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Evergreening, patent challenges, and effective market life in pharmaceuticals☆

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ABSTRACT

Observers worry that generic patent challenges are on the rise and reduce the effective market life of drugs. A related concern is that challenges disproportionately target high-sales drugs, reducing market life for these "blockbusters."

To study these questions, we examine new data on generic entry over the past decade. We show that challenges are more common for higher sales drugs. We also demonstrate a slight increase in challenges over this period, and a sharper increase for early challenges. Despite this, effective market life is stable across drug sales categories, and has hardly changed over the decade.

To better understand these results, we examine which patents are challenged on each drug, and show that lower quality and later expiring patents disproportionately draw challenges. Overall, this evidence suggests that challenges serve to maintain, not reduce, the historical baseline of effective market life, thereby limiting the effectiveness of "evergreening" by branded firms.

1. Introduction

A central challenge in health policy is the calibration of pharmaceutical patent laws to optimize the balance between innovation and access. In the United States, Congress set this balance by enacting the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch–Waxman Act. The Act is credited with a sharp subsequent increase in generic drug use, from less than 20 percent of prescriptions in 1984 (Frank, 2007) to 78 percent in 2010 (IMS Institute for Healthcare Informatics, 2011).

Part of the increase is due to a regulatory pathway permitting generic drug makers to challenge branded drug makers' patents, with a view to securing early Food and Drug Administration (FDA) approval and market entry. These patent challenges, which take the form of generic drug applications with so-called "Paragraph IV" certifications, provide a means for a generic firm to pursue entry when, in its view, the relevant patents are invalid or do not cover the proposed generic product.

Patent challenges are perhaps the most controversial feature of the Hatch–Waxman regime. The received wisdom is that challenges are on the rise, selectively target large sales drugs, and substantially reduce the effective market life of branded drugs. For example, Higgins and Graham (2009), writing in *Science*, worry that the rise in challenges shortens effective market life, and, by reducing the incentive to innovate, may contribute to the frequently noted dearth of new branded drugs. The generic strategy of frequent patent challenges has been given an evocative label, "prospecting" (Higgins and Graham, 2009; Grabowski and Kyle, 2007), which suggests a wide-ranging set of challenges filed in the hope of occasionally striking gold. The received wisdom has underpinned proposals from the National Academy of Sciences, academics, and industry to increase the data exclusivity period, during which new drugs' patents cannot be challenged, to between 10 and 12 years (Goldman et al., 2011; Higgins and Graham, 2009; National Academy of Sciences et al., 2007).

At the same time, other observers have identified the increasing acquisition of additional patents by brand-name drug makers, often of doubtful validity or applicability, in order to delay generic competition (Engelberg et al., 2009). This activity has been given

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the equally evocative label of "evergreening" (Thomas, 2005; Kesselheim and Avorn, 2006). Later issued, later expiring patents tend to be weaker, in the sense that a court is less likely to conclude that they are valid and infringed by a competing generic product. They tend not to be patents that cover the active ingredient—what we call "AI patents"—but patents pertaining to ancillary aspects of the drug. In the case of the blockbuster antidepressant Paxil (paroxetine), for example, the branded drug maker secured 10 such patents. The last expiring patent would, unless challenged, have blocked generic competition until 2019, compared to a successful challenge that secured generic approval and entry in 2003. Such patenting strategies are part of a larger set of tactics, which also include new formulations and other product line extensions, that can lengthen market exclusivity for therapies facing generic entry (Huskamp et al., 2008).

These debates about prospecting and evergreening have been the subject of much policy attention, but little analysis. We examine the causes and effects of patent challenges using a unique dataset of all instances of first time generic approval between 2001 and 2010, linked with information about each drug's patents, patent challenges, and other characteristics. We restrict attention to drugs that contain a novel active ingredient, so-called new molecular entities, or NMEs. This choice is significant. Concerns about prospecting are heightened when it comes to NMEs, sometimes considered the most innovative drugs (National Institute for Health Care Management, 2002). At the same time, evergreening is a less important concern for these drugs than for product line extensions, i.e., reformulations of drugs where the active ingredient was previously approved. For a line extension, an AI patent is likely to expire at an earlier point after product approval, if the drug even has an AI patent in the first place. Thus, this study places a lower bound on the extent of evergreening and the role played by patent challenges in curbing its effects.

Our descriptive results show that challenges are much more common for higher sales drugs. We also demonstrate a slight increase in challenges over this period, and a sharper increase for early challenges (those commencing within five years of drug approval). Despite this, effective market life is stable across drug sales categories, and has hardly changed over the decade, despite predictions to the contrary in previous research.

A second set of analyses, exploiting variation within each drug, explains this surprising result. While drug sales matter for the likelihood that a generic firm launches a patent challenge, so do patent characteristics. Fixed effects models show that within drugs, lower quality patents and those that, unless challenged, extend market life the most, are much more likely to be challenged. Patent challenges are disproportionately targeting patents, especially low quality ones, that aim to extend patent term. There is some evidence, though limited, that generics are more aggressive in challenging the "basic" (AI) patents for more lucrative drugs. However, challenges to these patents do not generally result in earlier entry, suggesting that generic drug makers seldom win these challenges. Overall, and contrary to their portrayal in current policy debates, patent challenges appear to be playing a restorative role, by ratcheting back the effective market life of drugs with long nominal patent terms.

Section 2 describes how patent challenges work and reviews previous research that provides context for our analyses. Section 3 describes our data. Section 4 reports basic descriptive statistics and traces trends in patent challenges, nominal patent term, and effective market life over the past decade. Section 5 presents drug-level and patent-level regression results about the causes and effects of patent challenges. Section 6 concludes.

2. Regulatory background and previous research

After a branded drug maker places a patented drug on the market, a generic firm may seek to market a competing version of the same drug by filing an Abbreviated New Drug Application, or ANDA, with the FDA. If the generic firm chooses not to challenge any branded drug patents, the FDA delays approval until all patents expire. A generic firm seeking pre-expiration entry files an ANDA asserting that one or more patents are invalid or not infringed by the proposed generic product. To encourage these challenges, the Act provides a bounty to the first challenger, a period of 180 days of exclusivity during which other generics cannot enter.

At the same time, the Act delays the onset of this challenge process, by prohibiting a generic firm from filing an ANDA during the first four years after branded drug approval.[1] This "data exclusivity" period is extended in practice by the subsequent challenge and FDA approval process, which typically require several years to complete, even where the generic firm's patent challenge is eventually successful.

Grabowski and Kyle (2007) offer the first systematic empirical analysis of how challenges affect market life. They examine market life (what they call the "market exclusivity period") for NMEs with first generic entry between 1995 and 2005. In their sample, average market life is 13.5 years. They find that market life is decreasing in sales: NMEs with annual sales less than $50 million have average market life of 15.1 years, compared to 12.7 years for drugs with sales greater than $500 million. Market life is falling slightly over time (13.6 years for 1995–2000; 13.4 years for 2001–2005). The authors also report that the ten drugs in their sample with sales exceeding $1 billion have progressively shorter market life over time: 13.8 years in 1995–2001, compared to just 11.2 years in 2002–2005.

Grabowski and Kyle suggest that patent challenges—and challenges that occur earlier in the life of a branded drug—may have caused the overall shorter market life for high-sales drugs and the decrease over time for blockbusters.[2] The authors call this potential generic strategy "prospecting"—a metaphor that has proven influential in later work (Berndt et al., 2007a; Branstetter et al., 2011; Higgins and Graham, 2009)—and draw particular attention to challenges of major drugs that occur early in the market life of a new drug (p. 498). In their regression analyses, the authors find that drugs with patent challenges have between 1.2 and 1.6 years less market life, depending on the specification (significant at the 10 percent level).[3]

Other work has examined the effects of patent challenges on branded drug makers. Filson and Oweis (2010) use an event-study framework to assess the effects of two court decisions that made patent challenges more likely, finding that these decisions are associated with a lower propensity for startup firms to form alliances.

[1] The four-year delay is limited, with minor exceptions, to patented drugs that are new molecular entities. If the generic firm decides to wait until patent expiration, or there are no patents, the delay is five years.

[2] For example, with respect to blockbusters, the authors note, "[A]ll but a few of these billion dollar drugs over the 1995–2005 period have been subject to [patent challenges]. . . . The fact that these challenges are now occurring earlier in the product life cycle may be one of the significant factors explaining the tendency toward shorter [market exclusivity periods] in recent years" (p. 497). As for the longer life of low sales drugs, the authors note that these differences are not necessarily due to patent challenges, but could also reflect the unprofitability of generic entry on such drugs.

[3] Grabowski and Moe (2008) emphasize the growth of early challenges as a rationale for longer data exclusivity terms, noting that the current period "affords branded products a floor of effective exclusivity of 5 to 7 years," a period that offers "insufficient time for most new drugs to recoup the up-front R&D costs and earn a positive return on this investment" (p. 25).

