Hurry Up or Wait?
Strategic Delay in the Introduction of Pharmaceutical Line Extensions

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Abstract

Pharmaceutical firm decisions on the timing of follow-on product introductions involve a strategic tradeoff. Follow-on drugs, termed line extensions, receive a fixed exclusivity period that starts upon approval. Thus, firms can choose to introduce a line extension earlier to attract new consumers, or delay introduction so the line extension's exclusivity extends beyond that of the original drug product. I show that the firm's incentive for delayed introduction increases with the share of line extension sales that would cannibalize sales of the original drug. I test for this behavior empirically using a novel dataset of over 700 pharmaceuticals approved in the United States from 1985-2016, linked to all subsequent line extensions in that period. Consistent with strategic delay, an original product is almost twice as likely to have a line extension approved in the period leading up to expected generic entry than three or more years prior. Using Monte Carlo simulations, I find that line extensions that are more cannibalizing are delayed up to 2.5 years, compared to an average of five months for those that are less cannibalizing, reflecting nuanced firm responses to regulatory incentives. Delays in the introduction of new products can create welfare losses for consumers and payers, and I consider implications for optimal innovation policy.

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1 Introduction

The pharmaceutical industry benefits from provisions like patents and regulatory exclusivity periods that are designed to incentivize firms to bring innovative new products to market. However, pharmaceutical firms make strategic decisions in response to the regulatory environment that may lead to outcomes that diverge from the social welfare goals of public policy makers and regulators. This study takes a detailed look at pharmaceutical firm decisions regarding the timing of the introduction of follow-on drug products. I examine the extent to which the entry of follow-on products may be strategically delayed in response to incentives that stem from fixed exclusivity periods that start upon product approval.

Pharmaceutical firms engage in a risky and often unpredictable research and development (R&D) process to bring new drugs—termed new molecular entities (NMEs)—to market.[1] To create incentives for firms to invest in innovation, small-molecule NMEs are protected by patents and, upon approval to enter the market in the United States, by regulatory exclusivity periods. Both patents and exclusivity periods grant pharmaceutical firms time-limited monopolies on NMEs.[2] By law, generic competitors to a branded drug can enter only after both its patent and exclusivity periods expire. Since generics typically take a large share of a drug's sales after they enter, in part due to generic substitution laws and insurance plans steering consumers to generics over brands [Berndt and Aitken, 2011; Frank and Hartman, 2015], pharmaceutical firms have a strong interest in maximizing a NME's revenues by extending its effective exclusivity period and expanding its customer base.

This paper studies a specific pharmaceutical firm decision: the strategic timing of follow-on medications, termed line extensions (LEs). A LE is a branded prescription drug that shares an active ingredient with a previously approved product by the same firm, which I refer to as

[1] Estimates of the average cost of bringing a new drug to market point to at least hundreds of millions per product (Adams and Brantner, 2006), with $2.6 billion on the high end of the range (DiMasi et al., 2016).

[2] NMEs under patent or exclusivity protection may still compete against other molecular entities that treat the same clinical condition. Patents and exclusivity periods give firms monopolies on specific molecules.

an original formulation (OF). By definition, OFs are NMEs, and LEs are not. Thus, though LEs may require evidence from clinical trials to enter the market, they do not require the full R&D investments that would be needed to launch an OF. As a result, they are much less costly to bring to market. LEs vary in how they are differentiated from their OFs and can be classified into various technological categories, like dosage changes or changes to the route of administration. Crucially, in the United States, if a LE undertook a clinical trial, regulation awards it an exclusivity period of fixed length that starts upon the LE's approval for market entry. The LE's exclusivity period usually lasts for three years and is separate from the patent and exclusivity periods that protect the OF.

For example, Exelon (rivastigmine tartrate) is a drug developed by Novartis that is used to treat Alzheimer's Disease. It is an oral capsule that was first approved in the United States in April 2000. A separate Novartis product, Exelon Patch (rivastigmine), was approved in July 2007. Exelon Patch, the LE, is a transdermal skin patch that shares the same active ingredient as Exelon, the OF, and its technological category is an administration route expansion. Another example, also in the therapeutic class for Alzheimer's Disease, is Eisai's Aricept (donepezil hydrochloride). Aricept was first approved in the United States as both 10 mg and 5 mg oral tablets in November 1996. In July 2010, Eisai had a LE approved—a 23 mg oral tablet of the same active ingredient that is marketed as Aricept 23. In both Exelon and Aricept cases, the OFs are new molecular entities and the LEs are not.[3]

LEs can increase firm profits in two ways. First, they can attract new customers who were not previously taking the OF, expanding the market for the molecule. For instance, though there is no evidence that Exelon Patch provides clinical efficacy over Exelon,[4] the route change from oral capsule to transdermal patch allowed patients unable to take the OF (due to swallowing difficulties often associated with advanced dementia) to take the drug in LE form.

[3]Appendix Section A provides a set of illustrative examples of LE products vis-à-vis their respective OFs.

[4]See Ontario's Ministry of Health and Long Term Care's 2009 memo on rivastigmine patch: `http://www.health.gov.on.ca/en/pro/programs/drugs/ced/pdf/exelon_patch.pdf`

Second, once a LE enters the market, some consumers may switch from the OF to the LE as a result of preferences for LE product characteristics, promotional efforts of the firm, formulary placement, or brand loyalty. Given any amount of switching to the LE product, once the OF's generic enters, fewer OF prescriptions will be subject to generic substitution laws because the generic will only be swapped for the OF—not the LE.[5] These two forces create a potential tradeoff for firms. The former encourages LE entry as soon as the drug is scientifically feasible to maximize the number of new customers, whereas the latter encourages delay of the LE introduction so that the LE's exclusivity period extends beyond the OF's to prolong the firm's period of monopoly profits.

