biological entities.[29] Goldman et al. find long-term gains in new drug introductions from increased R&D that would benefit future generations, but there are also intergenerational distribution effects. The first biosimilar approvals in the United States have taken place only recently. It is too early to say how different exclusivity periods and approaches to resolving patent challenges for biologicals and chemicals will affect R&D investments, follow-on imitative competition, and overall economic welfare. Nevertheless, this would appear to be an important priority issue for the continued attention of policy makers and researchers.

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