Panattoni (2011), also using an event-study framework, finds that Paragraph IV litigation decisions in favor of the brand (generic) significantly increase (decrease) branded firms' stock market value.

In a third line of research, Berndt et al. (2007a,b) use data on trends in challenges and "authorized generics"—generic products marketed under the branded firm's new drug approval—to argue that such products are unlikely to deter patent challenges, or thereby harm consumers. The authors also show a growth in early challenges (those commencing within six years of brand approval) over the 1991–2005 period. More closely related to our own work, Berndt et al. (2007a) hypothesize that an explanation for a rise in patent challenges by generic firms, beyond increased propensity to engage in prospecting, is that the quality of branded drug patents might have fallen over time, raising the likelihood of a successful challenge (p. 792).

Hemphill and Sampat (2011) find evidence in support of this latter hypothesis, showing that while patent challenges do reflect sales, drugs with "weaker" patents—defined as a patent in which no claim covers the active ingredient of the drug—are much more likely to draw challenges. This effect is particularly pronounced for weaker patents that lengthen what we call the "nominal patent term," the time between brand approval and expiration of the last expiring patent. However, that analysis was conducted at the drug level; it did not examine which patents pertaining to a drug were challenged. Moreover, this previous research also showed that nominal term increased sharply over the quarter century since the Hatch–Waxman Act was passed, a finding that seems to contrast with Grabowski and Kyle's finding of stable (or in some sub-samples, diminishing) market life over time.

In this paper, we follow the Grabowski and Kyle strategy of examining drugs with completed generic entry. We extend their work by studying the decade of generic entry between 2001 and 2010. The more recent data permits an assessment of whether market life has decreased over this period due to more aggressive challenges, as observers have feared. We also examine the characteristics of drugs and patents that draw challenges, to examine the effects of prospecting and evergreening directly. We begin with drug level models examining how a drug's sales and patent portfolio affect the likelihood it is challenged. To account for potential endogeneity of patent characteristics, we then proceed to estimate models with drug fixed effects, examining which patents within a drug's patent portfolio are challenged.

3. Data

We examine NMEs that were first subjected to competition from a therapeutically equivalent (TE) generic product between 2001 and 2010. For each brand-name drug, we restrict attention to the dosage form designated as an NME by the FDA.[4] Our dataset omits drugs approved by means of a Biologics License Application, drugs that were already available over-the-counter at the time of first generic approval, and drugs approved prior to the Hatch–Waxman Act.

For the generic product, we restrict attention to drugs that are bioequivalent to the brand-name drug and received an "A" rating of therapeutic equivalence from the FDA.[5] We limit attention to TE generic drugs because non-TE generics are not close competitors. They fail to trigger automatic substitution under state law and formulary rules, and thus generally achieve much lower market penetration. Our measure of effective market life is the time from brand approval until first FDA approval of a TE generic product. This measure of market life differs slightly from Grabowski and Kyle (2007), which uses a measure of generic launch rather than approval. In Appendix A we compare the two measures to assess the robustness of our results.

We identified brand-generic pairs from a list of first generic approvals maintained by the FDA (2011a), and confirmed TE status using the Orange Book, a second FDA resource (FDA, 2011b).[6] Archived editions of the Orange Book were our source for recent years (2000–2010); older data was provided by the FDA in response to a Freedom of Information Act (FOIA) request. Each drug was matched to a third FDA database, Drugs@FDA (FDA, 2011c), which reports the date of drug approval and various drug characteristics, including dosage form and NME, over-the-counter, and priority review status. We infer the route of administration from the dosage form.[7]

For each drug, we collected branded drug sales in the year prior to first generic approval from the National Sales Perspective database of IMS Health, the leading commercial provider. We converted all sales to 2010 dollars using the Producer Price Index.[8] We also determined the drug's therapeutic class (Department of Veterans Affairs, 2011).

We collected extensive information about the pertinent patent protection for each branded drug. Drug makers are required to furnish this information to FDA for inclusion in the Orange Book. Our focus is the effect of patents and patent challenges on generic entry, so we dropped a small number of drugs with no Orange Book-listed patents. Appendix B provides additional details about construction of the patent data.

For each of the 119 drugs in our final dataset, we calculated the nominal patent term as defined above, including any applicable six-month pediatric extension. We also coded each patent by type. One of the authors developed a coding guide and worked with a former PTO examiner of drug patent applications to code each patent according to whether it contains at least one claim covering the active ingredient. In other words, a patent with both active ingredient and non-active ingredient claims counts as an AI patent (Hemphill and Sampat, 2011). As discussed above, the goal is to capture "basic" compound patents, as opposed to patents on ancillary aspects of the drug. For example, patents covering the particular formulation or composition of the drug, or methods of use, are coded as non-AI patents. We take a narrow view of AI status.

[4] We use NME status, rather than 'new chemical entity" (NCE), a closely related FDA designation. The main difference is that a drug that contains a novel active ingredient, but also a previously approved active ingredient, is denied NCE protection for the novel substance. Two drugs in our dataset are NMEs but not NCEs.

[5] B-rated generic drug products are not considered therapeutically equivalent by the FDA, often because the specific dosage form is different, raising questions as to bioequivalence.

[6] We dropped a small number of non-TE first entrants, and confirmed by hand the absence of a later TE approval within our study period.

[7] We measure challenges at the drug level. As a technical matter, however, Paragraph IV certifications are made at the individual dosage strength level. Thus, it is possible that a successful challenger could challenge some strengths but not others; that there could be different successful challengers for different strengths; and even that those different successful challengers could challenge different patents. In practice, however, in our data the first approved generic received approval for all or nearly all strengths. With the exception of two drugs, the first approved generic received approval for strengths accounting for 80 percent or more of total sales, among all strengths challenged. For one drug, there was a one-week delay in approval of the generic product for certain strengths. For the remaining drug, the FDA awarded first approval on different strengths to different drug makers. The approvals occurred on the same day, and reflected challenges to the same patents.

[8] http://data.bls.gov/.

Table 1
Summary statistics.

Variable	Mean	Std. Dev.	Min.	Max.	*N*
Drug challenged (as to at least one patent)	0.66	0.48	0	1	119
AI patent challenged	0.24	0.43	0	1	119
Nominal patent term (in years)	15.89	5.28	1.15	34.55	119
Effective market life (in years)	12.15	3.14	5.84	19.04	119
Count of AI patents	0.89	0.58	0	3	119
Count of non-AI patents	1.79	2.11	0	10	119
Annual sales (millions of 2010 dollars)	747.68	1145.58	0.02	6557.29	119
Priority review	0.39	0.49	0	1	119
Oral dosage form	0.67	0.47	0	1	119
Class = Cardiovascular	0.23	0.42	0	1	119
Class = Central nervous system	0.20	0.40	0	1	119
Class = Cancer	0.13	0.33	0	1	119
Class = Hormone	0.10	0.30	0	1	119
Class = Gastrointenstinal	0.09	0.29	0	1	119
Class = Anti-infective	0.09	0.29	0	1	119
Class = Other	0.16	0.37	0	1	119

Thus, patents on alternative isomers, crystalline structures, salts, and metabolites are also coded as non-AI patents.[9] Several measures of construct validity confirm that our coding does distinguish basic versus ancillary patents for a particular active ingredient.[10]

Finally, we collected information about patent challenges. We determined whether the first approved generic firm's application included a Paragraph IV certification. This information was assembled from a list of approved ANDAs with Paragraph IV certifications, which we obtained from the FDA via a second FOIA request, and then verified against an FDA list of brand-name drugs that have attracted ANDAs with Paragraph IV certifications (FDA, 2011d), FDA correspondence, and information from a private data vendor, the Paragraph Four Report. For some drugs, there were multiple first approvals on the same day. In that instance, the drug was treated as attracting a patent challenge if one or more first-approved ANDAs contained a patent challenge.

For drugs with patent challenges, we also determined by hand which of the patents were actually challenged. We compiled this information from FDA approval letters, complaints filed in patent litigation, and SEC filings.

4. Descriptive statistics

Table 1 reports summary statistics for the resulting dataset. Of the 119 drugs, two-thirds are orally administered, and nearly two-fifths received priority review from the FDA. Cardiovascular and central nervous system drugs, the two most common therapy classes, each account for slightly more than one-fifth of the sample. Average annual sales are $748 million. The top-selling drug, Prilosec (omeprazole), has IMS-reported annual sales (adjusted for inflation) of $6.6 billion. To flexibly allow for potential non-linearity in the effects of sales (including whether "blockbuster" drugs at the very top of the sales distribution are different) we group the drugs by quintile of sales. The cutpoints are $55 million, $144 million, $397 million, and $1.1 billion.

Turning to patents, each drug has 2.7 patents on average (with a median of two patents), which yield an average nominal patent term of 15.9 years. By comparison, average effective life is 12.2 years, a difference of nearly four years. (The median values are 14.5 and 12.6 years, respectively.) The key difference between effective life and nominal term is patent challenges by the generic firm.[11] Absent the challenges, the generic firm would be forced to wait until the expiration of the last Orange Book-listed patent.