In this paper I examine the extent to which LE introductions are *strategically delayed* in ways that reflect the tradeoff between market expansion and exclusivity extension. I also show that firm responses to these incentives appear nuanced, distinguishing between LEs for which incentives to delay are stronger or weaker. By strategic delay, I mean a firm's decision to hold back on introducing a new LE that is scientifically feasible in response to anticipated profit incentives. Generally, the socially optimal introduction date of a new product is as soon as scientifically possible (Oi, 2007). However, because of the incentive to delay a LE, the socially optimal LE introduction date is not always equivalent to the firm's profit maximizing LE introduction date, which could be later.

LE exclusivity periods are of fixed length and start upon LE approval. Since the time from firm submission of drug applications to regulatory approval follows pre-specified timelines and firms may have information on their submissions that helps them predict where in the distribution of approval times they may fall, firms can generally predict the approval time of their products.[6] Thus, firms can roughly control when the exclusivity periods for their LEs

[5]Essentially a de facto extension of the OF's exclusivity period for the patients who migrated to the LE. In the case of Aricept, the OF could be taken in multiples of 5 mg (i.e., 20 and 25 mg doses were possible), so the 23 mg LE was often a clinical substitute. After introducing the LE, Eisai engaged in a marketing strategy to switch patients from the OF to the LE (Schwartz and Woloshin, 2012).

[6]The 1992 Prescription Drug User Fee Act (PDUFA) required the US Food and Drug Administration (FDA)

start and end by strategically timing their drug application submissions to regulators.

I focus on firm decisions on the timing of small molecule LEs without novel molecular patents.[7] These LEs are subject to a regulatory regime in which their approval date determines when their exclusivity periods will expire, changing incentives for firms. However, in addition to exclusivity upon approval, some LEs are also protected by novel molecular patents that are separate from the OF's (despite the LEs not being considered as new molecular entities for approval purposes). These LEs receive a fixed patent period that starts when the patent is filed, typically years before the LE is approved to enter the market. In this respect, firms have an incentive to introduce patented LEs as soon as possible to maximize their time on market under patent protection. I return to these patented LEs as a useful comparison group.

To assess strategic delay for unpatented LEs, I first develop a theoretical model to characterize a pharmaceutical firm's profit-maximizing decision on when to introduce a LE. The model captures the firm's tradeoff between introducing a LE earlier to attract new sales and introducing it later to extend exclusivity. A key factor governing the tradeoff is the degree to which a LE cannibalizes sales from the OF.[8] As the share of sales that a LE cannibalizes from the OF increases, the firm's incentive to delay entry to extend the exclusivity period becomes more important than the incentive to introduce the LE early to capture new sales.

To test for this behavior empirically, I assemble a novel dataset of over 700 OFs approved by the U.S. Food and Drug Administration (FDA) between 1985 and 2016, matched to their LEs approved during that period. The data include 525 LE-OF pairs over 14 broad therapeutic classes. First, I study the differences in the introduction timing of LEs that did and did not

to review submissions within pre-specified timelines. 90% of standard submissions must have complete reviews within a year from application receipt. Some applications follow faster timelines. For more detail, see `https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments`. PhRMA, a trade group for the US pharmaceutical industry, says that "(PDUFA) provides the (FDA) with resources to support the efficient and predictable regulatory review of new medicines." See `https://www.phrma.org/en/Advocacy/Research-Development/PDUFA`.

[7] This paper studies small-molecule drugs, which are made by chemical synthesis. Large-molecule drugs (i.e., biologics) are created through more complex biologic manufacturing processes. For more detail, see Grabowski et al. (2007) and Scott Morton et al. (2018).

[8] "Cannibalization" in this context refers to OF sales that are lost when OF consumers switch to the LE.

have novel molecular patents, since each of these sets was subject to different timing incentives. Adjusting for covariates including the OF's expected market life (i.e., time from OF approval to presumed generic entry) and other drug characteristics, I find that patented LEs enter 1.8 years earlier than their unpatented counterparts, consistent with strategic delay among unpatented LEs.

I then analyze the set of over 300 LE-OF pairs in which the LE did not have its own drug substance patent (i.e., the set of LEs that was subject to delay incentives) and study patterns in LE introduction timing using survival analysis. Controlling for characteristics including level of sales and if the firm was in the top 20 firms by revenue, I find that an OF is almost twice as likely to have a LE approved in the period surrounding expected generic entry relative to a baseline of three or more years prior. These results are consistent with the strategic delay of LE introductions. In addition, I document variation in firm decisions across different types of LEs, with those that are plausibly *a priori* more cannibalizing, like dose changes and extended release formulations, more likely to be delayed compared to types that are not as clearly cannibalizing.

I interpret results from the survival analysis by using those estimates to run Monte Carlo simulations and quantify the average length of strategic delay. I find that LEs are approved on average 1 year after they would have been if LE entry were unrelated to presumed OF generic entry. As the theory predicts, there is heterogeneity in the length of delay by LE type. I find significant variation with dose changes and extended release line extensions having the longest delays of up to 2.5 years. This result suggests that firms view extended release LEs as more cannibalizing, which is consistent with theoretical predictions but not causally identified without an exogenous measure of cannibalization versus market expansion. The difference in delay times across groups of LEs is statistically significant and consistent with strategic behavior in which firms maximize profits in response to incentives created by regulation.

Strategic delay in the introduction of LEs can lead to welfare losses for patients and payer organizations in several ways. First, if a LE has additional clinical value beyond the OF for at

least some customers, then those patients must wait for the higher quality product to come to market, with losses accrued during the wait. Though this paper does not assess the incremental value of each LE relative to its OF, one result is that route expansion LEs, like Exelon Patch, are delayed on average by five months. In this case, some Alzheimer's patients with difficulty swallowing would have had to wait to start therapy with Exelon Patch, or switch to Exelon Patch from a competing product later than they otherwise would have.

