

PHARMACEUTICAL PATENT CHALLENGES AND THEIR IMPLICATIONS FOR  
INNOVATION AND GENERIC COMPETITION

HENRY GRABOWSKI <sup>A</sup>

CARLOS BRAIN <sup>B</sup>

ANNA TAUB <sup>B</sup>

RAHUL GUHA <sup>B</sup>

AEA CONFERENCE  
Boston, Massachusetts  
January 4, 2015

<sup>A</sup> Duke University Economics Department

<sup>B</sup> Cornerstone Research

Preliminary Draft: Do not quote or circulate without permission of authors

## I. INTRODUCTION

It is generally recognized that biopharmaceutical R&D has contributed to important advances in pharmacological entities to treat a wide spectrum of diseases and disabilities. (Cutler and McClellan, 2001; Murphy and Topel, 2003). New drugs are typically protected by patents that provide a period of market exclusivity. During this period of market exclusivity, pharmaceutical companies do not face generic competition. After generic firms enter market prices drop dramatically and innovator companies typically lose a large portion of the sales in the market. After generic entry innovator companies rarely make significant profits. Innovator companies, therefore, depend upon this period of exclusivity in order to earn a return on their investment in R&D. The biopharmaceutical R&D process is long, costly, and risky.<sup>1</sup>

In recent years, the pharmaceutical industry has experienced a wave of patent challenges. In this paper we examine what is driving these increased challenges, and whether they pose a threat to pharmaceutical innovation. Under the 1984 Hatch-Waxman Act, a generic firm can be given a 180-day exclusivity period if it is the first to file a patent challenge. This can be shared among multiple first filers. For the first decade after the 1984 Act was passed, paragraph IV challenges were relatively rare and tended to occur late in the branded product's life cycle when they did occur. A set of regulatory and legislative changes that took place between 1998 and 2003 greatly expanded the opportunities and conditions for generic firms to obtain 180-day exclusivity rights and was a key catalyst for the increased patent challenges occurring since the late 1990s.

The strategies of both generic and brand 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 AB rated 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 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 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). Some of the later listed patent awards can lead to longer potential exclusivity periods for the branded products, but may rest on narrower patent claims that are more vulnerable to patent challenges by generic firms.

Strategic behavior by generic and innovative firms can be expected in a legal and institutional environment encouraging patent challenges. In this paper we consider how regulatory and legislative changes changed the incentives for patent challenge and the strategic behaviors of generic and innovative firms. In particular, the key issue we wish to investigate is how the wave of patent challenges since the late 1990s is influencing innovation outcomes and generic accessibility, and how the balance of effects may be changing over time.

## II. THE LEGACY 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. One of its key provisions was to establish an abbreviated new drug application (ANDA) for generic applicants. Under the ANDA process, generic manufacturers need only demonstrate their product has an identical active ingredient and is bioequivalent to its reference product. This greatly reduced the cost of generic approvals compared to the pre-1984 Act situation, where generic firms had to submit original safety and efficacy data to gain approval.

Generic manufacturers also received a research exemption, (or “safe harbor provision”) to undertake bioequivalence studies and submit ANDAs prior to the expiration date on the reference product’s patents and not violate existing U.S. patent laws. This provision allowed generic firms to enter immediately after patents expire, and in effect moved the expected date of generic entry forward by a number of years compared to the pre-1984 period. (CBO, 1998)

The provisions of the 1984 Act served as a cornerstone for the growth of the generic drug industry. In particular, easier generic entry requirements combined with automatic drug state substitution laws and managed care incentives (e.g. tiered co-pay formularies and differential pharmacy dispensing fees) significantly increased generic usage. This is exemplified by the fact that generic products share of total prescriptions in the U.S. increased from 36 percent in 1994 to 84 percent in 2012. (IMS, 2013) The brand erosion curve after generic entry has also accelerated over time (the so-called patent cliff.) Specifically, generics that entered brand product markets in 2011-captured a 70 percent share of combined brand-generic total units within the first full month of generic competition, and over 80 percent by six months. (Grabowski, Long, and Mortimer, 2014) As the number of generic products for a particular entity increases, generic prices also decline toward marginal costs. 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. While the nominal life of a patent is 20 years from the date of submission, effective patent life for many core drug patents is significantly shorter since these patents are typically applied for early in the lengthy drug development process. The Hatch-Waxman Act provisions were designed to restore some of this patent time lost during the FDA regulatory and review periods. In particular, the 1984 law provides for an extension of restored patent term of up to five years on one of the firm's Orange Book listed patents, but the restored patent term cannot exceed 14 years including the extension. The patent term provisions have helped offset the potential negative impacts on R&D returns associated with the 1984 Act, but the CBO found that the faster and more intensive generic competition in the first decade after the Hatch-Waxman ACT was passed, on balance contributed to lower returns on R&D. (CBO, 1998)<sup>2</sup>

### III. THE INCENTIVES FOR PATENT CHALLENGES UNDER THE 1984 ACT

One of the most controversial provisions of the 1984 Act was the creation of incentives for generic firms to challenge brand-name patents before they expired. In particular, a generic firm can file an ANDA four years after the brand product's approval date with the claim that its product does not infringe the reference products patent(s), or that these patent(s) are invalid (a so-called paragraph IV challenge.) Assuming the brand name files suit against the generic within 45 days, there is a stay on FDA approval of the ANDA for up to 30 months to allow for courts to rule on the generics' claims, after which a generic can enter at risk if litigation is still ongoing at the district court level. Even if there is no suit by the brand firm, the earliest that a

generic can enter utilizing an ANDA application is five years after the reference brand's approval (generally referred to as the data exclusivity period.)

The first generic manufacturer to file a paragraph IV challenge resulting in entry prior to patent expiration (from either a court victory or settlement with patent owner) is granted a 180 day exclusivity period. The 180-day period of generic exclusivity generally is very profitable to a generic manufacturer because the firm can discount its price only moderately compared to the brand product and still gain most of the branded product's sales. In this regard, the typical generic receives an "AB" rating from the FDA certifying that it is therapeutically equivalent to the branded product, and then can benefit from the automatic state substitution laws as well as managed care generic utilization incentive programs.

Some have suggested the balance sought by Hatch-Waxman is threatened by a wave of Paragraph IV patent challenges to branded drugs in recent years. The number of patent challenges has increased rapidly since the late 1990s. In this regard, over 80 percent of the NMEs experiencing first generic entry in 2011-2012 experienced a patent challenge compared to an average of less than 20 percent prior to 1998. (Grabowski, Long and Mortimer, 2014) Correspondingly, patent challenges are occurring much earlier in time after the branded product's approval. As shown below, new drugs with significant sales frequently experience a paragraph IV challenge at the earliest point in time that such an FDA filing can occur (exactly four years after NDA approval), and often from multiple entrants.

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 patent challenge in court. After the 1998 Mova court decision overturned this interpretation of the Act, FDA regulations

were changed to grant generic exclusivity to first filers on the basis of a settlement with, or non-suit by, the patent owners, as well as a court victory. (FDA, 2003) As the FDA noted, in the years from 1994 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) <sup>3</sup>

The changes in generic exclusivity rules in 1998 created the further issue of shared exclusivity for generic firms submitting ANDA applications at the same time. In July 2003, the FDA issued guidance for industry on 180-day exclusivity when multiple ANDAs for a drug/dose are submitted on the same day. In that event, firms would share exclusivity on a patent-specific basis. (FDA, 2003) These rules on shared exclusivity were superseded in part by the December 2003 Medicare Modernization Act (MMA) amendments to the Hatch-Waxman Act. The revised provisions governing ANDAs submitted after December 2003 provided “product based” 180-day exclusivity in which exclusivity attaches to first-to-file challenger to any Orange Book patent on a particular drug/dose combination basis.

The MMA Act also added various provisions aimed at closing loopholes that could delay generic entry. With respect to branded firms, the legislation permits only one 30-month stay involving the patents that are listed in the Orange Book at the time of a paragraph IV ANDA filing for generic firms.<sup>4</sup> The 180 exclusivity is triggered by the first commercial marketing of a drug/dose and can be forfeited for failure to market under specific time constraints and various other conditions.<sup>5</sup> There is no rollover of 180-day exclusivity to subsequent paragraph IV ANDA filers if forfeiture occurs.

The regulatory and legislative changes in the 1998 to 2003 period effectively changed the business model of many generic firms. The business model of these firms essentially became

centered around patent challenges and the pursuit of 180-day exclusivity rights. Successful patent challenges can yield large first-mover profits for generic firms and attendant static welfare benefits in the form of lower drug prices for consumers and insurers.

Patent challenges, however can adversely affect innovation incentives by increasing uncertainty about market exclusivity periods and expected earnings, along with the costs of almost certain litigation for commercially successful drugs. Brand firms face increased costs and risks of discovering and developing new drugs on the front end of the product investment life cycle, and rapidly declining sales at the end of the product marketing life cycle after generics enter. If the patent challenges further compress market exclusivity periods, or create added uncertainty about market life, some promising drug candidates may generate insufficient expected sales to both cover R&D costs and earn an acceptable (risk adjusted) return.