Two-thirds of the drugs (78/119) include a patent challenge. Less than half of these challenges, affecting 24 percent of all drugs, target a basic (AI) patent. This is despite the fact that 78 percent of the drugs have an AI patent. On average, drugs have 0.89 AI patents. As Fig. 1 shows, most drugs have one AI patent, while a small number (12 drugs) have two or three such patents. Multiple AI patents can occur, for example, when an early patent claims a genus of compounds, and a later patent covers the specific active ingredient of the drug. By contrast, on average the drugs have 1.8 non-AI patents. While the modal drug has no non-AI patents, there is considerable variation: over a quarter of the drugs in the sample have three or more of these "lower quality" patents.

Fig. 2 shows that the likelihood that an ANDA includes a patent challenge increases sharply with drug sales. While generic entrants challenge patents for just 29 percent of drugs in the bottom quintile of sales, they do so for 96 percent of drugs in the top quintile (p-value < .01). The likelihood that a drug will be challenged "early," within five years of launch, is also increasing with sales. With the exception of the bottom quintile of sales (where the profitability of early generic entry and thus patent challenges would be lowest)

[9] Nevertheless, the coding may be overinclusive in minor respects, if the claim appears to cover a novel pharmaceutical ingredient, but in fact is merely a minor variant of a substance in the prior art.

[10] To assess construct validity, we examined which patent is selected for "patent extension." Under the restoration provisions of Hatch-Waxman, one patent per drug can be extended, for up to five years, to compensate the drug maker for delays during the FDA review process. A branded drug maker thus has a strong incentive to extend a patent that is likely to be found valid and infringed by potential generic products. A much higher share of AI patents was extended than non-AI patents (79 percent versus 13 percent), consistent with our characterization of these as more basic patents.
A second measure of patent strength is whether the patent is part of the first wave of patent applications on the drug. The industry literature on product lifecycle management suggests that drug makers tend to apply for patents on the compound first, and ancillary patents later. Comparing AI and non-AI patents, we find that of the AI patents, 77 percent are among the first filed patents (by application year) for the drug, compared to just 17 percent of non-AI patents.

[11] Other factors also matter for our measure of effective market life. Various FDA exclusivities can also delay entry. These include new chemical entity exclusivity (for NCEs) and orphan exclusivity (for drugs with orphan indications). Effective life can also be affected by factors unrelated to patents. For example, small market size may reduce incentives to file ANDAs quickly after patent expiration. This is the likely explanation for why effective life is longest for the lowest sales drugs: see Figure 2 below and also Grabowski and Kyle (2007). Nonetheless, conditional on all of these factors, the *difference* between effective market life and nominal patent term is almost always due to patent challenges. The exception to this generalization involves cases where FDA exclusivities last longer than the last expiring patent, such that patent protection is not the binding constraint. In such cases, the usual relationship between nominal and effective is reversed, and nominal patent term is less than effective market life. This occurred in two cases in our sample; excluding these cases does not affect main results.

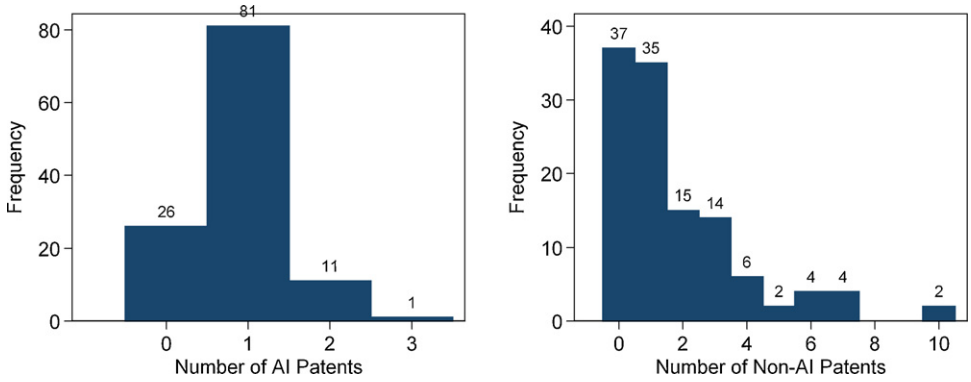

Fig. 1. Distribution of active ingredient (AI) and other (non-AI) patents. *Notes*: The left panel shows the distribution of AI patents for the 119 new molecular entities (with patents) for which first generic entry occurred between 2001 and 2010. The second panel shows the distribution of non-AI patents.

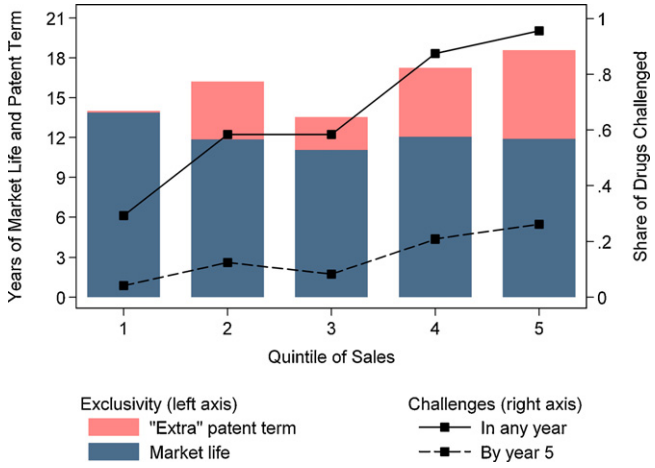

Fig. 2. Effective market life, nominal patent term, and challenges by sales. *Notes*: This chart shows average effective market life, nominal patent term, and challenges for the 119 new molecular entities (with patents) for which first generic entry occurred between 2001 and 2010. The horizontal axis is quintile of sales. The full height of each bar represents average nominal patent term for a sales category, and the navy portion average effective market life for the category, both measured (in years) on the left axis. Effective market life is the time in years between brand approval and first generic entry. Nominal patent term is the time in years between brand approval and expiration of last patent. The solid line shows the share of drugs with Paragraph IV patent challenges, and the dashed line the share with challenges within five years of approval, both measured on the right axis.

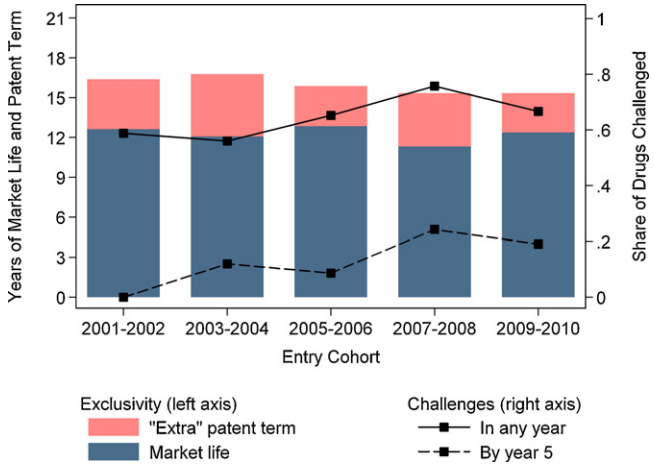

Fig. 3. Effective market life, nominal patent term, and challenges over time. *Notes*: This chart shows average effective market life, nominal patent term, and challenges for the 119 new molecular entities (with patents) for which first generic entry occurred between 2001 and 2010. The horizontal axis shows the approval cohort when first generic entry occurred. The full height of each bar represents average nominal patent term for a cohort, and the navy portion average effective market life for the category, both measured (in years) on the left axis. Effective market life is the time in years between brand approval and first generic entry. Nominal patent term is the time in years between brand approval and expiration of last patent. The solid line shows the share of drugs with Paragraph IV patent challenges, and the dashed line the share with challenges within five years of approval, both measured on the right axis.

effective market life is stable over the sales distribution. By contrast, nominal patent term increases sharply with sales, with the top sales quintile having almost four years more patent term than the bottom (p-value < .01).

Fig. 3 shows that patent challenges have increased slightly over the past decade. The drugs are grouped into five cohorts. The first (final) cohort contains drugs with first entry in 2001 or 2002 (2009 or 2010). Fifty-nine percent of first time entrants in the first cohort include patent challenges, compared to 67 percent by the end of the decade, though the shares fluctuate over time. We find a sharper and more consistent increase in early challenges. By the end of the decade, nearly 20 percent of first time generic entrants had early challenges compared to none in the first cohort. Even in the face of these trends, however, effective market life has remained roughly constant over this period.[12] Nominal patent term has decreased over this period, though the difference between the first and last cohorts is not statistically significant (p-value = .54).