Second, if the LE has no incremental value beyond the OF but cannibalizes the OF's patients, the patients that switched to the LE will pay higher prices from purchasing branded rather than generic versions of the drug through the period of LE exclusivity. For example, Aricept 23 had little evidence of clinical value beyond OF Aricept, yet Aricept 23 sold for $7.74 per pill in July 2012, versus $0.79 for OF Aricept, which had a generic at that time [Knopman, 2012].[9] Back-of-the-envelope calculations suggest that the introduction of a cannibalizing LEs is equivalent on average to a 17% extension of an OF's effective market life, which may lead to higher spending for patients and/or payers during that time.

Since strategic LE delay can lead to patient and payer welfare loss, understanding patterns in firm decisions on the timing of follow-on product introductions is paramount for the design and evaluation of regulatory and innovation policy. The projected losses due to each of these mechanisms is similar in magnitude: rough calculations place this loss at roughly $4,000 per product-patient. However, the incidence of this loss is different. Losses accrue primarily to the consumer when valuable products are delayed, but fall largely on the payer in situations where generic use is delayed. Strategic delay may also decrease branded drug competition within a therapeutic class by postponing the entry of an additional competitor—another factor that can lead to higher prices in affected product categories. After presenting results, I discuss policy implications. I argue that strategic delay can be mitigated by de-coupling exclusivity periods

[9]Some clinical experts have stated that "a difference of 23mg from 25mg or 20mg dosing almost certainly has no significance." See `https://www.bmj.com/content/344/bmj.e1086/rapid-responses`.

from approval, which need not decrease incentives for innovation.

This paper contributes to various literatures. First, it joins a large literature in economics, business and law that documents "life-cycle management" strategies in pharmaceutical markets.[10] This paper also relates to the literature on the impact of public policy and other factors on pharmaceutical innovation.[11] Related empirical studies have studied small sets of LEs and have examined marketing [Huskamp et al. (2008)], utilization [Huskamp et al. (2009), Huckfeldt and Knittel (2012)], spending [Egilman et al. (2019)], and the welfare effects of LE entry timing on consumers [Shapiro (2016)]; these are discussed in more detail below. This paper is the first to conceptualize and test firms' decisions on the timing of follow-on pharmaceutical product introductions using a large sample of LEs.

This paper is organized as follows: Section 2 provides background on LEs and the regulatory context. Section 3 describes the strategic considerations the firm faces on LEs and develops a theoretical model of the firm's decision on LE introduction timing. Section 4 discusses the data. Section 5 presents the empirical strategy. Section 6 details results. Section 7 discusses policy and welfare implications, and concludes.

[10] See, for example, Hemphill and Sampat (2012) on patent "evergreening," Ellison and Ellison (2011) for strategic investments, Kesselheim et al. (2011) for pay-for-delay settlements, Drake and McGuire (2019) for accelerator clauses, Carrier and Shadowen (2016) for LEs, Reiffen and Ward (2007) for authorized generics, and Carrier and Minniti (2016) and Feldman et al. (2017) for FDA Citizen Petitions. Ellery and Hansen (2012) and Feldman and Frondorf (2017) discuss strategies from the firm and regulator perspectives, respectively.

[11] See, for example, Acemoglu and Linn (2004), Blume-Kohout and Sood (2013), Dranove et al. (2014), and Dubois et al. (2015) for the effect of market size; Cockburn and Henderson (2001) for the effect of firm size; Lichtenberg and Waldfogel (2009) for the effect of the Orphan Drug Act; Budish et al. (2015) and Gaessler and Wagner (2019) for the effect of effective duration of market exclusivity; and Ridley et al. (2006) and Berndt et al. (2005) for the effect of regulatory review duration. Lakdawalla (2018) provides a detailed review of the literature on pharmaceutical innovation.

2 Background and Regulatory Context

2.1 Patents and Exclusivity Periods

New pharmaceuticals require high upfront development costs but once a small-molecule drug is developed, replicating the drug is generally technically uncomplicated, and marginal costs of production are low [Scott Morton and Kyle, 2011]. Accordingly, special incentives are necessary to encourage innovation. In pharmaceutical markets there are two primary mechanisms that ensure time for sales protected from competition: patents and exclusivity periods. Both forms of exclusivity grant pharmaceutical firms time-limited monopolies on new molecular entities and can run concurrently. Generics can enter the market and compete directly with branded drugs once patent and exclusivity periods both expire, in what is commonly known as the end of a branded drug's "life-cycle."

In the United States, patents have a length of 20 years and are awarded by the United States Patent and Trademark Office. The first patent on a branded drug often covers its active chemical compound and small variations, and is known as a primary or drug substance patent. Primary patents are usually filed when a chemical compound appears to be viable, prior to the pre-clinical and clinical trial stages of R&D [Ellery and Hansen, 2012]. Because the 20-year patent clock starts years prior to when a drug is marketed, the effective monopoly period these patents provide is less than 20 years.[12] The validity of patents can be challenged in court by potential generic entrants, creating uncertainty for firms on when their patent protection will effectively expire (i.e., when generics will actually enter). Pharmaceuticals can have additional patents that cover other attributes of the drug and methods of use, but primary drug substance patents are generally harder for generic manufacturers to successfully challenge in court [Hemphill and Sampat, 2012]. The United States Hatch-Waxman Act, signed into law

[12] Van Norman (2016) documents an average of 7-12 years from pre-clinical testing to FDA approval, leaving 8-13 years of effective patent time.

in 1984, allows firms to recoup up to five years of patent time lost during FDA review, though total time post-approval cannot exceed 14 years. One patent can be extended for each drug.

The Hatch-Waxman Act also established exclusivity periods as another mechanism for firms to have a temporary monopoly on their products. During an exclusivity period, the FDA will not review and/or approve generics for the branded drug, effectively excluding generic competitors. Three types of exclusivity exist: new molecular entities approved for the first time receive five years, drugs that treat orphan conditions receive seven, and drugs that are not new molecular entities but required new clinical trials receive three.