The strategies of branded firms have also evolved over time. In this regard, branded pharmaceutical companies often apply for and obtain multiple patents relating to a product's active ingredient product formulations and methods of use. This can be done in either an offensive or defensive manner in part as a response to the increased likelihood of patent challenges for most new drug introductions. Method of use and formulation patent applications are often filed later in the development process than patents on the active ingredient, as a drug candidate's profile of benefits and side effects becomes more evident through clinical trial outcomes and experience.

A patent claim on the active drug ingredient (AI) provides the most protection in terms of scope but not necessarily length. Methods of use and formulation patents are more limited in scope, while often expiring later in time have been characterized as “weaker” or “lower quality” patents. (Hemphill and Sampat, 2012) However, they vary significantly in quality and degree of



patent protection. They can provide the essential core patent protection for new molecular entities (for example when a drug active ingredient patent is not available or has a very short market life.) This was true in the case of the first AIDS therapy, AZT. It 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 an AIDS therapy provided a strong method of use patent claim that survived legal challenge.

#### IV. ACADEMIC RESEARCH ON PATENT CHALLENGES AND DRUG INNOVATION

As discussed by a number of studies have examined the effects of generic competition emanating from the 1984 Act. Analyses of the specific role of patent challenges, and particularly their impacts on innovation incentives, are more limited.<sup>6</sup> In this section, we summarize three studies that focused on this issue.

Grabowski and Kyle (2007) provided 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 examined a sample of new molecular entities (NMEs) that first experienced generic competition in the 1995 to 2005 period. They found the average market life was 13.5 years over the entire period. MEPs declined only moderately over time (13.6 years of 1993-2000 and 13.4 years for 2001-2008.) More significantly, however the MEPs were shorter for larger selling drugs and a stronger downward trend in MEPs was observed in the case of the very largest drugs, entities that presumably would be the target of more patent challenges. Grabowski and Kyle also undertook regression analyses that found that drugs with

patent challenges, other thing equal, had between 1.2 and 1.6 years less MEP (statistically significant at the 10 percent level.) Their analysis did not investigate the outcomes of patent challenges, but only included a variable for whether a challenge had occurred for a particular NME.

In a more recent study of the role of patent challenges and their effects on market exclusivity periods, Hemphill and Sampat (2012) utilize a comparable data sample to Grabowski and Kyle, but updated the analysis to NMEs experiencing first generic competition to the 2001-2010 periods. Consistent with Grabowski-Kyle's regression analysis, they find that NMEs with challenges generally have two to three years less market life (statistically significant at the one percent level.) At the same time, the average effective market life of 12.2 years is stable and over time and across drug sales and categories (with the exception that their lowest quintile sales category experiences the least challenges and has the highest MEPs.)

Hemphill Sampat's (2012) paper was the first to categorize patents by type (active ingredient vs non-active ingredient patents) and conduct analyses at both the NME and patent levels. They find the most prevalent behavior was for generic firms to challenge late-expiring non-AI patents with long nominal patent terms. Their results indicate a greater tendency for firms to challenge AI patents in the case of drugs with the largest sales, and also a negative relationship between exclusivity periods and AI challenges for the top two quintiles. However, this relationship was not statistically significant, and on that basis they infer patent challenges to AI challenges are unlikely to be successful or adversely affect innovation incentives.<sup>7</sup>

In the first study to look at the outcomes of patent challenges, Panattoni (2011) has examined the impact of district court decisions on the stock market values of brand drug pharmaceutical firms using an event study analysis. She found that paragraph IV court decisions

involve a disproportionate share of highest revenue brand name drugs, and the period of exclusivity at issue was a large portion of the average length of patent protection. In terms of the impact of court outcomes, her event analysis found that paragraph IV decisions have substantial value consequences for branded and generic firms in terms of both positive abnormal stock returns (court victories) and negative abnormal stock returns (court losses.) She found a relatively even split of brand and generic victories at the district court level. Panattoni's analysis did not investigate how patent characteristics influence the court decisions on patent challenges or the consequences for market exclusivity times.

Panattoni's study provides suggestive evidence of why brand firms have considerable incentives to settle patent challenge cases and avoid the uncertainty and potential losses in profits associated with these decisions. As a number of studies has shown, the distribution of returns on R&D is highly skewed. Only the top few deciles of new drug introductions cover the average cost of development. A small proportion of large selling drug provide a disproportionate share of overall returns on R&D. (Grabowski, Vernon & DiMasi, 2003) (Vernon, Golac, & DiMasi, 2010) These top decile products are the most likely to be challenged by generics early in their market life.

## V. SCOPE OF OUR ANALYSIS RELATIVE TO PRIOR LITERATURE

At this point, the existing literature provides suggestive insights on the effects of patent challenges but leaves open a number of open issues for research. All of the studies indicate that the number of patent challenges increased dramatically in the late 1990s after the first filing generic firms obtained increased 180-day exclusivity rights. In addition, patent challenges have been observed to occur sooner in time after the reference product's approval. However, there is

more uncertainty concerning the effect of patent challenges on innovation incentives. In particular, the data sample and analysis undertaken on prior empirical studies are not well suited to examine the dynamic changes in generic firm behavior after the regulatory and legislative changes that occurred in the 1998 to 2003 period.

Hemphill and Sampat's (2001) study provides the most beneficial view of patent challenges, indicating they provide earlier generic entry with little adverse consequences for innovation incentives. This inference is based on the fact that average market exclusivity for NMEs first experiencing generic competition in the 2000-2010 period have remained relatively constant and patent challenges for the NMEs have been focused on later expiring, "weaker," non-AI patents. However their analysis provides a limited framework to examine the effects on innovation of patent challenges. First, their sample consists of drugs that experienced their initial generic entry between 2001 and 2010. These drugs were approved beginning in the 1980s and many of them were already in the mature phase of their lifecycle when the regulatory regime changed in the 1998 to 2003 period. In particular this sample is not a good basis for investigating the increased likelihood of racing behavior and other expected shifts in generic incentives in the wake of this regime change.

Second, except for Panattoni's analysis, prior studies do directly look at outcomes of patent challenges. As Panattoni's study suggests, even if the prospects of winning a patent challenge are low for the generic firm, the innovating firm may choose to settle rather than risk losing a lawsuit on a major selling drug. Moreover, it is reasonable to postulate that the incentives to do so likely changed as more patents became subject to challenge after 1998.

While Panattoni's study is insightful, it does not analyze court outcomes by patent type, nor does it specifically consider the impacts of settlements.

The regulatory changes after 1998 can trigger a number of strategic changes by generic and brand firms. One hypothesized consequence of enhanced exclusivity for generic first filers is a race to file ANDAs with patent challenges at the FDA, especially in the case of the very largest selling branded products. In its 2003 guidelines, the FDA addressed the issue of several generic firms filing ANDAs with Paragraph IV challenges on the first day that a patent challenge can occur (four years after the branded product's FDA approval) and codified the basis for shared exclusivity on a patent-specific basis. (FDA, 2003) As noted, the 2003 MMA amendments superseded these guidelines and provided for shared exclusivity on a product-specific basis for ANDAs filed after 2003.

The prospect of patent races and shared exclusivity in turn can increase the incentives for a generic firm to challenge all of a reference product's listed patents, including its AI patents. A typical situation is that AI patents, which provide the broadest patent protection, are applied for early on in the R&D process and method of use and formulation patents are applied for later on as clinical trial evidence accumulates on a product's uses and attributes. If a firm challenges only the firm's later-listed patents, it risks losing first-mover advantages if a rival with shared exclusivity is successful in its challenge on an earlier expiring AI patent through settlement or court litigation.<sup>8</sup> The incremental litigation costs of challenging a branded firm's stronger AI patents also may be relatively small, compared to the potential loss in first mover advantages. Hence, patent challenge races can lead to more challenges of stronger AI patents, given the threat of a rival's expected actions. Correspondingly, brand firms can respond to the increased likelihood of broad challenges to its patent portfolio by increasing the number of patent filings at the U.S. Patent Office, and Orange Book listings of patents granted by this agency.

In light of the various developments influencing patent challenges, we wish to investigate the following hypotheses in the current analysis:

- (1) The proportion of new drug introductions subject to patent challenge have increased and the time to patent challenge decreased in the wake of the legal and regulatory changes occurring 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 and increased incentives for generic firms to challenge AI patents as well as method of use and formulation patents for NMEs approved after 1998.
- (3) Correspondingly, there is an increased incentive for innovative firms to increase the size of their patent portfolio in response to the wave of patent challenges after 1998.
- (4) In terms of patent outcomes, AI patents have the highest likelihood of being upheld in court litigation, followed by method-of-use patents, with formulation patents being the easiest for generic firms to challenge on the grounds of novelty, obviousness, or non-infringement.
- (5) While settlements will reflect expected litigation outcomes, innovating firms may decide to settle patent litigation in the case strong AI patent claims in order to avoid the risk of low probability adverse legal decisions for their large selling drug products.

## VI. DATA SAMPLE CHARACTERISTICS

To provide further insights into whether patent challenges are affecting innovation incentives and exclusivity periods, we have assembled a data set of new chemical entities based on year of NDA approval for the period 1994 to 2006. The goal of our research is to analyze the hypotheses presented above on the determinants and outcomes of patent challenges. A particular focus of our research is on patent challenge outcomes for the sample of the large selling drugs that accounts for a disproportionate share of sales and R&D returns.