Fig. 4 shows the distribution of nominal patent term and effective market life for the 78 drugs where entry occurred via patent challenge, with each row representing a drug. For drugs that are challenged, the mean decrement to nominal patent term resulting from challenges is 6.4 years (median = 6.2 years). The drugs that were challenged had aggregate sales of over $81 billion in the year prior to challenge. Given the large difference between brand and generic prices, the static welfare gains to consumers as a result of these challenges is likely large.[13]

[12] A referee pointed us to a new analysis by Danzon and Furukawa (2011) which confirms, using different data, that market life has remained roughly stable over the past decade.

[13] Branstetter et al. (2011) provide the first formal analysis of consumer surplus gains, from patent challenges on anti-hypertensive drugs. The authors begin by calculating total surplus from the sale of 38 molecules during the 1997-2008 period, using demand estimates from discrete choice models to estimate per period surplus, and standard instruments (measures of "multimarketness" and competition) to account for endogeneity of price and advertising. About half of the drugs in their sample included patent challenges. To examine the welfare effects of challenges,

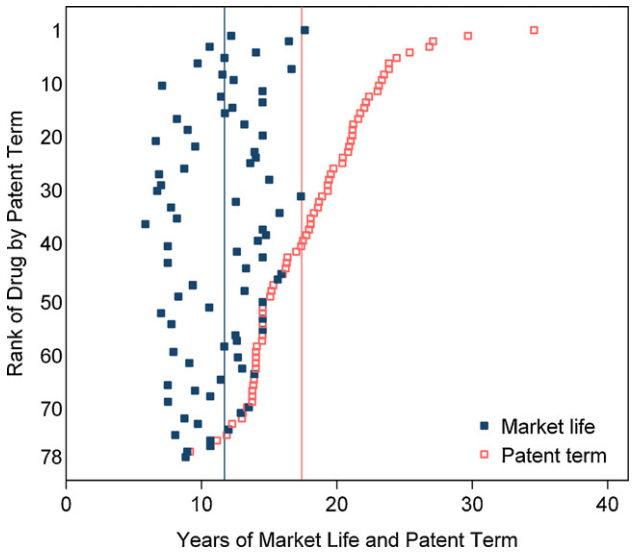

Fig. 4. Market life and patent term by drug, for drugs with challenges. *Notes*: This chart shows average effective market life, nominal patent term, and challenges for the 78 drugs for which first generic entry occurred between 2001 and 2010 where generic entry involved a Paragraph IV patent challenge. Effective market life is the time in years between brand approval and first generic entry. Nominal patent term is the time in years between brand approval and expiration of last patent. Each row represents a drug. The solid navy reference line indicates median effective market life for drugs with challenges (11.7 years) and the solid red line indicated median nominal patent term for these drugs (17.4 years).

Overall, Figs. 2–4 indicate that drugs that draw challenges have similar effective market life to other drugs. That result in turn suggests the hypothesis that challenges might be targeting and reducing the effective life of drugs with large nominal patent terms, i.e., responding to evergreening. We examine this in a regression framework below.

5. Regression analyses

We begin by exploring the determinants of nominal patent term and effective market life. First, we examine how nominal patent term relates to sales and other drug characteristics:

$$NOMINAL_i = \alpha_0 + \alpha_1 X_i + \alpha_2 SALES_i + \varepsilon_i,$$

where *NOMINAL* is nominal patent term (i.e., patent term in the absence of challenges), and *X* is a vector of brand-name drug characteristics, including indicators of oral administration and priority review status, and fixed effects for the drug's therapeutic class and year of generic entry. *SALES* measures drug sales in the year prior to generic entry, which we parameterize using quintiles of sales.

We then examine correlates of effective market life, and update Grabowski and Kyle's (2007) estimates of the association between patent challenges and this variable:

$$EFFECTIVE_i = \beta_0 + \beta_1 X_i + \beta_2 SALES_i + \beta_3 PPORT_i + \beta_4 DCHALLENGE_i + \varepsilon_i,$$

where *EFFECTIVE* is effective market life, *PPORT* is a vector of characteristics of the drug's patent portfolio (including years of patent term and counts of AI and non-AI patents), and *DCHALLENGE* indicates whether the drug attracted a challenge as to at least one patent. We will estimate models with subsets of these variables, and also the fully nested model with all of them. We use Huber–White robust standard errors to account for potential heteroskedasticity.

Next we estimate linear probability models relating whether the drug draws a patent challenge to a set of drug characteristics, including sales and patent characteristics:

$$DCHALLENGE_i = \gamma_0 + \gamma_1 X_i + \gamma_2 SALES_i + \gamma_3 PPORT_i + \varepsilon_i.$$

One drawback of the linear probability model is that it can generate predictions outside the zero-one range. However, these models provide reasonable estimates of marginal effects, our focus here (Wooldridge, 2002). Another drawback of the linear probability model is heteroskedasticity: accordingly for these models too we use Huber–White standard errors.[14]

As we discuss in more detail below, these patent challenge models are prone to potential endogeneity. In particular, the coefficients on the patent portfolio variables would be biased if unobserved heterogeneity in profits (e.g., through expected profitability not captured by our sales measures) led to more aggressive patenting and more challenges, or if the expectation of challenges to basic (AI) patents led firms to patent more aggressively (accumulating more non-AI patents). Accordingly, we also estimate fixed-effects models of which patents were challenged, exploiting within-drug variation in the patents that draw challenges:

$$PCHALLENGE_{ik} = \delta_0 + \delta_1 PCHAR_{ik} + \delta_2 \psi_i + \varepsilon_{ik}.$$

In these models, the unit of analysis is an individual patent, and the dependent variable is an indicator for whether patent *k* on drug *i* is challenged. Explanatory variables include measures of patent strength and duration, *PCHAR*, as well as drug fixed effects (ψ_i) that absorb any fixed drug-level characteristics that affect likelihood of challenge. These models thus allow us to use within-drug variation in the patent measures to examine whether particular types of patents are more associated with challenges. Here, in addition to correcting standard errors for heteroskedasticity, we cluster the standard errors on drugs to account for potential correlation across observations.

Finally, returning to drug level analyses, we examine the causes and consequences of challenges to basic (AI) patents on market life. These models are similar in structure to the effective market life models described above, but focus on the relationship between market life and whether the AI patent on a drug was challenged (instead of whether any patent was challenged).

5.1. Drug-level analyses: nominal patent term, effective market life, and challenges

We first examine how nominal patent term and effective market life relate to drug sales and other characteristics—in essence, a more fine-grained analysis of the data in Fig. 2. Table 2 reports the results. Column 1 shows that nominal patent term increases sharply with sales, with the top quintile of drugs having almost six years more nominal term than the bottom quintile. Column 2 shows there is no clear relationship between effective market life

they reset generic entry date to what it would have been absent challenges—in other words, comparing effective market life and nominal patent term—and calculate surplus under this counterfactual "no patent challenges" scenario.

[14] A practical advantage of these models is that in some of the logit models we estimated in robustness checks there were "quasi-separations," i.e., combinations of explanatory variables perfectly predicted outcomes, and maximum likelihood estimates for some variables could not be computed. For the drug-level models, collapsing categories (e.g., aggregating the top two quartiles of nominal patent term into one) solved this problem. Results from these models are qualitatively similar to those from the linear probability models reported in the text, and are available on request. We also estimated conditional logit analogs of the patent level models with drug fixed effects, but many of these models encountered convergence difficulties.

Table 2
Nominal patent term and effective market life versus sales, drug characteristics, and patent portfolio.

	(1) Nominal	(2) Effective	(3) Effective	(4) Effective	(5) Effective	(6) Effective
Second quintile sales	3.032 (1.628)	−1.003 (0.885)	−1.266 (0.904)	−0.552 (0.862)	−0.922 (0.790)	−1.072 (0.806)
Third quintile sales	0.378 (1.711)	−1.966* (0.886)	−1.999* (0.856)	−1.365 (0.987)	−1.066 (0.856)	−1.468 (0.813)
Fourth quintile sales	4.433** (1.590)	−0.574 (0.871)	−0.959 (0.915)	0.523 (0.948)	0.262 (0.923)	−0.277 (0.965)
Top quintile sales	5.683** (1.571)	−0.708 (1.092)	−1.201 (1.200)	0.444 (1.114)	−0.0535 (1.116)	−0.280 (1.094)
Priority review	1.021 (1.245)	1.024 (0.700)	0.935 (0.693)	0.979 (0.680)	0.730 (0.634)	0.767 (0.591)
Oral dosage form	−1.671 (1.513)	−1.622* (0.734)	−1.477* (0.727)	−1.470* (0.728)	−1.012 (0.653)	−1.024 (0.647)
Years of patent term			0.0867 (0.0558)		0.216** (0.0601)	0.259** (0.0734)
Challenged?				−1.956** (0.692)	−3.197** (0.650)	−2.852** (0.654)
Count of AI patents						1.041 (0.583)
Count of non-AI patents						−0.235 (0.201)
Constant	13.42** (1.503)	12.70** (0.851)	11.53** (1.040)	13.39** (0.755)	10.93** (1.075)	9.961** (1.117)
R squared	0.217	0.317	0.334	0.377	0.456	0.510
F statistic	1.965	3.302	3.431	5.138	7.036	6.787
p value	0.036	0.000	0.000	0.000	0.000	0.000
Observations	119	119	119	119	119	119

Notes: Sample comprises new molecular entities for which first generic entry occurred between 2001 and 2010. Each observation represents a drug. Effective market life is the time in years between brand approval and first generic entry. Nominal patent term is the time in years between brand approval and expiration of last patent. Estimates are from ordinary least squares regressions. All models include indicators for therapeutic class and generic approval year. Heteroskedasticity-consistent standard errors in parentheses.