Exclusivity and patent periods can run concurrently, but though the validity of a drug's patents can be challenged in court, exclusivity periods cannot. Unlike primary patents, which are effective before a drug reaches the market, exclusivity periods are usually fixed periods that start when a branded drug is approved for marketing by the FDA.[13]

Though OFs often have a drug substance patent as well as five years of exclusivity, LEs do not always have drug substance patents. However, LEs receive an exclusivity period of three years upon approval.[14] The coupling of approval with a fixed-length exclusivity period can create incentives for firms to delay applications to the FDA for approval.

2.2 Generic Drugs in the United States

The Hatch Waxman Act also aimed to spur generic competition and entry by streamlining the generic approval process. Instead of requiring generic manufacturers to duplicate clinical trials, the Act created Abbreviated New Drug Applications (ANDAs) for generics, which allow generic firms to gain approval by demonstrating that their products are bio- and pharmaceutically equivalent to a branded reference drug. ANDAs reduced the cost of generic entry in the United

[13]The exception is pediatric exclusivity, which corresponds to six months of exclusivity added to a drug's existing exclusivity and patent period if a pharmaceutical firm performs pediatric trials.

[14]Both LEs and OFs can obtain seven years of exclusivity on approval if they have an indication to treat an orphan disease. Products can be approved for multiple indications, but the exclusivity applies only to the indication, which means that generics can be approved under other unprotected indications.

States. Thanks to this and other provisions,[15] the Hatch-Waxman Act greatly increased generic competition [Grabowski and Vernon, 1992].

Generic substitution laws exist in all states and mandate that pharmacists dispense generic instead of branded drugs if these are "AB"-rated substitutes, which means the generic and brand are both bio- and pharmaceutical equivalents. There are exceptions if a prescriber explicitly notes "brand medically necessary" or "dispense as written." Still, because of generic substitution laws and other factors, such as drug insurance plans encouraging the use of generics over brands, once a generic drug its branded counterpart quickly loses market share. In the pharmaceutical industry, loss of patent and exclusivity protection on a branded drug is referred to as the "patent cliff," which reflects the precipitous loss of revenue a branded drug faces after generics enter. Since the mid-1990s, market share erosion to generic competitors within the first year of generic entry is estimated at 65 to 90% [Frank and Hartman, 2015].[16] As time passes, generic penetration can reach above 95% in certain therapeutic classes like lipid regulators and calcium channel blockers [Berndt and Aitken, 2011].

2.3 Line Extension Drug Products

Though a large literature has documented other post-market strategies to protect pharmaceutical firm revenues from impending generic competition,[17] I focus on the timing of LEs.[18] A LE is a branded, prescription drug that is based on the same active ingredient as a previously approved OF by the same firm. LEs are not bio- and pharmaceutically equivalent to their OFs

[15] ANDAs require the generic firm to certify that it is not infringing the branded drug's patents or file a "Paragraph IV" certification claiming the patents are invalid or not infringed. This often leads to litigation. Generics have an incentive to be the first Paragraph IV filer because they gain 180-day marketing exclusivity.

[16] In some cases, generic penetration takes less time. Vasotec, a drucg by Merck for the treatment of hypertension, lost 75% of its sales within two months after generic entry in 2000. See Harris (2002).

[17] These include "pay for delay" settlements between brand and generic firms to delay generic entry, introducing "authorized" generics to pre-empt or compete with generics, moving drugs from prescription to over-the-counter, and filing FDA citizen petitions to delay generics. See Ellery and Hanson (2012) and Feldman and Frondorf (2017).

[18] A LE strategy not studied in this paper is the "hard switch," in which a firm discontinues an OF before OF Expiry, forcing consumers to switch to the LE. When the OF's generic enters, there are very few OF prescriptions left. There have been few cases of hard switches and they have attracted antitrust scrutiny.

and can be classified into different technological categories depending on how they differ from the OF: route expansions, formulation and/or dose changes, extended release, combinations, enantiomers and other molecular changes, and changes unrelated to the active ingredient (see below and Table 1 for more detail on each of these categories).[19]

A route expansion LE is administered via a different route than its OF, as in the case of Exelon (oral) and Exelon Patch (transdermal). Formulation change LEs involve a LE and OF that share a route of administration but differ in their formulation. For example, within the oral route of administration, formulations include tablets, capsules, orally dissolvable tablets, and syrups. Dose change LEs change the amount of active ingredient in the OF, as with Aricept 23. LEs can also be extended release versions of an OF. These products release an active ingredient gradually into the body, allowing consumers to take fewer doses.

Other LEs may combine the OF's active ingredient with other active ingredients. The LE's active ingredient could be either a generic or another of the manufacturer's on-patent drugs. When a combination LE includes all active ingredients in one product, it is known as a fixed dose combination. Other combination LEs involve two or more separate products that are packaged together instead of combined into one product. These co-packaged LEs often involve drugs that are complements but must be taken at different times.

LEs may also tweak the molecular structure of the active ingredient for some OFs. For example, Celexa is an antidepressant made up of two mirror-image molecular structures known as enantiomers. Celexa's LE, Lexapro, removes one of these mirror-images. Enantiomer LEs do not necessarily have the same chemical properties as the OF, and may offer clinical advantages to some patients, like fewer side effects.[20] Still, there is heterogeneity within this type of LE, as some enantiomer LEs are more differentiated from their OFs than others. Other LEs change an OF's non-active ingredients, adding excipients, flavorings or vitamins.

[19] See Fowler (2017) for further examples and detail.

[20] Huskamp et al. (2009) find that Lexapro is associated with decreased probability of discontinuation versus Celexa.

FDA regulations require generics to be bio- and pharmaceutically equivalent to a reference branded product. Since a LE is not bio- and pharmaceutically equivalent to its OF, a generic to the OF is not a generic to the LE. This distinction means that when a generic to the OF enters, the OF loses most of its sales to the generic, usually due to insurance restrictions and generic substitution laws [Berndt and Aitken, 2011; Frank and Hartman, 2015]. However, LE sales are not as affected. To the extent that patients switch from an OF to a LE before the OF's generic enters, firms can retain revenues that would otherwise have been lost to the generic (and firms may direct promotional activities to encourage this switch). In this sense, LE introduction can be strategic, and in the industry vernacular, introducing a LE to insulate OF revenues from generic competition is known as a "product hop."