Another objective is to investigate how the regulatory regime changes that granted new exclusivity rights for generic first filers influenced generic and innovative firm behavior. NMEs approved beginning in 1999 were the first cohort to experience the full effects of these changes given they were first subject to ANDAs with a patent challenge in 2003 and beyond. Our sample of NMEs 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 these regulatory changes.

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, OTC 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 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 methods 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 (see data appendix).

This approach produced a sample of 213 NMEs approved between 1994 and 2006. For these 213 NMEs there are 639 Orange Book listed patents at issue.<sup>8</sup> Many patents have AI claims combined with method-of-use and or drug product formulation claims. In Figure 1, we show how these various combinations occur in the case of the patents at issue. In the analysis which follows, we employ a hierarchical ordering approach reflecting accepted patent expert's views on patent scope and strength, with AI patent being the strongest in terms of the scope of patent claims and drug product claims being the weakest in this regard. 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 a method-of-use only claim, or a method of use plus a drug product claim.
3.     Drug Product patent: All patents with drug product claims only.

Utilizing this hierarchical approach, the data presented in Figure 1 imply AI patents constitute 40 percent of the total patent sample. Correspondingly, method-of-use patents constitute 42 percent, and drug product patents constitute 8 percent of our total sample of patents respectively. These data also imply that an NME in our drug product sample has, on average, 1.18 AI patents, 1.26 method-of-use patents, and 0.56 drug product patents (for a total of 2.90 average patents per NME.)

As discussed on Section II, 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. AI and other core patents will typically be applied for early in the clinical trial period, or in the pre-clinical period. 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.<sup>9</sup> If an active ingredient patent is unavailable, or has very short patent term remaining on approval of the NME, firms often elect patent term extension on a key method-of-use patent, or in more limited circumstances for a drug product (formulation) patent. In the analysis which follows, we designate patents granted a patent term extension by the U.S. Patent Office as an NME's "core" patent. This set of patents is a particular focus of interest with respect to patent challenges over time.

The first part of our statistical analysis involves an examination of patent challenges by patent type for the sample of NMEs approved between 1994 and 2006. For this analysis we are particularly interested in whether the regulatory changes enhancing first filer generic exclusivity led to an increased likelihood of racing behavior and challenges to patents with active ingredient claims in accordance with the hypotheses above. As indicated, we expect the likelihood of racing behavior and broad patent challenges by generics will be most focused on the largest selling drug products. We have assembled data on a drug product's peak U.S. sales, based on IMS audits 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 over the period 1994-2006. As discussed, the potential impact on R&D incentives from an economic standpoint is particularly significant for the top quintile of new drug approvals. These drugs, 42 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.)

Analyses of court decisions and settlements pose the most challenging task in terms of data construction. In particular, there are multiple patents per NME with different claims and are also multiple possible generic challenges and different settlements and court outcomes, including appeals. Data in our analysis is collected on a case-by-case basis for the 42 top quintile products starting with the patents listed in the Orange Book. Data from FDA listings and correspondence, legal documents, Paragraph IV.com and SEC regulatory filings are then utilized to compile information on which patents were challenged and the outcomes in terms of litigation decisions and settlements. Further details are presented in a separate data appendix.

One particular data limitation should be noted in the case of the realized outcomes for samples categorized by year of introduction. When NMEs are categorized by year of first generic introduction, one can compute market exclusivity periods for the reference brand product exactly. This is not the case for NMEs categorized by year of introduction. Many of these more recently approved NMEs do not yet have generic competition. One can compute the expected date of generic based on the published information on settlements and court decisions in the case of patents challenge decisions on NMEs. If a product has not received a patent challenge, one can look at Orange Book listed patent expiry dates when generic entry can first occur. The NMEs with smaller market sales in the later years of our sample are particularly subject to some censoring, given patent challenges may occur later in a drug product life cycle for these NMEs.<sup>10</sup> The Cox proportional hazard model analyses considered below take account of censoring for drugs that have not yet experienced generic entry.

## VII. SAMPLE CHARACTERISTICS AND DESCRIPTIVE STATISTICS

In this section, we consider various descriptive statistics and time trends with respect to patent challenges for our 213 NME sample. In Figure 2 we plot the percent 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. There is an increase from 48 percent for patent challenges on the 1995 NME cohort to a peak of 73 percent for the 2003 cohort. Similarly, the percentage of NMEs that have their core patents challenged increases from 34 percent in 1995 cohort to a maximum of 85 percent in 2003 cohort. Some right censoring is likely in the number of NMEs experiencing patent challenges in the last few NME approval years in Figure 2. While large selling products typically experience patent challenges early in time after approval, they can occur over a longer time cycle than smaller selling ones as shown below.

In Figure 3 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 some supportive evidence concerning the racing behavior hypotheses discussed in the previous section. 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 NME approvals, but this median value declined to just over four years for 1999 NMEs, and was exactly four years for most NME approval years thereafter.

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 was over ten years in the 1994 and 1995 NME cohorts, and there is a decline to less than six years for 2003 cohort. As in

the case of NMEs subject to challenge, the last few years are subject to right censoring, particularly for smaller selling NMEs that frequently experience patent challenges later in their market life.

Table 1 provides drug level summary statistics on the characteristic of patent challenges and market exclusivity periods. For the overall sample, 58 percent of NMEs experience a challenge to at least one of their patents. In addition, 39 percent of the NMEs experience a challenge to an AI patent and 45 percent to the NME's core patent. As described above, the mean number of AI patents per NME is 1.18, with a range from 0 to 6 AI patents. Furthermore, there are 1.82 non-AI patents per NME with a range of 0 to 11 non-AI patents. Peak annual U.S. sales for the 213 NMEs average \$669 million with a range from 0 to \$9.5 billion in value.<sup>11</sup>

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 15.3 years. By contrast, the effective market life is 13.2 years for the sample of 161 NMEs for which generic entry either has already occurred or where the generic entry data can be determined from Orange Book patent expiration listings based on available information. The final row shows an effective market life of 12.7 years for the top quintile of 42 drugs. This is a subsample for which we researched outcomes in detail, and which are the focus of the analysis in section IX below.

Table 2 presents these summary statistics by sales group with NMEs classified as those with peak sales of less than \$500 million, those with sales between \$500 million and \$1 billion, and those with sales greater than \$1 billion. In accordance with our hypotheses in Section V, the percentage of AI and core patent challenges per NME increases as sales increase in value across these three categories. In the case of the 35 drug products with peak sales in excess of \$1 billion,

91 percent of NMEs experienced a patent challenge. Furthermore, 86 percent of these NMEs experience an AI patent challenge and 79 percent experience a core patent challenge. For this “blockbuster” sample of products, there is a strong likelihood of a patent challenges including an AI or core patent challenge. For the cohort of NMEs with peak sales below \$500 million, slightly less than half (45 percent) of the NMEs experienced a patent challenge, including 25 percent with an AI challenge and 33 percent with a core patent challenge. There is a relatively small variation in effective market life across the three sales groups (ranging from 12.3 to 13.3 years.) There is some observed tendency for the mean number of patents per NME to increase with peak sales values in Table 2, particularly in the case of listed AI patents for products with sales greater than \$500 million.

Table 3 provides summary statistics on patent challenges grouped by years, specifically those approved in the years 1994 to 1998 and those approved between 1999 and 2006. This table supplements information on time trends presented in Figures 2 and 3. In particular, this table shows that the number of NMEs with an AI patent challenge increased from 30 percent in the 1994–1998 NME cohort to 46 percent in the 1999-2006 cohort, with a similar upward trend in core patent challenges (35 to 53 percent.) The count of both AI patents and non-AI patents also increased significantly over these two periods from 1.05 to 1.27 AI patents per NME, and from 1.26 to 2.24 non-AI patents.

In summary, the trends and descriptive statistics presented here generally support the hypotheses that the regulatory regime change that took place in the 1998 to 2003 period not only increased the number of NMEs experiencing patent challenge, but also increased the likelihood of challenges to AI and core patents. Drugs with large peak sales (e.g. exceeding \$1 billion in sales) were subject to patent challenges exactly four years after approval for the majority of these

NMEs approvals after 1999 (consistent with racing behavior on the part of generics) and as a group overwhelmingly experienced challenges to both AI and non-AI patents. Another notable feature in the data is the increase in AI and non-AI patents by innovative firms for NMEs approved after 1999.

## VIII. STATISTICAL ANALYSES OF PATENT CHALLENGES

In this section, we investigate the hypotheses set forth above on the determinants and effects of patent challenges utilizing NME product as well as patent level data. We utilize a logistic regression framework to examine the factors influencing the likelihood of patent challenges and Cox proportional hazard models to examine factors affecting the time to generic entry.

In Table 4, we examine the likelihood that a particular NME experiences a challenge in the fourth year after approval utilizing a logistic regression specification. This table provides support for the racing behavior hypothesis by generic firms previously suggested in the median time to patent challenges by NME approval year (Figure 3). In particular, large selling NMEs are more likely to experience a paragraph IV challenge exactly four years after approval (statistically significant at the one percent level); in addition, more recent approvals are likely to experience a challenge at the earliest possible date for four years. In this regard, both a linear approval time variable and the indicator variable for NMEs approved between 1999 and 2006, are statistically significant when specified independently or when included together in the regression. The number of AI and non-AI patents per NME are included as additional control variables, but are not statistically significant.