* $p < 0.05$.

** $p < 0.01$.

and sales, controlling for entry cohort and drug characteristics.[15] In Column 3 we relate effective market life to nominal patent term and find no relationship between the two, all else equal. This result underscores that looking at effective market life or nominal patent term alone may be misleading in answering the question of what has happened with "patent life" over time.

As we noted in Section 2, Grabowski and Kyle (2007) examined the association between patent challenges and market life in an earlier decade, finding a negative but insignificant relationship. For comparison, we re-estimated their model across our more recent sample of drugs in the models reported in Columns 4 and 5. Column 4 shows a strong, negative, and statistically significant association between the two. Drugs with patent challenges have much quicker entry: market life is 2 years lower. Column 5 also shows that there is an even larger negative relationship between challenges and market life after controlling for nominal patent term. This is as expected, since patent challenges are the major source of difference between patent term and market life.[16] In this model, the effect of nominal term is positive and significant: conditional on whether a drug is challenged, nominal term is related to market life.[17] Column 6 controls for the counts of AI and non-AI patents on the drug, neither of which has a statistically significant relationship with effective life. However, even with these controls, challenges have a strong negative coefficient. This finding is consistent with Grabowski and Kyle's (2007) theoretical prediction that, conditional on various drug characteristics, drugs with patent challenges are associated with shorter market life.[18]

However, patent challenges are not randomly distributed. Challenges focus on drugs that would enjoy particularly long market life absent a challenge—that is, on drugs with long patent terms. This is seen in our next set of regressions, where we examine the characteristics of drugs attracting challenges.[19] Table 3 reports the results from a linear probability model where the dependent variable is whether entry involved a patent challenge. The estimates in Column 1 show that this likelihood is increasing with sales, with drugs in the top quintile of sales having a 59 percentage point

[15] In light of recent proposals to incentivize drug development for tropical diseases using "priority review vouchers," it is also interesting that priority drugs—those that receive quicker reviews—have no additional effective market life.

[16] Recall that without a patent challenge, the generic firm cannot receive FDA approval until patent expiration. In that case, effective market life will be at least equal to the nominal patent term.

[17] We also estimated models using the natural log of sales (instead of indicators of sales quintiles) as an explanatory variable. The point estimates on the challenges variable and nominal patent term are similar in these models (and statistically significant). The only notable difference is in Model 1: the natural log of sales has a positive but statistically insignificant association with nominal patent term. In another robustness check, we also controlled for whether the drug received pediatric exclusivity, which also had no effect on the main results.

[18] Of course, patent challenges are not randomly distributed, as we will emphasize below; we present these estimates mainly for comparison to Grabowski and Kyle (2007). Note, however, that under hypothetical random assignment of challenges, which would recover their true causal effect, challenges must have a non-positive effect: either generics are not winning the challenges (in which case the effect would be zero) or are winning some (in which case the effect would be negative, relative to identical control drugs which were not challenged). So concern about omitted variable bias would be not about the sign, but the magnitude of the coefficient. Our analyses here do control for the other variables that we will later show matter for challenges: sales, patent portfolio characteristics, and nominal patent term. The main remaining threat to identification is unobserved ease of entry, which we expect would be positively correlated with likelihood of challenge and negatively correlated with effective life, even absent challenges. Omission of unobserved ease of entry measures would lead the estimated coefficient on patent challenges to be biased away from zero, i.e., the challenges variable would be absorbing some of the negative effect on effective life really due to ease of entry for drugs that draw challenges. Under this scenario, candidate instrumental variables would be correlated with challenges but not ease of entry. We experimented with the timing of various legal changes affecting the likelihood of challenge, including a successful generic challenge (on the blockbuster Prozac) that might have pointed the way for other generic firms, and a Supreme Court case (*KSR v. Teleflex*) that made invalidity claims easier to establish. However, there was no strong first stage over our relatively short panel. (Note also that the rise in challenges over our sample period is not sharp, as Figure 3 showed.) Future research might exploit longer time series of data on first time entry to assess the causal impact of challenges on effective market life. Recent court decisions that may differentially affect incentives to challenge patents for NMEs relative to non-NMEs (e.g. *KSR*) might be exploited in future work in a difference-in-difference approach to assess the effects of challenges on effective market life.

[19] These regressions complement Hemphill and Sampat (2011) which examines, for a set of approved branded drugs, what explains the hazard of challenge. Here, we start with instances of successful generic entry, and examine the characteristics of drugs that are associated with the likelihood that the entry involved a patent challenge.

Table 3
Drug challenged versus sales, drug characteristics, and patent portfolio.

	(1) Challenged?	(2) Challenged?	(3) Challenged?	(4) Challenged?	(5) Challenged?
Second quintile sales	0.230 (0.161)	0.108 (0.142)	0.162 (0.148)	0.212 (0.147)	0.199 (0.143)
Third quintile sales	0.307 (0.160)	0.292* (0.128)	0.259 (0.135)	0.339* (0.140)	0.301* (0.129)
Fourth quintile sales	0.561** (0.153)	0.382* (0.147)	0.395* (0.157)	0.615** (0.140)	0.470** (0.154)
Top quintile sales	0.589** (0.141)	0.359* (0.146)	0.378* (0.151)	0.488** (0.138)	0.396** (0.147)
Priority review	−0.0229 (0.102)	−0.0642 (0.0886)	−0.0522 (0.0935)	−0.0518 (0.0988)	−0.0435 (0.0957)
Oral dosage form	0.0778 (0.125)	0.145 (0.103)	0.0883 (0.103)	0.0301 (0.121)	0.0812 (0.110)
Years of patent term		0.0405** (0.00590)			
Second quintile nominal term			0.305* (0.118)		0.319** (0.116)
Third quintile nominal term			0.228 (0.158)		0.214 (0.154)
Fourth quintile nominal term			0.468** (0.117)		0.398** (0.116)
Top quintile nominal term			0.600** (0.105)		0.478** (0.127)
Count of AI patents				−0.0172 (0.0823)	−0.0531 (0.0819)
Count of non-AI patents				0.0793** (0.0223)	0.0346 (0.0249)
Constant	0.355* (0.145)	−0.188 (0.139)	0.0729 (0.142)	0.238 (0.139)	0.0556 (0.156)
F statistic	4.375	10.47	8.120	5.210	7.396
p value	0.000	0.000	0.000	0.000	0.000
Observations	119	119	119	119	119

Notes: Sample comprises new molecular entities for which first generic entry occurred between 2001 and 2010. Each observation represents a drug. Dependent variable is whether drug was the target of a patent challenge. Estimates are from linear probability models. All models include indicators for therapeutic class and generic approval year. Heteroskedasticity-consistent standard errors in parentheses.

* $p < 0.05$.

** $p < 0.01$.

higher likelihood of challenge than those in the bottom quintile. Columns 2 and 3 show that conditional on sales, the likelihood of challenge is also strongly related to nominal patent term, suggesting that generic challenges are more common when patents generate extra nominal patent term. Moreover, Column 4 shows that drugs with more non-AI patents are also more likely to draw challenges.[20] However, in Column 5, when we introduce the patent count and nominal term variables together, the magnitudes of each decrease, reflecting collinearity between the two. (Non-AI patents tend to be issued later, and drugs with more non-AI patents tend to have longer patent terms.) Nonetheless, the models suggest that challenges are most common for drugs with nominal patent term in the fourth and fifth quintiles. Overall, the results point to non-AI patenting and long nominal patent terms as being important predictors of challenges, suggestive evidence that challenges are responses to "evergreening."

5.2. Patent-level analyses: exploiting within-drug variation in which patent challenged

One difficulty in interpreting the results reported above as causal evidence that non-AI patents and those with long term are driving challenges is that it is possible that firms accumulate these "low quality" patents in anticipation of challenges to the basic patents, i.e., the causality goes in the opposite direction. Another possibility is that both non-AI patent accumulation and drug challenges are more common for drugs with high unobserved market potential that is not captured by the sales measure. Since patent accumulation generally precedes generic entry—on average, AI patents are filed 22 years prior to first generic entry, and non-AI patents 14 years prior—any such unobserved factor would have to be fixed over the life of the drug under this scenario.