Other research has examined the LE strategy in some settings: Huskamp et al. (2008) study firm strategies to extend market exclusivities on drugs in an antidepressant therapeutic class from 1997 through 2004. They find that firms often try to shift demand from OFs to LEs prior to OF generic entry, via promotional dollars. Carrier and Shadowen (2016) note potential harm to LE consumers when prescribers are encouraged to switch patients from the OF, and develop a framework to assess whether these LE introductions are anticompetitive. In a paper closely related to this one, Shapiro (2016) conducts a case study of a LE introduction and estimates the effects of delay on consumer welfare. He estimates a demand system to disentangle the extent to which the adoption of Ambien CR, a reformulation of Sanofi-Aventis' Ambien (a prescription sleep aid), is driven by the drug's attributes or by advertising. He concludes that if Ambien CR had launched when Ambien was launched instead of seven years later, consumers would have seen a welfare gain of $723M. The caveat concerns innovation: if Ambien CR's exclusivity had not existed, the product might not have been developed.

3 Conceptual Framework: Timing of a LE Introduction

This section develops a model of a firm's decision on the timing of a LE introduction in the context of FDA exclusivity policy, where exclusivity for the LE starts upon FDA approval. The FDA must approve a drug application for it to enter the market, and though there is variation in time from application submission to approval, there are pre-specified review timelines.[21] Thus, the firm's decision is when to submit a LE application to the FDA, whereas I assume the firm controls approval time with its decision on the timing of its submission.

LEs can be thought of as falling on a continuum of substitutability with respect to their OFs: on one extreme, LEs and OFs are perfect substitutes; on the other, LEs and OFs are independent in demand. I operationalize this idea by recognizing that a LE has two types of consumers: switchers, who formerly consumed the OF and switched to the LE, and consumers who are new to the OF-LE franchise. As I show below, the degree of switching is an important determinant of the firm's decision about the timing of LE introduction.

I model a profit maximizing firm's decision on when to introduce a LE. For simplicity, I assume prices are fixed across products and increased revenues are driven by quantities. I assume no costs of production, so revenues are equal to profits. A firm sells an OF with a market size normalized to 1. The OF has a market life of L, which is given. At L, the OF loses patent and exclusivity protection (i.e., "OF Expiry") and generics for the OF enter, capturing all OF sales. The firm introduces the LE at a date denoted $L - t$, where t is the time between LE entry and OF Expiry. The firm's choice variable is t.

Upon entry, the LE receives an exclusivity period of E, which is given. After E, generics for the LE capture all LE sales. When the firm introduces the LE, its sales start at zero and

[21] Since 2002, the FDA aims for 90% of new drug applications (NDAs) to have filing to approval times of a year for standard review or 7-8 months for priority review. These targets began in 1992 (see above). Firms may request priority review, but the FDA decides within 2 months of NDA receipt. My review of approval letters for a random sample of LEs from 1995-2017 shows variation in the distribution of months from NDA filing to approval (min: 3.5, p25: 9.9, p50: 10, p75: 16.6, max 83.5). Firms may have information on their filing that helps them predict where they are likely to fall in this distribution of times.

increase at a given rate of ρ until OF Expiry. Some sales from the LE expand the market, and others come from the OF. The fraction that expand the market is captured by another parameter, γ, with $0 \leq \gamma < 1$. γ represents the share of LE sales that are market expanding, and $\gamma\rho$ is the rate of market expanding LE sales from LE entry up to OF Expiry.[22] In this model, both ρ and γ are given.[23]

After OF Expiry, low-priced generics to the OF are available and the growth in LE sales changes slope. The cannibalizing share of sales plateaus—there are no more switchers from the branded OF (which is now generic) to the LE, and anecdotally, it is hard to get patients to switch back to an OF once they are on the LE, even if the OF is generic.[24]

In the general case, the market expanding LE sales continue to grow after OF Expiry, but at a rate of $\alpha\gamma\rho$, with $0 \leq \alpha < 1$, such that $\alpha\gamma\rho < \gamma\rho$. This general case captures how LE sales may continue to grow upon the entry of the OF's generic, though at a (potentially) lower rate than before as there is now a low-cost competitor to the OF on the market. Since the LE and the OF are substitutes, as the price of the OF's generic falls, growth in LE sales is reduced.

For illustrative purposes, in what I denote as the base case of the model, I set $\alpha = 0$ as a simplifying assumption. When $\alpha = 0$ all LE sales plateau after OF Expiry, yet the firm's tradeoff and the model's predictions still hold. Figure 1 depicts the base case.[25] Given OF and LE exclusivities (L and E), and LE sales parameters (ρ and γ), the firm decides when to launch the LE by choosing t, the time between LE entry and OF Expiry. Early entry allows the firm to ramp up LE sales from switchers and new consumers, at the expense of exclusivity

[22]LEs and OFs may be differentiated in a variety of ways that may drive market expansion. For example, a LE may be approved for an indication that an OF was not approved for, or a LE may treat the same condition as an OF, but for a different population. However, market expansion is not merely a clinical or chemical property of the LE. It is an economic concept that includes elements like advertising and the presence of competitors

[23]To the extent that these parameters are endogenous, I assume the firm picks optimal values of both, and its choice variable given those optimal values is t.

[24]Carrier and Shadowen (2016) cite an internal quote on Namenda, a medication for Alzheimer's Disease by Forest Labs: "if we do the [...] switch and [...] convert patients and caregivers to once-a-day therapy versus twice a day, it's very difficult for the generic to then reverse-commute back." They also cite an empirical report from Bernstein Research (that I was unable to obtain) that says that LEs do not lose share once the OF goes generic, regardless of technological change.

[25]A depiction of the general case can be found in Appendix Figure C.1.

time post-OF Expiry because more of the OF and LE's market lives would overlap. Later entry shifts the LE's exclusivity so that more of it is post-OF Expiry but reduces overall LE sales.