In Table 5 we consider the likelihood that a core patent will be challenged as a function of an NME's approval time and peak sales. Table 5 provides support for the hypothesis an NME's core patent has a greater likelihood of being challenged in the case of large selling drugs and more recent approvals. An NME's maximum yearly sales variable is statistically significant in all three specifications at the one percent level. The linear approval date variable and the indicator variable for the 1999 to 2006 grouping of NMEs are statistically significant at the one percent level when present in the regressions separately, but not when specified together (likely reflecting the presence of multi-collinearity between these variables.)

In Tables 6 and 7, we utilize patent level data to investigate hypotheses on the likelihood of a challenge to an NME's core patent term and AI patent in terms of 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. In addition to variables on approval time and maximum year sales, we include an indicator variable that takes the value of one if a patent is core patent (Table 6), or if it is an AI patent (Table 7), and zero otherwise. We also include interactive term variables between these core and AI patent variables and the approval time and minimum yearly sales variables. As shown in Table 6, a core patent is less likely to be challenged than a non-core one, other things being equal, but the interactive terms indicate that large selling drugs and NMEs approved after 1999 have a higher likelihood of a patent challenge to a product's core patent. Table 7 present essentially similar findings in the case of challenges to an AI patent. Given the fact that an NME's core patent is typically an active ingredient patent, the similarity of the results in these two tables is not surprising.

In Table 8, the dependent variables are the number of total patents per NME, and the number of AI and non-AI patents, respectively. As shown, the number of patents, including both

AI and non-AI patents, is greater for more recent approvals (statistically significant at the one percent level.) This is generally consistent with the hypothesis that innovators are increasing the number of patents as more are challenged in recent years. An NME's maximum year sales was statistically significant variable in the case of total and AI patents, but not non-AI patents.

The final table in this section investigates factors affecting the time to generic entry for the 213 NMEs in our sample using a Cox proportional hazard model specification. The analysis takes into account censoring for drugs that have not yet experienced generic entry. In these Cox proportional hazard models, values greater than one imply shorter times to generic entry, while values smaller than one imply longer times to generic entry.

In Table 9, the Cox proportional hazard model on time to generic entry includes as the independent variables an indicator variable denoting whether a particular NME is subject to a patent challenge, the approval time variables, an NME's maximum yearly sales, and the number of an NME's active and non-active ingredient patents. The NMEs experiencing patent challenges have substantially shorter time to generic entry. Drugs approved after 1999 and those with higher maximum yearly sales also experience shorter time to generic entry. All these variables are statistically significant. By contrast, NME's with greater AI and non-AI patents have longer time to generic entry, with the number of AI patents having greater delaying effects on time of entry.

Overall, the results of the Cox model specifications suggest that the increased number of patent challenges experienced by larger selling NMEs approved after 1999 is resulting in faster time to generic entry for these NMEs. To further consider the role of patent challenges on market exclusivity periods and time to generic entry, we look at the outcomes of challenges to



the top quintile of NMEs in our sample that account for a large share of sales across the NME approvals.

## IX LITIGATION OUTCOMES FOR TOP QUINTILE OF NMES

As discussed, a number of studies have pointed to the skewed nature of the sales distribution in the case of biopharmaceutical drugs. In this regard, the top quintile of NMEs in our sample account for over 70 percent of total peak sales obtained by all the 1994 to 2006 approvals. The regression analyses undertaken in the last section indicate that these top quintile 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.

Our basic hypothesis on litigated outcomes, enumerated in Section V above, is that brand challenges to 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. While innovative firms have a greater likelihood of prevailing in the case of AI patents, they may elect in many circumstances to settle challenges by offering somewhat earlier entry to the generic firm(s) filling patent suits to avoid the risk of low probability adverse legal decision and a significantly adverse effect on their market valuations. (Panattoni, 2011)

To test these hypotheses, 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 4 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 whether the outcome results in a generic loss or win; next there is a category to denote settlements between the generic and brand firm that results in early entry by the generic product relative to the expiration date of patent at issue. In addition, there is a residual category for ongoing cases at the present time.

As shown in Figure 4, brand firms have won a majority of court decisions on AI patents. In particular, the breakdown of outcomes on AI challenges across the categories is 37 percent wins by brand firms, 23 percent wins by generic firms, and 40 percent result in settlements between the brand and generic firms. Even though brand firms win a majority of AI patent court decisions (60 percent of court decided outcomes), generic firms gain early entry in the majority of AI patent cases when settlements are also taken into account.

For method-of-use patents, the odds of success favor generics winning in court decided outcomes. The breakdown here is 29 percent wins for generic firms, 24 percent wins for branded firms, and 44 percent of method-of-use patent challenges resulting in settlements (2 percent of the cases are ongoing.) In the case of drug-product-only patents, generics prevail in virtually all the patent cases, winning 65 percent in court decisions, while 31 percent are resolved through settlements with the brand firms and 4 percent are ongoing.

The court outcomes for top quintile products shown in Figure 4 are generally consistent with expert patent experts' opinions on the strength and scope of biopharmaceutical patents. At the same time, the proclivity of innovative firms to settle many patent suits even for AI patents where their patent claims are ostensibly very strong is consistent with Panattoni's event study findings that innovative firms have much to lose from an adverse court decision and generics win a significant number of times to make this a real possibility.

In Figure 5 we examine average effective patent life for these top quintile products categorized by litigation outcomes. A key finding here is that for NMEs with a successful AI challenge by generic firms, through either a court decision or settlement, average market exclusivity is 11.8 years. This compares to an average effective patent life of just over 13 years for NMEs not challenged or those with only a successful non-AI challenge. Hence, these NMEs that experience a successful AI patent challenge have approximately 2.5 years less of market exclusivity on average than those NMEs that do not. All of the sample cells in Figure 5 are small, but the 17 NMEs with a successful AI patent challenge represent 40 percent of the top quintile drugs in our sample. This finding reinforces our Cox proportional hazard model results that indicate patent challenges to large selling drugs have resulted in significantly shorter times to generic entry, with a considerable variability observed across NMEs.

## X. CONCLUSION

Our results indicate that the regulatory changes emanating from the 1998 Mova court decision that broadened the market exclusivity rights for the first generic firms filing patent challenges have had important consequences for the biopharmaceutical industry. Prior research studies indicated that more NMEs subsequently became subject to a challenge and challenges tended to occur sooner after the reference branded product's approval. While earlier studies indicated patent challenges were focused on non-AI patents with long nominal terms (Hemphill and Sampat, 2012), we find that patent challenges for NMEs approved after 1999 increasingly extend to the ostensibly stronger AI and core patents. In the case of the very largest selling products, almost all NMEs are subject to challenges. In our Cox proportional model specifications, we also find 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 U.S. sales. Given the highly skewed distribution of sales in the pharmaceutical industry, these products account for a disproportionate (over 70 percent) share of total NME sales and they are a key driver of expected returns on R&D investments. In accordance with prior expectations, we found brand firms are more likely to prevail in court decisions involving an active ingredient patent, while generics win more often in the case of non-AI patents involving method-of-use and drug product formulation patents. While the odds of winning court decisions on active ingredient patents may favor innovative firms, the risks in terms of lost future revenues and market valuation are sufficient for innovative firms that many cases are settled to allow earlier entry. In this regard we found that market exclusivity period in cases where a generic wins an active ingredient patent case through either a court decision or settlement are on average 2.5 years shorter than those cases where this is not true.

These findings raise issues of whether the intended balance between incentives for generic price competition and innovation incentives embodied in the Hatch-Waxman Act has been disrupted by the growth of patent challenges over time. Clearly there is a tradeoff between static and dynamic welfare impacts, and patent challenges that result in earlier generic competition than would otherwise be the case can lead to welfare benefits in the form of lower prices to consumers. But pervasive patent challenges also can increase uncertainty about expected returns to R&D and result in reduced investment in R&D for new drug therapies. The

welfare tradeoff between static and dynamic benefits is a fruitful issue for further research concerning patent challenges.

From a policy perspective, concerns have been raised whether current market exclusivity periods, even after taken account of the patent restoration provisions, provide adequate incentives for large and risky investments such as oncology therapies where FDA requires long-term survival data rather than surrogate endpoints for approval. (Budish, Roin and Williams, 2013) In particular, in cases of perceived market failure, Congress has extended the exclusivity periods for innovations to encourage increased R&D investments. Congress, for example, in the GAIN Act of 2012, has recently extended the data exclusivity period by an extra five years in recognition of a growing threat of antibiotic resistance to existing therapies and a relatively paucity of new antibiotic approvals over the past decade. Congress has also extended or provided special exclusivity rights to encourage pediatric clinical studies and to encourage increased R&D in other targeted areas such as orphan drugs and diseases. (Grabowski, DiMasi and Long, 2015)

As discussed earlier, biologics were omitted in the present study since they are essentially covered by a different statute, the 2010 Biosimilar Price Competition and Innovation Act (BPCIA). This Act established an abbreviated approval pathway for so-called biosimilars that are referenced to large molecule biological entities. It is noteworthy that in the case of biologics, which account for an increasing share of new drug therapies, Congress established a longer regulatory exclusivity period for innovators (12 years compared to the 5 years for new chemical entities.) Congress also did not create an exclusivity period for 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 potential litigation then can proceed in accordance with specific timelines. (Grabowski, DiMasi and Long, 2015) It is too early to know how this alternative policy approach will work out in the case of biologics since no biosimilars have been approved yet under the BPCIA. The different regulatory exclusivity provisions of the BPCIA and 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 this regard, Goldman et al (2011) modeled the effects of extending data exclusivity for all small molecule new drugs to 12 years and found long term benefits that would benefit future generations. This remains an important question for further research on how to optimally balance the incentives for short term and long term welfare benefits.