To account for these sources of potential bias, we also examine within-drug variation in which patents are challenged. Evidence that the low quality patents are disproportionately the ones challenged within drugs would weigh against the argument that the basic patents are the real targets. In these models, drug fixed effects also absorb any unobserved time-invariant expectations about market potential that may be correlated with both challenges and patent portfolio accumulation.

Table 4
Patent type versus patent challenge.

	Patent challenged?		
	No	Yes	Total
Non-AI	54	159	213
AI	75	31	106
Total	129	190	319
Pearson chi2(1) = 60.5751		Pr = 0.000	

We begin with a simple comparison of which patents are challenged. Table 4 shows a cross-tabulation of whether a patent is an AI patent and whether it was challenged. Of the 319 patents, nearly three-fifths (190) were challenged. More than 80 percent of the patents that were challenged did not cover the active ingredient. And while 75 percent of the non-AI patents were challenged, only 29 percent of the AI patents were challenged. This suggests that challenges focus on the lower quality non-AI patents.

Table 5 shows results from the fixed effects models relating the likelihood a patent was challenged to patent characteristics and drug fixed effects. These models exploit within-drug variation in patent characteristics and challenges to identify the relationships between the two. The first specification (Column 1) confirms the crosstab result: within drugs, there is a 42 percentage point lower likelihood of challenge for AI patents. Column 2 shows that patents that generate more nominal life are more likely to be challenged. Column 3 shows that this effect is increasing monotonically with the amount of nominal patent term generated by a patent. The next three columns are estimated only over drugs where at least one patent was challenged. The sample for these models comprises the 251 patents (challenged and unchallenged) for the 78 drugs where at least one patent was challenged. (As Table 4 indicates, 190 of the patents were challenged.) The results are similar to those in Columns 1–3. Taken together the models in Table 5 provide strong

[20] This evidence is consistent with the finding in Hemphill and Sampat (2011) that both sales and the extent of evergreening matters for challenges. That previous analysis also shows that drugs with low quality patents—those with low citations, low family size, those that arrive later in time, and those that do not cover the drug's active ingredient—are most likely to have challenges.

Table 5
Patent challenge versus patent characteristics, with drug fixed effects.

	Patent challenged?					
	(1)	(2)	(3)	(4)	(5)	(6)
AI patent	−0.424** (0.0967)			−0.498** (0.103)		
Years of patent term		0.0601** (0.00697)			0.0643** (0.00716)	
Second quintile nominal term			0.427** (0.121)			0.536** (0.128)
Third quintile nominal term			0.619** (0.121)			0.718** (0.112)
Fourth quintile nominal term			0.910** (0.113)			1.023** (0.0876)
Top quintile nominal term			1.020** (0.105)			1.115** (0.0912)
Constant	0.737** (0.0321)	−0.294** (0.103)	0.00236 (0.0707)	0.890** (0.0274)	−0.254* (0.113)	0.0230 (0.0607)
F statistic	19.28	74.34	24.14	23.48	80.60	43.98
p value	0.000	0.000	0.000	0.000	0.000	0.000
Observations	319	319	319	251	251	251

Notes: The sample for Models 1–3 comprises all 319 patents on the 119 new molecular entities for which first generic entry occurred between 2001 and 2010. The sample for Models 4–6 excludes drugs where no patents were challenged. The unit of observation is a patent, and the dependent variable is whether that patent was challenged. Estimates are from ordinary least squares regressions. All models include drug fixed effects. Heteroskedasticity-consistent standard errors, clustered on drugs, in parentheses.

* $p < 0.05$.

** $p < 0.01$

evidence that patent challenges target low quality patents and those that extend market life, as opposed to basic patents. Moreover, since these models include fixed effects for each drug, they control for the various unobserved drug characteristics that we suggested might have been sources of bias in the drug-level regressions reported in Table 4.[21]

However, it is possible that generics are more aggressive for higher sales drugs (Grabowski and Kyle, 2007). One reason why they might be is that for the most lucrative drugs, early entry is particularly beneficial, so generics take a chance on challenging basic patents even if these are unlikely to succeed. Moreover, a generic challenger may be forced to challenge all patents for a particularly lucrative drug, if it believes that other generic firms will also file patent challenges for the drug (see, e.g., Berndt et al., 2007a,b) and might challenge the basic patents. If another firm won the basic patent challenge, the less aggressive generic firm would have to wait until expiration of the 180-day exclusivity period.[22] In other words, challenges to AI patents could reflect a racing dynamic.

To examine whether there is more generic aggressiveness for higher sales drugs, we also estimated patent-level models (with drug fixed effects) in which the AI patent indicator (whether the patent is an AI patent) is interacted with sales (a drug level variable). Comparison of coefficients across quintiles thus indicates whether generics are less discriminating across patent types (or "prospecting") for higher selling drugs. If generics were more likely target AI patents for blockbusters, for example, we would expect the interaction term for the top quintile to be smaller in absolute value than for lower quintiles.

Table 6 provides some evidence in support of this hypothesis. Column 1 shows that across all drugs (those with and without challenges), the differential likelihood of challenge between AI and other patents is smallest in magnitude (and statistically insignificant) at the top of the sales distribution. However, the coefficients vary haphazardly over the sales distribution. And the point estimate for the top quintile is not significantly different from that of the bottom quintile ($p = .68$). Column 2 focuses only on the drugs with challenges, and their 251 patents. Here there is more consistent evidence of increasing generic aggressiveness for higher sales drugs, though the difference between the top and bottom quintiles remains statistically insignificant ($p = .39$).[23]

These results thus provide some evidence—though it is limited—for the argument that generics are more aggressive (less discriminating across patents) for the highest selling drugs. The same can be said for analogous drug-level regressions where the dependent variable is whether a basic (AI) patent was challenged, in Table 7, estimated over the 93 drugs that have an AI patent. While the point estimates indicate that the likelihood that a basic patent is challenged is highest for "blockbuster" drugs, the difference between the top and bottom sales quintiles is not statistically significant ($p = .12$).[24]

[21] Note that in models 5 and 6 some of the predictions (i.e. for the drugs with the highest nominal term) are outside of the zero-one range, one drawback of linear probability models. Nonetheless, these models provide reasonable approximations of marginal effects, our focus here (Wooldridge, 2002).

[22] Another reason to challenge a basic patent, despite the low probability of success, is that a failure to challenge the patent would leave an opening for another generic firm to receive shared eligibility for the exclusivity period by later challenging an unchallenged patent.

[23] Note that the coefficients for the top two quintiles are identical across the models. This is because the set of drugs over which they are identified is effectively the same. Most drugs in the top two quintiles have at least one patent challenged (as Figure 2 indicates) and the few that do not have only one patent. Drugs with only one patent do not contribute to identification in the models with drug fixed effects, since there is no within-drug variation to exploit.

[24] Logit models yield similar results.

Table 6
Patent challenge versus patent-sales interactions, with drug fixed effects.

	(1) Patent challenged?	(2) Patent challenged?
AI × first quintile	−0.403 (0.230)	−0.569* (0.262)
AI × second quintile	−0.570** (0.177)	−0.846** (0.0832)
AI × third quintile	−0.390 (0.202)	−0.451* (0.217)
AI × fourth quintile	−0.531** (0.181)	−0.531** (0.174)
AI × top quintile	−0.265 (0.253)	−0.265 (0.242)
Constant	0.740** (0.0316)	0.892** (0.0256)
F statistic	5.370	24.56
p value	0.000	0.000
Observations	319	251

Notes: The sample for Model 1 comprises all 319 patents on the 119 new molecular entities for which first generic entry occurred between 2001 and 2010. The sample for Model 2 excludes drugs where no patents were challenged. The unit of observation is a patent, and the dependent variable is whether that patent was challenged. Interaction terms multiply whether a patent is an AI (active ingredient) patent with the sales quintile for the drug. The coefficients on the interaction terms thus indicate the differential propensity for AI patents to draw challenges (relative to non-AI patents) for drugs with different sales levels. Estimates are from ordinary least squares regressions. All models include drug fixed effects. Heteroskedasticity-consistent standard errors, clustered on drugs, in parentheses.

* $p < 0.05$.

** $p < 0.01$.

Table 7
Basic patent challenge versus sales and drug characteristics.

	Was AI patent challenged?
Second quintile sales	−0.169 (0.136)
Third quintile sales	0.0562 (0.117)
Fourth quintile sales	0.0319 (0.159)
Top quintile sales	0.249 (0.157)
Priority review	−0.0827 (0.0981)
Oral dosage form	0.273* (0.105)
Constant	0.403* (0.178)
F statistic	3.434
p value	0.001
Observations	93

Notes: Sample comprises new molecular entities for which first generic entry occurred between 2001 and 2010 that have at least one active ingredient (AI) patent. Each observation represents a drug. Dependent variable is whether the AI patent was challenged. Estimates are from linear probability models. All models include indicators for therapeutic class and generic approval year. Heteroskedasticity-consistent standard errors in parentheses.

* $p < 0.05$.