In Figure 1, the firm picks t to maximize the area of the market expanding triangle plus the LE sales rectangle post-OF Expiry. The larger t (i.e., the earlier the LE enters), the more time there is for LE sales to ramp up, which increases both the level of post-OF Expiry sales and the area of market expanding sales when $\gamma > 0$. However, a longer t reduces the length of time in which sales are achieved post-OF Expiry.

The incremental profit from LE introduction is the shaded area in Figure 1. The total profit of the OF and LE franchise is the sum of the profits across each of the three periods:

$$L + \frac{1}{2}t(t\gamma\rho) + t\rho(E - t) \tag{1}$$

The first order condition for the firm to pick the profit maximizing t is

$$t\gamma\rho + \rho E - 2t\rho = 0 \tag{2}$$

The profit maximizing t^* in the base case is

$$t^* = \frac{E}{2 - \gamma} \tag{3}$$

The profit maximizing t is increasing (i.e., LE introduction is earlier) in both γ and E. Note that ρ, the rate of growth of LE sales, does not enter into the solution. Rather, it is the share of sales that is market expanding versus cannibalizing that creates an incentive for earlier versus later LE introduction. The key takeaway of the model is that with a fixed E, if a large share of LE sales is from switchers, (i.e., as γ gets smaller), there is an incentive for the firm to delay the introduction of a new LE.

In one special case, $\gamma = 0$ and all LE consumers are switchers. As shown in Appendix

Figure C.2, there are no profits from market expanding sales pre-OF Expiry. Thus, the firm picks t to maximize LE sales post-OF Expiry only. The profit maximizing $t^* = \frac{E}{2}$, the latest profit maximizing LE introduction time the firm would consider. It is not optimal for the firm to introduce the LE at the last possible moment before OF Expiry because there would not be enough time to switch patients to the LE from the OF, and those patients would end up taking the OF's generic instead.

On the other extreme, $\gamma = 1$ and 100% of LE sales are from new customers. The products would be independent, and LE would be unaffected by OF Expiry.[26] In this case, the firm would introduce the LE as early as it can.

As described earlier, strategic delay leads to welfare loss. Though this model holds prices constant, the welfare losses can still be appreciated. First, because the firm has an incentive to delay, products enter later than they otherwise would, and their exclusivity period extends beyond OF Expiry. This means that consumers have to wait to access valuable products. If LEs do not add value beyond the OF but are strategically delayed, any switcher from the OF to the LE (possibly due to the firm's marketing efforts), will pay brand prices instead of generic prices after OF Expiry.

The framework here can be used to assess other, more complex firm decisions regarding LE introductions. For example, a firm may decide to launch multiple LEs for a given OF. Presumably, the firm would start with the most market expanding LE. After, the firm will continue to launch LEs after considering both the cannibalization over the OF and other LEs already on the market that had not yet gone generic, as well as the new LE's market expanding potential for the entire franchise. With multiple LEs, exclusivities start to "chain" outwards. The model is more complex, but the framework applies.[27]

[26] Recall that in the model setup γ is strictly less than 1.

[27] This framework could also be used to model OF discontinuation following a LE introduction, which is known as a "hard switch". In this case, the firm makes two decisions: when to introduce the LE and whether to discontinue the OF before OF expiry, at which the LE would immediately capture all OF sales. In practice, this is a strategy that is risky because of potential regulatory scrutiny, which could be modeled. This framework

In sum, this model shows that firms have an incentive to strategically delay LE introductions, and that the extent of the delay depends on the degree to which the LE cannibalizes the OF. It is in the firm's interest to wait longer to introduce LEs with a larger share of sales that are cannibalizing. However, the LE will be introduced before the OF goes generic to ensure consumers have time to switch before generic entry. A LE that is on net more market expanding than cannibalizing has an earlier optimal introduction time.

4 Data

To test for strategic delay, I construct a novel dataset of OFs approved by the FDA from 1985 through 2016, matched to LEs approved in that timeframe. The steps to construct the data were (1) identifying OFs and potential LEs, (2) matching OFs and LEs, and (3) calculating OF Expiry dates. The final dataset is at the OF-LE level, allowing for OFs to not have LEs. The data include OF and LE attributes as well as key dates for each pair: OF and LE approval dates, and calculated OF Expiry dates.

4.1 Data Construction

The data used in this paper comes from nine sources that are described in detail in Table 2. The data include approval, patent and exclusivity data from three FDA sources, patent and Hatch-Waxman restoration data from the US Patent and Trademark Office, high-level therapeutic classes from the World Health Organization and National Institutes of Health, indicators of whether a drug is a best-seller from industry publications and news articles, and firm-level data from industry publications. I consider both OFs and LEs at the New Drug Application (i.e., NDA) level, which is what firms submit to the FDA for drug approval. NDAs may include

may also be useful in a situation where the first decision on timing of LE introduction is based on an expected value of ρ and γ, and the decision to discontinue the OF is based on the realized values and cost of doing so.

multiple products of different strengths.[28]

Appendix Table B.1 provides detail on how I arrive at the dataset that includes 710 OFs, 444 without a LE, and 266 OFs mapping to 525 OF-LE pairs. Of these, 341 OF-LE pairs include LEs that did not have their own drug substance patent. The remaining 184 pairs correspond to LEs that have their own drug substance patents (and as such were not subject to the incentive for delay). I return to a subset of these as a comparison group. As noted in Section 2, LEs that do not have their own drug substance patents are subject to the incentive for strategic delay.

To assemble the dataset of OFs and LEs, I first use the drugs@FDA database and National Drug Code Directory to identify NDAs approved from 1985 through 2016. I exclude biologics, over-the-counter products, and medical gases, which do not face generic competition in the same way as small-molecule prescription drugs. I also exclude tentative approvals. This leaves a set of 2,562 NDAs.