## REFERENCES

Lee Branstetter, Chiranlan Chatterjee and Matthew J. Higgins, 2013. “Regulation and Welfare: Evidence from Paragraph IV Generic Entry in the Pharmaceutical Industry”. National Bureau of Economic Research Working Paper 17188.

Eric H. Budsh, Benjamin H. Roin and Heide Williams, 2013. “Do Fixed Patent Terms Distort Innovation? Evidence from Cancer Clinical Trials.” Cambridge (MA): National Bureau of Economic Research (NBER Working Paper No. 19430) available from <http://www.nber.org/papers/w19430.pdf>

CBO. 1998. “How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry” A Congressional Budget Office Study, July. Available online at: <http://www.cbo.gov/publication/10938>

David Cutler and Mark McClellan, 2001. Is Technological Change in Medicine Worth It? *Health Affairs*, Vol 20, No. 5, 11-29.

Joseph A. DiMasi and Henry G. Grabowski. 2007. “The Cost of Biopharmaceutical R&D: Is Biotech Different?” *Managerial and Decision Economics*, Vol. 28, 469-479.

Joseph A. DiMasi, 2014. “Innovation in the pharmaceutical industry: new estimates of R&D costs. Briefing: Costs of Developing a New Drug, 2014 Nov. 18 [Internet]. Boston (MA);

Tufts Center for the Study of Drug Development, Tufts University. Available from  
[http://csdd.tufts.edu/news/complete\\_story/cost\\_study\\_press\\_event\\_webcast](http://csdd.tufts.edu/news/complete_story/cost_study_press_event_webcast)

W. Emmons and A. Nimgade, 1991. “Burroughs Wellcome and AZT:” Harvard Business School Case 9-792-004, Cambridge, MA: Harvard Business School.

FDA, 2003. FDA Guidance for Industry, 180 day exclusivity when multiple ANDAs are submitted on the same day. July 2003. Available from  
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072851.pdf>

Dana P. Goldman, Darios N. Lakdawalla, Jessie D. Malkin, John Romley and Tomas Philipson. 2011. “The Benefits from Giving Makers of Conventional ‘Small Molecule’ Drugs Longer Exclusivity Over Clinical Trial Data. *Health Affairs (Millis)* Vol. 30, No. 1:84-90.  
<http://content.healthaffairs.org/content/30/1/84.full>

Henry G. Grabowski, Joseph A. Dimasi and Genia Long. 2015. “The Roles of Patent and Research and Development Incentives In Biopharmaceutical Innovation.” Forthcoming in *Health Affairs*.

Henry G. Grabowski, Genia Long, and Richard Mortimer. 2014. “Recent Trends in Brand Name and Generic Drug Competition.” *Journal of Medical Economics*, March, Vol. 7, No. 3, 207-214



Henry G. Grabowski, John Vernon, and Joseph DiMasi. 2002. “Returns on Research and Development for 1990s New Drug Introductions.” *PharmacoEconomics*, Vol. 20, Suppl. 3, 11-29.

C. Scott Hemphill and Bhaven N. Sampat. 2012. “Evergreening, Patent Challenges, and Effective Market Life in Pharmaceuticals”, *Journal of Health Economics* Vol. 31, 327-339.

Kevin M. Murphy and Robert Topel, 2003. “The Economic Value of Medicine Research” in *Measuring Gains from Medical Research; An Economic Approach*. Kevin M. Murphy and Robert H. Topel, eds (Chicago University of Chicago Press) 47-73.

Laura E. Panattoni. 2011. “The Effect of Paragraph IV Decisions and Generic Entry Before Patent Expiration on Brand Pharmaceutical Firms.” *Journal of Health Economics*, Vol. 30, 126-145.

Wendy H. Schacht and John R. Thomas. “The Hatch-Waxman Act: A Quarter Century Later: Congressional Research Source, CRS Report for Congress, March 13e, 2012. Available on [www.crs.gov](http://www.crs.gov)

John A. Vernon, Joseph H. Golec and Joseph A DiMasi, 2010. “Drug Development Costs When Financial Risk is Measured Using the Fama-French Three-Factor Model.” *Health Economics*, Vol. 8, August, 1002-1005.

## NOTES

<sup>1</sup> The R&D investment to discover and develop a new molecular entity has been estimated recently by the Tufts Center for the Study of Drug Development to average more than a billion dollars in out of pocket expenditure, and only one in eight drug candidates investigated in human clinical trials result in a new drug introduction. (DiMasi, 2014) (DiMasi and Grabowski, 2007)

<sup>2</sup>The CBO found that the post-1984 patent restoration provision increased effective patent life by an average of nearly three years. However, this was effectively countered by the safe harbor research exemption provisions that resulted in generic entry within one month of patent expiration under the Hatch-Waxman Act, compared to an average of three years pre-1984. As a consequence, the faster generic erosion after 1984 essentially outweighed the patent restoration features in terms of the negative impacts on R&D returns. The CBO estimated that the Hatch-Waxman Act resulted in a 12 percent decrease in the discounted value of returns from R&D in the first decade after the Hatch-Waxman Act.

<sup>3</sup> 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.

<sup>4</sup> One practice some brand firms utilized to delay entry prior to the MMA Amendments was to list new patents after an ANDA was filed in order to obtain a new 180-day stay on these late-listed patents. This was prohibited under the MMA Amendments. For further information on the provisions of Hatch-Waxman Act and its various amendments see Schacht and Thomas, (2012).

<sup>5</sup> These conditions include a generic firm's failure to market within 75 days of a final court decision or consent decree that the patents challenged are invalid or non-infringed, as well as a final decision by the FTC or the courts that an agreement with the patent owner violates anti-trust laws. (Schacht and Thomas, 2012)

<sup>6</sup> For a recent analysis of the static welfare benefits from patent challenges increasing generic competition, see Branstetter, Chartergee and Higgins, 2013.

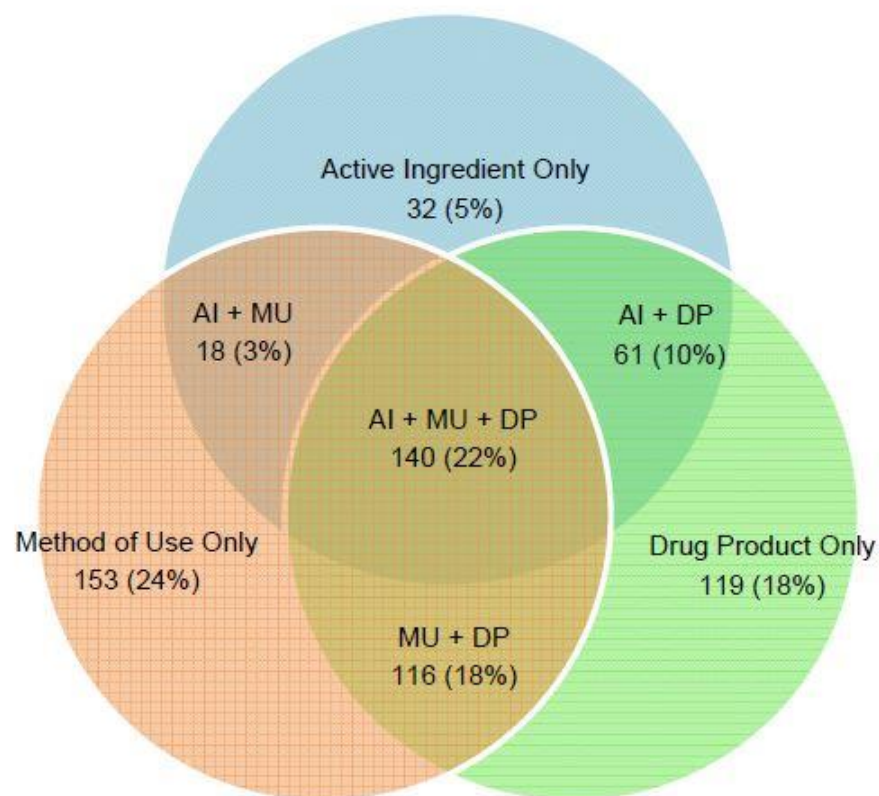
<sup>7</sup> In a separate fixed effects model in which patents rather than MNEs are the unit of observation, they find AI patents are challenged less frequently than the "weaker," non-AI ones with longer lasting patent times. They also find the likelihood of an AI patent challenge increases with a branded product's sales in various regression specifications, providing some evidence for prospecting behavior by generics. However, given a statistically insignificant negative relation between MEPs and AI challenges for the largest selling MNEs, they infer these AI challenges have a low probability of success, in contrast to non-AI patent challenges, and therefore, it is unlikely they affect innovation incentives.

<sup>8</sup> As discussed in the data appendix, 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 and in most of our analyses. Later listing patents are less likely to affect timing of entry.