Overall, we view the result in Tables 6 and 7 as providing only weak evidence of prospecting. Moreover, even if challenges to the basic patents were more common for high sales drugs, that may have little impact on market life. After all, it is difficult to invalidate a compound patent. A non-infringement strategy seems even more doubtful, as a generic must use the same active ingredient as the brand-name firm in order to establish bioequivalence.

However, this is ultimately an empirical question.[25] While we do not have information on the outcomes of the litigation following challenges,[26] we do know timing of generic approval. Table 8 reports regression results from models relating effective market life to whether the basic patent was challenged. For drugs with challenges (Column 1), there is a negative effect of basic patent challenges on effective market life, but it is statistically

Table 8
Effective market life versus whether AI patent challenged, sales, and drug characteristics.

	(1) Effective	(2) Effective
AI patent challenged?	−0.594 (0.720)	−1.447 (1.068)
Second quintile sales	−3.618* (1.599)	
Third quintile sales	−3.009 (1.563)	
Fourth quintile sales	−0.414 (1.451)	
Top quintile sales	−1.839 (1.509)	
Priority review	1.119 (1.144)	−0.258 (1.341)
Oral dosage form	−4.084** (1.211)	−4.509 (2.574)
Constant	18.11** (3.024)	20.14** (4.802)
R squared	0.628	0.740
F statistic	4.842	1.878
p value	0.000	0.135
Observations	59	33

Notes: The sample for Model 1 comprises all new molecular entities for which first generic entry occurred between 2001 and 2010 that have at least one active ingredient (AI) patent, and at least one patent that was challenged. The sample for Model 2 is the subset of these drugs with sales in the top two quintiles. Each observation represents a drug. The dependent variable in both models is effective market life, the time in years between brand approval and first generic entry. Estimates are from ordinary least squares regressions. All models include indicators for therapeutic class and generic approval year. Heteroskedasticity-consistent standard errors in parentheses.

* $p < 0.05$.

** $p < 0.01$.

insignificant. Overall, challenges to AI patents are not leading to significantly earlier approval. Column 2 shows this is true even at the top of the sales distribution, where basic patent challenges are more common. Taken together, there is very little evidence that challenges to basic patents are significantly reducing market life for even the most important drugs.[27]

6. Conclusion

The average nominal patent term is 16 years for drugs with first generic entry between 2001 and 2010. By comparison, average effective market life for these drugs is 12 years, not much different than in the previous decade, and greater than in the decade before Hatch–Waxman (Grabowski and Vernon, 1996). Patent challenges are the key driver of the gap between nominal patent term and effective market life. Our research confirms predictions that challenges are more prominent for large sales drugs. We also find a rise in early challenges, suggesting growing sophistication by generic firms in a race to secure first-to-file status, and thus eligibility for exclusivity. These findings may provide some justification for those concerned about increasingly aggressive generic challengers.

However, the conventional prospecting account is too simple. After all, as our descriptive data show, the average market life for new molecular entities is essentially stable over time. And the largest sales drugs do not have very different effective market life compared to drugs in other categories, even though they are more likely to be challenged, and challenged early.

The full story is more complicated. Generic challenges disproportionately target drugs with weak, late-expiring patents. While

[25] While an FTC study (FTC, 2002), reviewing litigation over both NMEs and product line extensions, found a generic win rate of 73 percent for cases concluding by June 2002, this study does not distinguish between wins against basic compound patents and others.

[26] In ongoing research we are directly examining differences in litigation outcomes between compound and other patents, as part of a more general analysis of the outcomes of Paragraph IV litigation.

[27] What if we instead defined AI patents more broadly, to include patents on alternative isomers, crystalline structures, salts, and metabolites as well? Under this broader definition, there are more AI patents (139 instead of 106), AI patents have a higher likelihood of being challenged (42 percent are instead of 29 percent), and the differentially lower likelihood that AI patents are challenged (relative to others) is less pronounced (but still statistically significant). Moreover, there is stronger evidence of generic aggressiveness at the very top of the sales distribution, in models analogous to those in Tables 6 and 7. However, even with this broader definition, models similar to those in Table 8 show no statistically significant impact of AI patent challenges on effective market life.

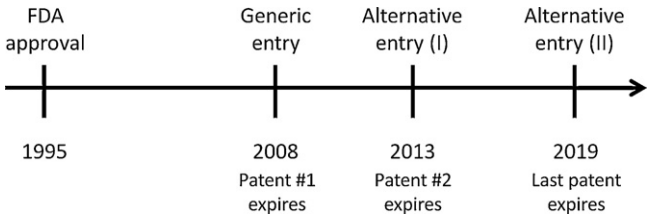

Fig. 5. Market life timeline for Fosamax (alendronate).

it is possible that these drug-level models reflect unobserved heterogeneity, the fixed effects models also show that within drugs, challenges reflect the extent of evergreening. There is only limited evidence for the prospecting story, which would predict that challenges to "basic" patents are more common for higher sales drugs. Moreover, challenges to AI patents are not associated with significant reductions in market term.

Taken together, our results show that challenges are playing a restorative role, ratcheting back the effective market life of drugs with large nominal patent terms to about 12 years. They are particularly likely for large sales drugs, as critics of these challenges warn. However, this appears to reflect that evergreening is also particularly likely for these drugs.

In drugs, and in other industries, resource-constrained patent examiners at the U.S. Patent and Trademark Office may lack the incentive or capacity to thoroughly assess each of the hundreds of thousands of patent applications they process annually (Jaffe and Lerner, 2004). And the FDA does not independently assess the merits of patents (confining their role to an evaluation of safety and efficacy), instead deferring to PTO decisions. In this context, generic patent challenges may reflect society's strongest defense against non-meritorious patents that would harm payers and patients.

To be sure, challenges reduce market life. But compared to what? Our analyses underscore the importance of choosing the right baseline in answering this question. Consider the case of Fosamax (alendronate), a blockbuster osteoporosis drug made by Merck. Higgins and Graham (2009) offer this drug as their leading example of a troubling drug patent challenge. As the authors note, after Merck lost its patent challenge, the generic drug entered the market in February 2008—"~4 years before the Fosamax patents were due to expire"—which produced a sharp drop in Fosamax sales.

Fig. 5 shows how the choice of baseline affects our understanding of the Fosamax example. Higgins and Graham appear to focus on patents due to expire in 2013. A successful generic challenge permitted entry in 2008 (when another patent expired). That account is incomplete, however, in two respects. First, the drug was approved in 1995, meaning that Fosamax enjoyed 12.5 years of exclusivity before generic entry. More important, 2013 was not the end of Merck's patent protection. Merck had also acquired 9 other patents on the drug, the last of which is due to expire in 2019. Had the generic firm not challenged these later expiring patents, the total market life for the drug would have been almost a quarter century.

Even if generics are now more aggressive than they once were, it does not follow that strong, basic patents are routinely being invalidated or invented around, thereby leading to early generic entry. On average, current exclusivity is already about 12 years, even for the most lucrative quintile of drugs. If firms make R&D choices based on expectations of market life, it is unlikely that a rise in challenges has blunted R&D incentives or otherwise contributed to the current pipeline problem in pharmaceuticals.

Of course, there is variation across drugs, and a longer data exclusivity term would provide certainty, itself a useful policy goal.[28] But if the argument is that 12 years is the "right" amount of protection, perhaps it should serve as an upper as well as lower bound. A plausible *quid pro quo* would be to trade longer data exclusivity for restrictions on evergreening. One means to accomplish the latter would be to subject all Orange Book-listed patents to immediate re-examination by the PTO, where they would get a strong second look.[29]

Branstetter et al. (2011) find the short run welfare gains from patent challenges to be large, $93 billion between 1997 and 2008 for the hypertension market alone. Like their analysis, this paper focuses on static rather than dynamic effects of patent challenges, so we can only speculate on the latter.[30] If "low quality" patents are on innovations that do not require costly R&D (e.g., obvious changes to the drug) their elimination may not meaningfully affect R&D incentives. Under this scenario, Paragraph IV challenges would appear to be a net social benefit, even considering dynamic effects. On the other hand, it is possible that the increment to market life from "bad" patents is needed to stimulate "good" innovation. We can imagine two possible stories along these lines. A first is that non-AI patents do in fact represent costly and socially valuable innovation, but patent standards are misaligned with the social value of inventions (Roin, 2009), making these patents legally vulnerable. A second is that these non-AI patents themselves are not innovative, but the additional market life they generate for the underlying basic inventions supports important R&D: that is, the optimal patent term for NCEs is greater than 12 years on average, and "weak" patents help sustain this. We do not attempt to answer these questions there, but raise them as important ones for future work on patent challenges.

Appendix A. Alternative measure of effective market life

The measure of effective market life employed in our analysis is the time elapsed between brand approval and final FDA approval for the first generic product. An alternative measure, employed in a previous analysis of effective market life (Grabowski and Kyle,

[28] About 30 percent of the drugs in our sample have less than 10 years of effective patent life, and 40 percent have less than 12. These shares are fairly stable across the top four sales categories. The makers of these drugs would benefit from the proposed longer data exclusivity periods. Data exclusivity would also be important for NMEs without patents (not in our sample), of course, though the limited term for these drugs cannot reflect patent challenges, but other factors.