To obtain OFs, I restrict this set of NDAs to those approved as Type 1[29] as well as six others in which an new molecular entity was paired with a long-time generic active ingredient.[30] After merging therapeutic classes to each OF, I exclude diagnostic radiopharmaceuticals, urea breath tests and contrast agents, which are diagnostic classes, leaving an OF sample of 710 NDAs.

To identify potential LEs, I restrict the set of 2,562 NDAs to those approved as Type 2 (New Active Ingredient), Type 3 (New Dosage Form), Type 4 (New Combination), Type 5 (New Formulation or Manufacturer), and as combinations of certain types: Type 1/4 (excluding the six that I consider OFs), Type 2/3, Type 2/4, and Type 3/4.[31] I drop NDAs flagged in the National Drug Code directory as being an authorized generic, as this is not a strategy that I

[28]Like OF Aricept, which was approved as both a 5 mg tablet and a 10 mg tablet under the same NDA.

[29]Type 1 is the designation for new molecular entities that have never been previously approved by the FDA, either on their own or in combination with another active ingredient.

[30]For example, oral contraceptive Yasmin, approved in 2001, pairs new molecular entity drospirenone with long-time generic ethinyl estradiol, which has been on the market since the 1960s [Dhont, 2010]

[31]Type 2 approvals include enantiomers and prodrugs. LEs in this paper are never Type 1, Type 6 (New Indication), Type 7 (Drug Marketed without Approved NDA), Type 8 (Partial Rx to OTC Switch), Type 9 (New Indication Submitted as Distinct NDA) or Type 10 (New Indication Submitted as Distinct NDA - Not Consolidated).

study. This yields 1,664 potential LE NDAs.

I match the 710 OF NDAs with the 1,664 potential LE NDAs. To match, an OF and LE must share an active ingredient. I account for terminology that denotes slight modification to active ingredients, consistent with my definition of a LE. For example, I include enantiomers as LEs by flagging active ingredient prefixes (e.g., levo-, etc.), and account for other forms of an active ingredient (e.g., "hydrochloride" is a water-soluble version of an active ingredient).

I then use a two-step process to restrict the OF-LE matches to those that were submitted to the FDA (i.e., "sponsored") by the same pharmaceutical firm. I first standardize sponsor name spellings in the FDA application data. For example, this step combined separate sponsors listed as *MSD MERCK CO*, *MERCK AND CO*, and *MERCK SHARP DOHME* into one standardized sponsor, *MERCK*. The second step identifies whether two or more distinct sponsors were subsidiaries of the same firm. This could happen if different divisions of a parent firm had distinct names, or if a merger or acquisition occurred. I researched each sponsor to identify its parent firm and relevant dates of affiliation. To illustrate, this step maps sponsors *JANSSEN*, *ORTHO MCNEIL*, and *JOHNSON AND JOHNSON* to the same parent firm, *J&J*.

Finally, I restrict OF-LE matches to keep only those that were (1) associated with the same sponsor, (2) associated with different sponsors that belonged to the same parent firm, or (3) joint ventures by different sponsoring firms. I drop pairs where the LE was approved prior to the OF, and merge covariates using NDA identifiers, active ingredients, routes of administration, and pharmaceutical firms. This process leaves 525 OF-LE pairs. I determine whether the LE in each of these pairs has its own drug substance patents using the FDA's Orange Book.

This matching algorithm leads some LEs to be paired with multiple OFs, usually when the LE is a combination of previously approved new molecular entities by the same manufacturer. Many of the 1,664 potential LEs do not match to any OFs in my data. This happens if a LE's OF was approved prior to 1985, or if an OF was not approved as a new molecular entity.[32]

[32]For example, Apil's Asacol (mesalamine) was approved by the FDA in 1992 as a new dosage form ("Type

Finally, if a LE was approved as a new molecular entity, it will not match to a previous OF as a LE.[33]

I classify the OF-LE pairs in my sample into seven types described below, which are based on their technological categories (see Table 1). This typology follows clinical and industry publications.

- Combination: The LE has additional active ingredients in relation to the OF. The combinations category includes fixed dose combinations and co-packaged LEs.

- Route Expansion: The LE has a different FDA-listed route of administration than the OF. I aggregate routes of administration to oral, transdermal, injectable/IV, inhaled, and other.[34]

- Formulation Change without Dose Change: The LE has the same administration route and active ingredient strength as the OF, but their listed formulations are different.

- Dose Change without Formulation Change: The LE and OF have the same administration route and formulation, but the LE has at least one product with a different active ingredient strength than the OF.

- Formulation Change and Dose Change: The LE and OF have the same administration route, but their formulations are different and the LE has at least one product with a different active ingredient strength than the OF.

- Extended Release: The LE formulation is listed as "delayed" or "extended" release and the OF's formulation was not.

3") of a previously approved active ingredient (specifically, Mylan's Rowasa (mesalamine), which the FDA approved as a new molecular entity in 1987). Though Apil later launched Asacol HD and Delzicol, both mesalamine follow-on products to Asacol, none of these Apil products appear in the data because Asacol was not an OF per my definition.

[33]Pristiq, a LE of Effexor, received a Type 1 approval and as such is in my dataset as an OF and not a LE.

[34]Oral includes oral, dental and sublingual routes of administration. Topical includes transdermal and topical routes of administration. Other includes implant, intravesical, otic, vaginal, and rectal routes.

- Other: All remaining LEs, which can be classified broadly into:
  - Change to the active ingredient: The LE received a "Type 2" approval, is an enantiomer, or is otherwise innovative.
  - Changes in non-active ingredients: These changes can be due to change fillers or inactive ingredients, or a new indication that was approved a as a new product.

When multiple LEs are associated with an OF, a particular LE's classification is driven by the incremental change it makes relative to the OF and any previous LE. So, for example, if the 1st LE is a combination and 2nd LE is an extended release version of the combination, I classify the second as extended release and not as a combination.