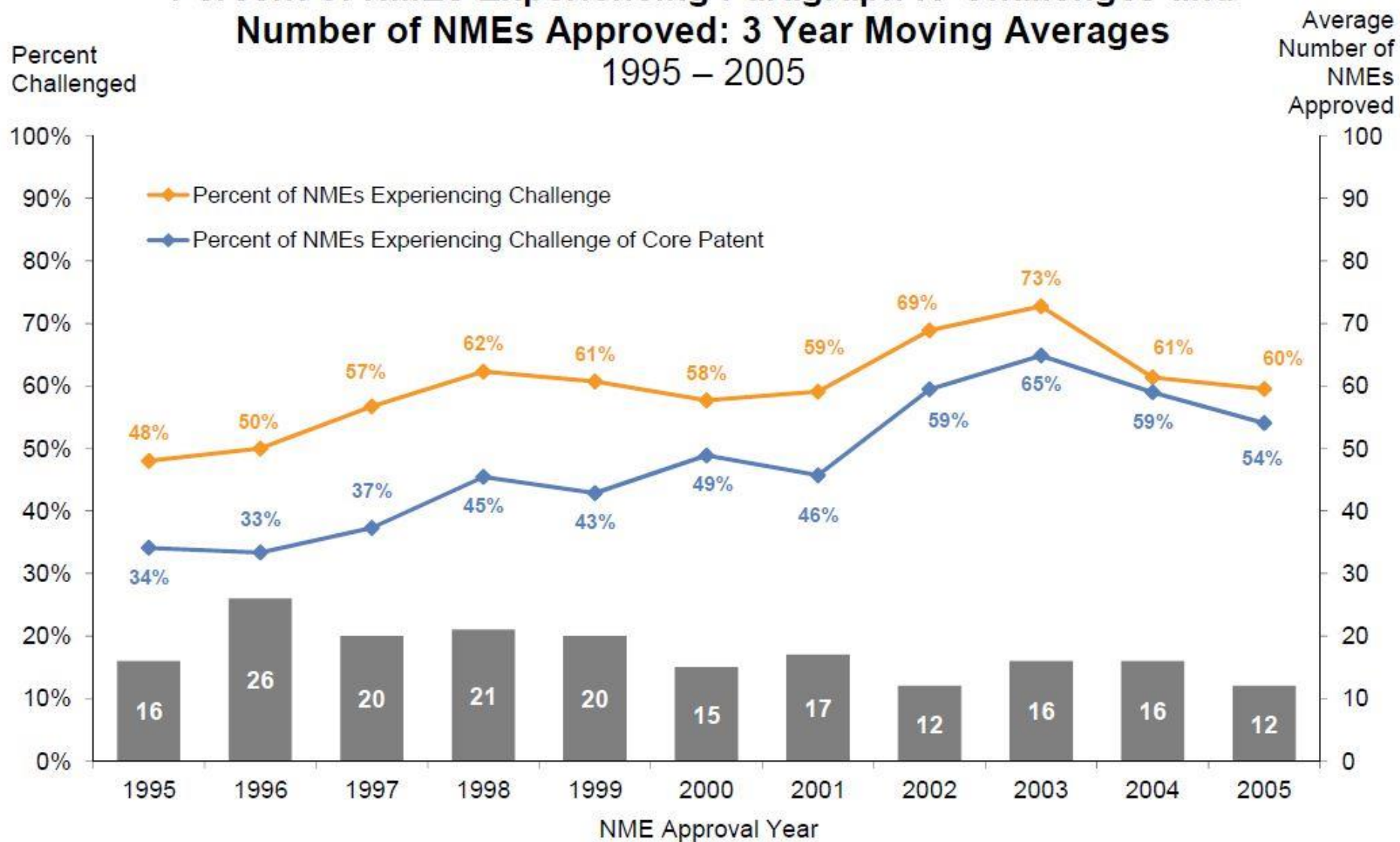
<sup>9</sup> As noted in Section II, patent extensions are capped at 14 years of effective patent life, including the extensions. A small number of products in our sample have active ingredient patents in excess of 14 years even before any extension, and are observed to not have a patent extension. These patents are also treated as core patents in the current analyses.

<sup>10</sup> In the case of the outcomes analysis of top quantile drugs, patent challenges typically occur four years after NDA approval, and stays expire two and one half years later, so these large selling NMEs are not likely to be subject to a censoring issue given the last year of NME approval in our sample is 2006 and first filing ANDAs for this cohort can begin in 2010. However, patent challenges for smaller selling drugs often occur on a more extended timeline than large selling drug products. Settlements also often carry stipulations of earlier entry if other generic firms manage to enter the market sooner than the negotiated date with the first filing generic firm.

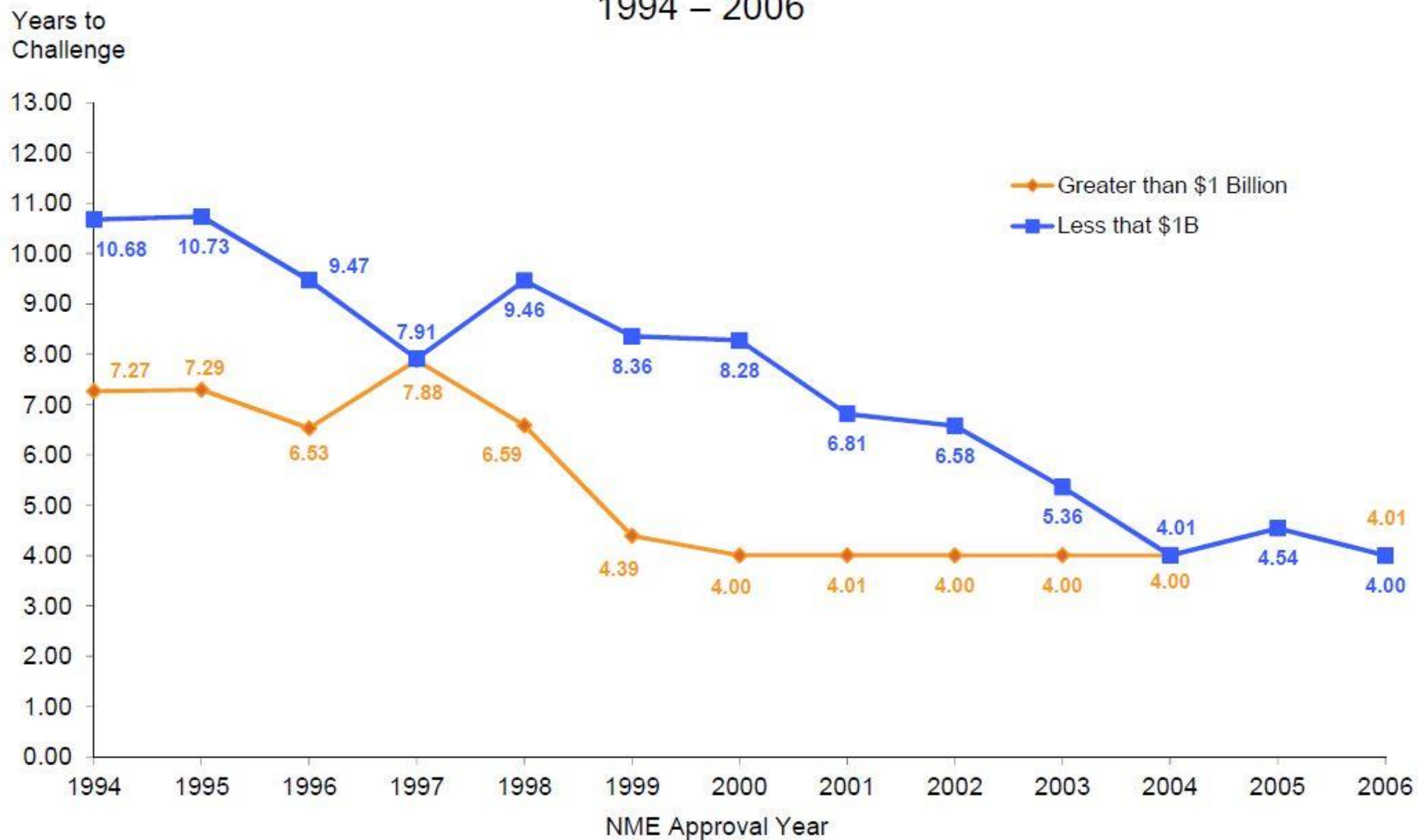
**Figure 1**  
**Patent Type (N=639)**  
**Orange Book listed Patents, 1994 – 2006 NMEs**