[29] The Patent Reform Act of 2011 includes a post-grant opposition mechanism, through which third parties can challenge patents within nine months of their issue. This too could help restrict evergreening. However, it is uncertain whether third parties will have strong incentives to file these oppositions. Opposition creates collective action problems, since successful invalidation of patents would benefit many parties, not just the opposer. (Indeed, this is one of the rationales for the "bounty"—in the form of 180-days exclusivity—that Hatch-Waxman provided to successful challengers.) Moreover, the short window may make it difficult to identify the most important patents (e.g., those on valuable drugs) effectively. Finally, while improving patent quality through re-examination, post-grant opposition, or similar patent reforms could reduce Paragraph IV challenges based on invalidity, it would not affect noninfringement challenges.

[30] The comparative efficacy of different institutions for screening drug patents is another issue that is important in evaluating the welfare effects of patent challenges. The Hatch-Waxman regime harnesses market incentives to monitor patent quality, and leads to questionable patents on important drugs (those likley to generate the largest static deadweight losses) getting a strong second look. This may have advantages over stronger *ex ante* review by the Patent Office as a means to police patent quality, since it is hard at the time of patent application for patent examiners to know which patent applications are likely to be important, and thus for which ones more thorough scrutiny would be worth the cost. However, stronger *ex ante* review might have other advantages over *ex post* review through patent challenges, such as avoiding uncertainty, litigation costs, and potential gaming of the Hatch-Waxman system (see FTC, 2002): these are topics of ongoing research. See Lemley (2001) for a discussion of the costs and benefits of *ex ante* versus *ex post* approaches to improving patent quality.

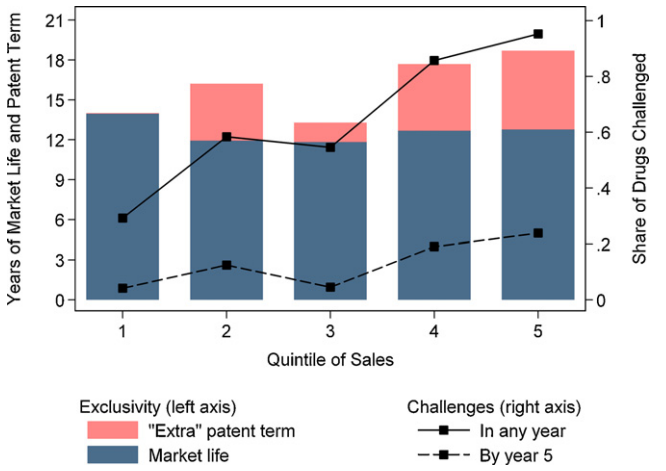

Fig. A1. Effective market life (alternative measure), nominal patent term, and challenges by sales. *Notes*: This chart shows average effective market life, nominal patent term, and challenges for the 112 new molecular entities (with patents) for which first generic entry occurred between 2001 and 2010 and where there was generic launch by 2010. Nominal patent term is the time in years between brand approval and expiration of last patent. Effective market life is the time between brand approval and first generic launch (rather than the time between brand approval and first generic approval, as in our main analyses). The full height of each bar represents average nominal patent term for a sales category, and the navy portion average effective market life for the category, both measured (in years) on the left axis. The solid line shows the share of drugs with Paragraph IV patent challenges, and the dashed line the share with challenges within five years of approval, both measured on the right axis.

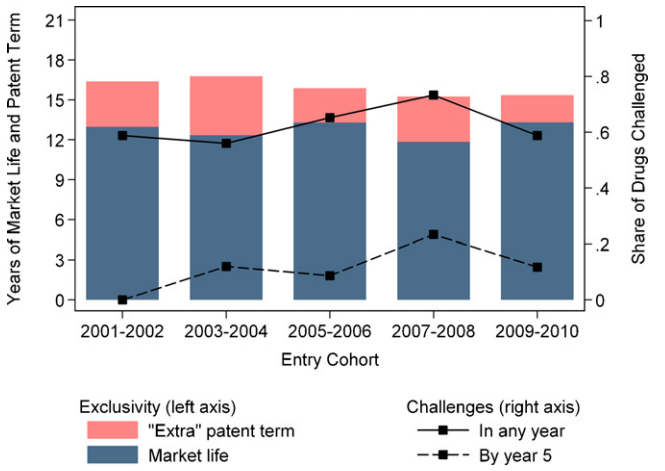

Fig. A2. Effective market life (alternative measure), nominal patent term, and challenges over time. *Notes*: This chart shows average effective market life, nominal patent term, and challenges for the 112 new molecular entities (with patents) for which first generic entry occurred between 2001 and 2010 and where there was generic launch by 2010. Nominal patent term is the time in years between brand approval and expiration of last patent. Effective market life is the time between brand approval and first generic launch (rather than the time between brand approval and first generic approval, as in our main analyses). The full height of each bar represents average nominal patent term for a cohort, and the navy portion average effective market life for the category, both measured (in years) on the left axis. The solid line shows the share of drugs with Paragraph IV patent challenges, and the dashed line the share with challenges within five years of approval, both measured on the right axis.

2007), is the time between brand approval and first generic launch. The two measures are not identical because generic firms do not always launch immediately upon FDA approval. We believe an approval-based measure is superior for the analysis of patent challenges, since this measure is less influenced by factors other than patent challenges (for example, unrelated delays in how quickly a generic firm launches post approval). However, in this appendix we demonstrate that the main trends reported above are consistent with those from analyses using the alternative measure.

For this analysis, we determined the generic launch date for each drug using press releases, CardinalHealth's "new generics" database, and information from IMS Health. A small number of drugs with generic approval but no generic launch ($n=7$) were dropped from the analysis. For the remaining 112 drugs, time to first generic approval is highly correlated with time to first generic launch ($r=.97$).

Figs. A1 and A2 show trends in effective market life over time and by sales category. These show results broadly consistent with those reported above. Market life is stable across the top four quintiles of sales, and, as with the approval measure, higher for the bottom quintile of sales. Market life has also remained quite stable over the past decade.

Appendix B. Construction of patent data

This appendix describes our patent data collection in greater detail.

We collected patent data for each brand-name drug from the FDA's compendium of Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. For early editions, we collected the patent data by hand, augmented by the results of a FOIA request to the FDA. For data from 2000 to the present, we rely on archival electronic versions of the Orange Book. Our final dataset contains only those drugs with Orange Book-listed patents.[31]

The Orange Book contains a comprehensive, though not perfectly exhaustive, account of patent protection relevant to each drug. For patents issued before NDA approval, a brand-name drug maker is required to list any patent containing at least one claim that covers the drug's active ingredient, its formulation, or any method of use pertaining to an approved indication.[32] For patents issued after NDA approval, listing is not required, but there is a strong incentive to do so. If the patent is not listed, the generic firm filing an ANDA need not certify that the patent is invalid or not infringed as a condition for FDA approval. Nor can the unlisted patent provide a basis for an automatic stay of approval, ordinarily enjoyed by brand-name drug makers that file a timely patent suit in response to an ANDA containing a patent challenge. Because late-listed patents are unlikely to affect the decision to challenge or the timing of entry, we restricted attention to patents that were first listed prior to the year of ANDA approval.

Occasionally, patents are listed in the Orange Book briefly, then removed. Such patents were listed by mistake, or were de-listed because they were later deemed irrelevant, and do not matter for the timing of generic entry. If the patent was listed for three or fewer years, and removed three or more years before patent expiration or generic approval, we dropped the patent from our set. Nine patents were dropped on this basis.

In some cases involving method of use patents, the generic firm is able to sidestep the decision to challenge the patent or else wait

[31] The exclusion also applies to a small number of antibiotic drugs that were not subject to the Orange Book listing and Paragraph IV patent challenge procedures until 2008, when a statutory change subjected them to these procedures.

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

until patent expiration. If a patent covers a method of use for which the generic firm does not seek FDA approval, the generic firm can make a "section 8" filing as to that patent. A section 8 filing is different from a patent challenge: it cannot serve as the basis for 180 days of generic exclusivity, nor does it ordinarily lead to litigation with the brand-name firm. Because it does not serve as an impediment to generic entry in the same way as other patents, we dropped 24 patents with section 8 filings from the final dataset.[33]

We also collected data from the Orange Book on patent expiration dates. The expiration dates listed in the Orange Book account for any patent extensions, including patent term restoration and pediatric exclusivity awards. These final expiration dates are the relevant ones for analyses of patent challenges: absent challenges, these are the dates when entry could occur.

Finally, we used information from the USPTO's Cassis database to determine application and issue dates for each of the patents.

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[33] If these patents are included and treated as challenged, the substantive results are unchanged. These results are available on request.