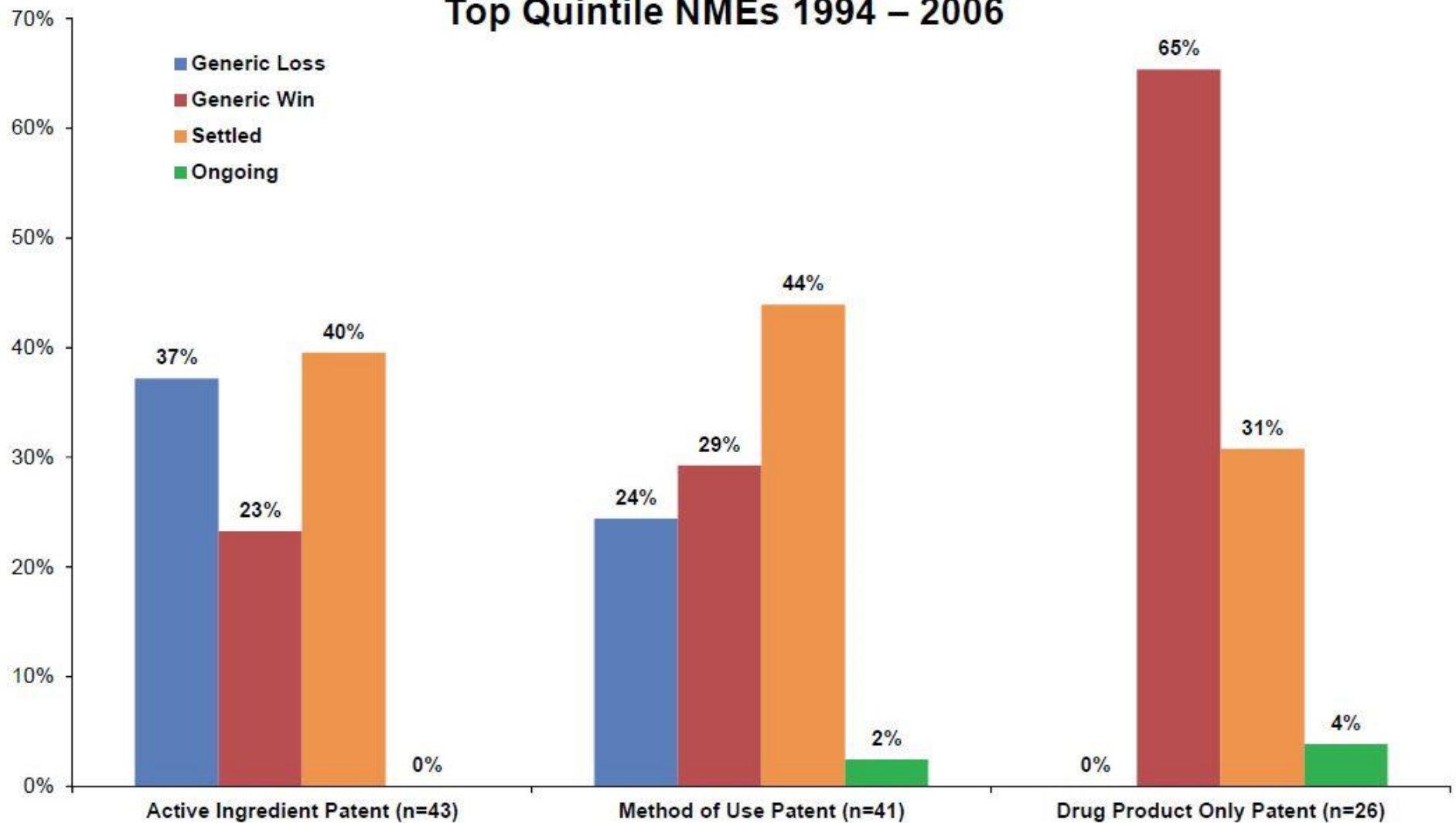
**Figure 2**  
**Percent of NMEs Experiencing Paragraph IV Challenges and**  
**Number of NMEs Approved: 3 Year Moving Averages**  
 1995 – 2005



**Figure 3**  
**Median Years From Approval to Paragraph IV Challenge**  
1994 – 2006



**Figure 4**  
**Litigation Outcomes by Patent Type<sup>1</sup>**  
**Top Quintile NMEs 1994 – 2006**

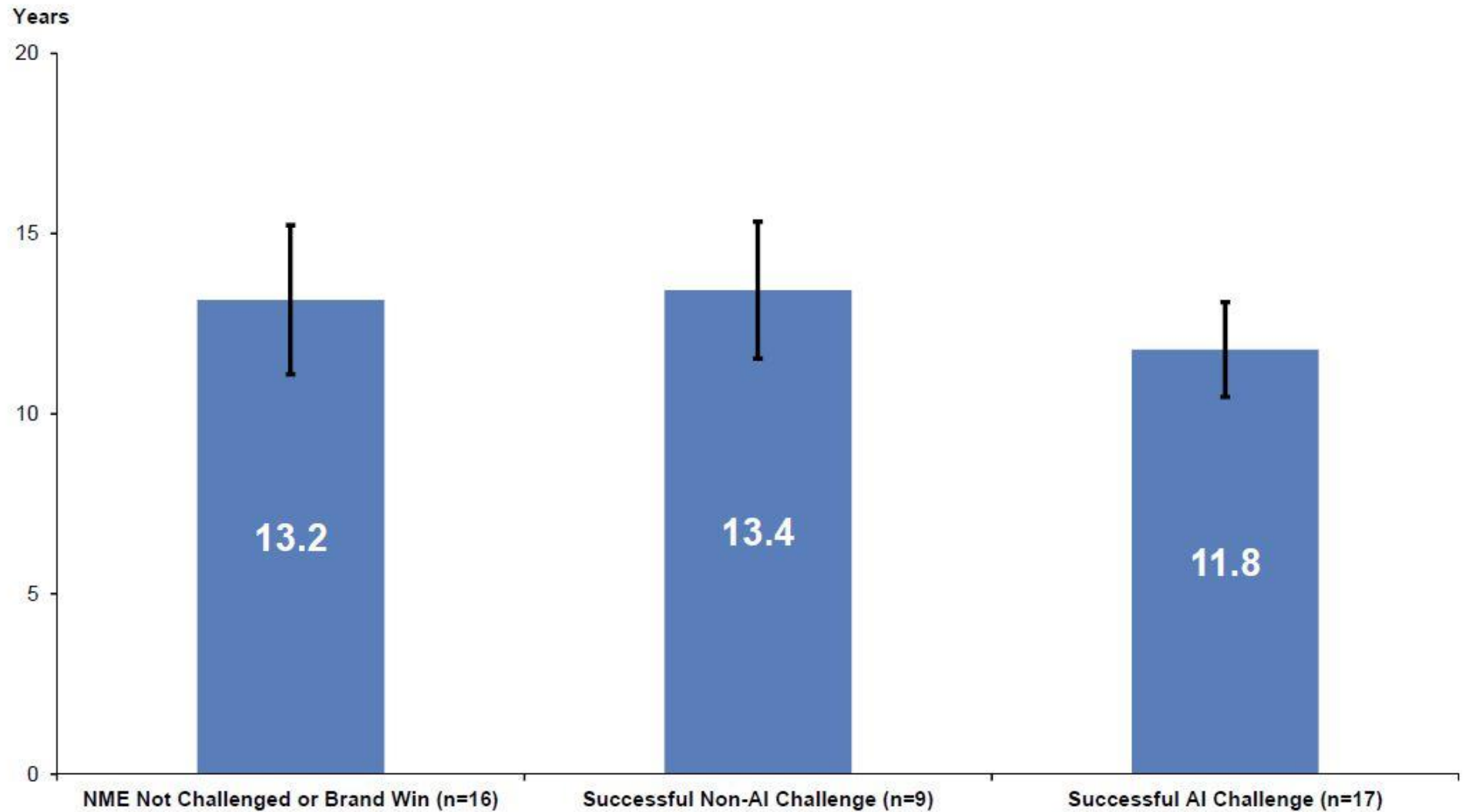


Note:

[1] Patents can hold multiple designations. Patents holding any active ingredient designation are classified under active ingredient. Patents holding a method of use designation but not an active ingredient designation are classified under method of use. Patents with only a drug product designation are classified under drug product.



**Figure 5**  
**Average Effective Patent Life**  
**Top Quintile NMEs 1994 – 2006 (n=42)**



**Table 1**  
**Drug-Level Summary Statistics<sup>[1]</sup>**

	Mean	Std. Dev.	Min.	Max.	N
Drug Challenged	0.58	0.49	0	1	213
AI Patent Challenged	0.39	0.49	0	1	213
Core Patent Challenged	0.45	0.50	0	1	185
Count of AI Patents	1.18	0.87	0	6	213
Count of non-AI patents <sup>[2]</sup>	1.82	2.19	0	11	213
Annual Sales (\$ millions)	669.55	1,212.80	0.00	9,549.44	213
Nominal Patent Term (in years)	15.32	3.42	1.70	22.72	213
Effective Market Life (in years) <sup>[3]</sup>	13.12	3.48	5.01	22.19	161
Effective Market Life for Top Quintile Drugs (in years) <sup>[4]</sup>	12.66	3.42	6.44	21.59	42

Source: IMS data; Orange Book 1994–2011; FDA NME data; FDA Paragraph IV Challenges data; Biologics data; CR analysis

Note:

[1] Late-listed patents that first appear in the Orange Book more than 5 years after drug approval are excluded from the analysis.

[2] There are on average 1.26 Method of Use patents and 0.56 Drug Product patents for each drug.

[3] Effective market life is calculated as the time between approval and the earlier of either the date of patent expiration or generic entry. Drugs that were challenged but for which litigation outcome information is not available have been excluded from the calculation.

[4] Effective market life is calculated as the time between approval and the earlier of either the date of patent expiration or generic entry. Litigation outcomes research was performed for these drugs. Calculation includes only drugs for which litigation outcome data is available.

**Table 2**  
**Summary Statistics by Sales Group<sup>[1]</sup>**

	Less than \$500M					Between \$500M and \$1B					Greater than \$1B				
	Mean	Std. Dev.	Min.	Max.	N	Mean	Std. Dev.	Min.	Max.	N	Mean	Std. Dev.	Min.	Max.	N
Drug Challenged	0.45	0.50	0	1	146	0.81	0.40	0	1	32	0.91	0.28	0	1	35
AI Patent Challenged	0.25	0.43	0	1	146	0.53	0.51	0	1	32	0.86	0.36	0	1	35
Count of non-AI patents <sup>[2]</sup>	0.33	0.47	0	1	122	0.59	0.50	0	1	29	0.79	0.41	0	1	34
Count of AI Patents	1.08	0.87	0	6	146	1.38	0.98	0	4	32	1.40	0.65	1	3	35
Count of non-AI patents	1.73	2.13	0	11	146	2.09	2.40	0	9	32	1.94	2.27	0	10	35
Annual Sales (\$ millions)	163.10	148.63	0.00	491.97	146	694.05	121.99	503.08	950.89	32	2,759.76	1,861.21	1,006.51	9,549.44	35
Nominal Patent Term (in years)	15.05	3.57	1.70	22.72	146	15.63	2.96	9.67	21.02	32	16.15	3.07	9.13	21.59	35
Effective market life (in years) <sup>[3]</sup>	13.31	3.45	5.01	22.19	107	12.27	3.86	6.44	20.56	20	13.03	3.40	6.50	21.59	34
Effective Market Life for Top Quintile Drugs (in years) <sup>[4]</sup>	–	–	–	–	0	11.10	3.25	6.44	14.51	8	13.03	3.40	6.50	21.59	34

Source: IMS data; Orange Book 1994–2011; FDA NME data; FDA Paragraph IV Challenges data; Biologics data; CR analysis

Note:

[1] Late-listed patents that first appear in the Orange Book more than 5 years after drug approval are excluded from the analysis.

[2] There are on average 1.26 Method of Use patents and 0.56 Drug Product patents for each drug.

[3] Effective market life is calculated as the time between approval and the earlier of either the date of patent expiration or generic entry. Drugs that were challenged but for which litigation outcome information is not available have been excluded from the calculation.

[4] Effective market life is calculated as the time between approval and the earlier of either the date of patent expiration or generic entry. Litigation outcomes research was performed for these drugs. Calculation

**Table 3**  
**Summary Statistics by Year Group<sup>[1]</sup>**

	1994 to 1998					1999 to 2006				
	Mean	Std. Dev.	Min.	Max.	N	Mean	Std. Dev.	Min.	Max.	N
Drug Challenged	0.53	0.50	0	1	91	0.62	0.49	0	1	122
AI Patent Challenged	0.30	0.46	0	1	91	0.46	0.50	0	1	122
Count of non-AI patents <sup>[2]</sup>	0.35	0.48	0	1	80	0.53	0.50	0	1	105
Count of AI Patents	1.05	0.67	0	3	91	1.27	0.98	0	6	122
Count of non-AI patents	1.26	1.60	0	7	91	2.24	2.47	0	11	122
Annual Sales (\$ millions)	832.40	1,544.57	0.00	9,549.44	91	548.08	876.22	2.00	5,192.37	122
Nominal Patent Term (in years)	15.45	3.40	5.01	22.72	91	15.22	3.44	1.70	21.42	122
Effective market life (in years) <sup>[3]</sup>	13.53	2.91	5.01	22.19	81	12.70	3.96	5.31	20.44	80
Effective Market Life for Researched Drugs (in years) <sup>[4]</sup>	13.61	2.60	9.53	21.59	21	11.71	3.92	6.44	19.12	21

Source: IMS data; Orange Book 1994–2011; FDA NME data; FDA Paragraph IV Challenges data; Biologics data; CR analysis

Note:

[1] Late-listed patents that first appear in the Orange Book more than 5 years after drug approval are excluded from the analysis.

[2] There are on average 1.26 Method of Use patents and 0.56 Drug Product patents for each drug.

[3] Effective market life is calculated as the time between approval and the earlier of either the date of patent expiration or generic entry. Drugs that were challenged but for which litigation outcome information is not available have been excluded from the calculation.

[4] Effective market life is calculated as the time between approval and the earlier of either the date of patent expiration or generic entry. Litigation outcomes research was performed for these drugs. Calculation includes only drugs for which litigation outcome data is available.



**Table 4**  
**Likelihood of Patent Challenge in 4th Year After**  
**Approval: Logistic Regression at the Drug Level**

Variable	(1)	(2)	(3)
Approval Date	0.00111***		0.000684***
Approved 1999-2006		3.942***	2.625**
Maximum Yearly Sales	0.0624***	0.0759***	0.0804***
# Active Ingredient Patents	0.0102	0.0113	-0.0193
# Non-Active Ingredient Patents	0.00410	0.0393	-0.000529
Constant	-18.66***	-5.151***	-14.50***
# Observations	213	213	213

Note:

1. Values marked with \*\*\* are significant at 1%, values marked with \*\* are significant at 5%, and values marked with \* are significant at 10%.
2. Sample consists of new molecular entities approved in the year 1994 or later.

**Table 5**  
**Likelihood of Core Patent Challenged: Logistic**  
**Regression at the Drug Level**

Variable	(1)	(2)	(3)
Approval Date	0.000376***		8.89e-05
Approved 1999-2006		1.126***	0.932
Maximum Yearly Sales	0.134***	0.136***	0.136***
Constant	-6.498***	-1.628***	-2.827
# Observations	185	185	185

Note:

1. Values marked with \*\*\* are significant at 1%, values marked with \*\* are significant at 5%, and values marked with \* are significant at 10%.
2. Sample consists of new molecular entities approved in the year 1994 or later.

**Table 6**  
**Likelihood of Core Patent Challenged: Logistic**  
**Regression at the Patent Level**

Variable	(1)	(2)	(3)
Approval Date	0.000211***		0.000140
Approved 1999-2006		0.267	-0.0409
Maximum Yearly Sales	0.0210***	0.0180**	0.0189**
Core Patent Flag	-0.550**	-1.187***	-1.165***
Core Patent Flag*Approved 1999-2006		0.858**	0.860**
Core Patent Flag*Maximum Yearly Sales	0.108***	0.118***	0.117***
Constant	-3.481***	-0.441*	-2.357
# Observations	567	567	567

Note:

1. Values marked with \*\*\* are significant at 1%, values marked with \*\* are significant at 5%, and values marked with \* are significant at 10%.
2. Sample consists of new molecular entities approved in the year 1994 or later.

**Table 7**  
**Likelihood of AI Patent Challenge: Logistic**  
**Regression at the Patent Level**

Variable	(1)	(2)	(3)
Approval Date	0.000159**		9.09e-05
Approved 1999-2006		0.0817	-0.124
Maximum Yearly Sales	0.0242***	0.0210**	0.0217**
AI Patent Flag	-0.408**	-1.118***	-1.118***
AI Patent Flag*Approved 1999-2006		0.956**	0.969**
AI Patent Flag*Maximum Yearly Sales	0.0472**	0.0544***	0.0543***
Constant	-2.752***	-0.374*	-1.610
# Observations	639	639	639

Note:

1. Values marked with \*\*\* are significant at 1%, values marked with \*\* are significant at 5%, and values marked with \* are significant at 10%.
2. Sample consists of new molecular entities approved in the year 1994 or later.



**Table 8**  
**Number of Orange Book Listed Patents per**  
**Drug: Linear Regression at the Drug Level**

Variable	(1) Number of Patents	(2) Number of AI Patents	(3) Number of Non-AI Patents
Approval Date	0.000574***	0.000112**	0.000462***
Maximum Yearly Sales	0.0294**	0.0113**	0.0180
Constant	-5.658***	-0.552	-5.106***
# Observations	213	213	213
R-Squared	0.116	0.048	0.078

Note:

1. Values marked with \*\*\* are significant at 1%, values marked with \*\* are significant at 5%, and values marked with \* are significant at 10%.
2. Sample consists of new molecular entities approved in the year 1994 or later.

**Table 9**  
**Time to Generic Entry: Cox Proportional Hazard Model**

Variable	(1) Hazard Ratio	(2) Hazard Ratio	(3) Hazard Ratio	Time to Generic
Approval Date	1.000		1.000*	
Approved 1999-2006		1.404	2.391**	Sooner
Maximum Yearly Sales	1.015**	1.018***	1.018***	Sooner
# Active Ingredient Patents	0.685**	0.665**	0.663**	Later
# Non-Active Ingredient Patents	0.890*	0.882*	0.876**	Later
Challenge Flag	3.895***	3.769***	4.014***	Sooner
# Observations	213	213	213	

Note:

1. Estimated hazard ratios are shown above. Hazard ratios less than one imply a longer than expected survival time.
2. Values marked with \*\*\* are significant at 1%, values marked with \*\* are significant at 5%, and values marked with \* are significant at 10%.
3. The analysis above takes into account censoring for drugs that have not yet experienced generic entry.
4. Sample consists of new molecular entities approved in the year 1994 or later.