4.1.1 OF Expiry Calculation

OF Expiry is a key component of my empirical analysis, as I use it as a proxy for generic entry. What I am interested in is the date of actual generic entry, which is when a firm would start to lose OF revenues. Generics can only enter once patent and exclusivity periods on the OF expire. The precise date of generic entry may be uncertain at the time of OF approval, as OF patents can be challenged in court by generic manufacturers who may or may not be successful. Thus, though I leverage data on patents and exclusivities, there is some uncertainty in my estimated OF Expiry date as a measure for potential generic entry.

To calculate OF Expiry for each of the 710 OFs in my sample, I start with Hatch Waxman Patent-Term Restoration data. A provision of the Hatch Waxman act allows pharmaceutical firms to recover time on one patent that was lost during FDA review. This applies to OFs only, and the patent firms choose is often the strongest [Beall et al., 2018]. For each NDA in the Patent-Term Restoration data, I record the expiration date of the chosen patent.

I then turn to the FDA Orange Book and flag all NDA patents that included a drug substance claim. Using the US Patent and Trademark Office data, I obtain the filing dates for each of

these drug substance patents. For each NDA in the Orange Book, I record the expiration date of its first drug substance patent that was filed prior to the NDA's approval (i.e., I do not include drug substance patents that were filed after the drug was approved by the FDA). I also obtain expiration dates of 7-year Orphan Drug Exclusivity and 5-year New Chemical Entity Exclusivity for each OF NDA.

These steps yield up to four dates per OF: restored patent expiry, first drug substance patent expiry, New Chemical Entity expiry and Orphan Drug Exclusivity expiry. If an OF did not have any of these, I impute a date of five years after FDA approval to reflect New Chemical Entity exclusivity, which is granted to all new molecular entities the first time they are approved. In this paper, OF Expiry is the latest of these four dates plus six months if pediatric exclusivity was noted in the Orange Book. The result is a measure that only considers secondary patents if they were selected for Hatch-Waxman restoration. Hemphill and Sampat (2012) show that drug substance patents are harder to invalidate in court than secondary patents are.

I validate the estimated OF Expiry date by comparing it to actual generic entry dates for the 313 OFs in my sample of 710 that had a generic enter by December 31, 2016 (44%). I follow Orange Book guidance to match generic ANDAs to OF NDAs, and identify the date of first and subsequent generic approvals for each of the 710 OFs in my sample. Figure 2 plots the distribution of the difference between actual first generic entry and estimated OF Expiry, for the 313 OFs that had a generic on the market by December 31, 2016. The median difference between actual first generic approval and estimated OF Expiry is 1.03 years. The 25th percentile is 0.003 years and 75th percentile is 3.96 years. For over 75% of the OFs that had generics, the estimated OF Expiry was earlier than generic approval. For just under 30% of OFs the measure was early by a year or less.

If firms are introducing LEs with regard to expected generic entry, for which I am using OF Expiry as a proxy, then the estimated OF Expiry measure is early for 75% of the OFs that actually had a generic. In terms of precision of the measure, just under a third of the 313 OFs

had a first generic approval within a year of estimated OF Expiry.[35] For those OFs that did not have a generic enter, the measure is likely conservative as it does not account for all secondary patents.[36]

Individuals familiar with pharmaceutical firm decision making state that it is difficult to pinpoint precise dates of presumed generic entry, and oftentimes they must make do with ranges. My OF Expiry measure is replicable and a reasonable proxy for generic entry, though it errs on the early side.[37]

4.2 Original Formulation Descriptive Statistics

Table 3 summarizes OF attributes for all 710 OFs together as well as separately for OFs with and without LEs. I define OF market life as the time from OF approval to calculated OF Expiry. Across the 710 OFs, average market life is 9.98 years, with a standard deviation of 3.90 years, and a range of 5 to 18 years (see Table 3). This mean is on the lower end of market life usually cited in the literature, reflecting the conservative nature of the OF Expiry measure.

The covariates I use in my analysis are at the OF level and are summarized in Table 3. 45% of OFs came from a Top 20 pharmaceutical firm, which is a binary variable that designates if the OF's sponsor was in the Top 20 by revenues in industry publication Pharmaceutical Executive's annual ranking in the year after OF approval. The Best Seller variable is 1 for OFs that appeared on lists of Top Selling Drugs in the US, by revenue. 21% of all OFs in the dataset were bestsellers, but only 12% of OFs that did not have a LE were bestsellers compared

[35] Feldman and Frondorf (2017) outline cases when generics might enter prior to patent and exclusivity expiration. A generic manufacturer might win a Paragraph IV challenge or reach a settlement with the OF firm, allowing entry.

[36] It is important to note that the data I use for this validation exercise is on generic approvals, which are not always the same as generic launch dates, which are of strategic concern to the OF firm. For example, the OF Expiry date I calculate for Lunesta, a branded sleep medicine, is August 2014. An April 2014 press release from generic firm Teva announces the actual market launch of Lunesta's first generic. However, in the FDA data, Teva's approval for this generic was granted in 2011. This discrepancy between approval date and market launch date means that Lunesta appears on the histogram at -3.2 years, though the difference between actual generic entry and my measure is 0.3 years.

[37] I am grateful to two legal scholars who have discussed OF Expiry estimation with me.

to 35% of those that did. 27% of OFs had orphan exclusivity, as listed in the FDA Orange Book. The OF's NDA product count is a tally of how many products are in the initial OF. For instance, Aricept had two: a 5mg tablet and a 10 mg tablet, both approved under the same original NDA. OFs in the sample have an average of 2.2 products, with a standard deviation of 1.55. OF patent count captures the total number of patents that protect an OF, including its drug substance patent, and each OF has an average of 4.05 (standard deviation 4.37).

OF vintage is a categorical variable that captures the five- and in one instance six-year period in which an OF was launched (i.e., 1985-1989, 1990-1994, 1995-1999, 2000-2004, 2005-2009, and 2010-2016). These "vintage" categories capture changes over time. For instance, demand might change over time with insurance expansions (for example Medicare Part D started in 2006, and this increase in insured people has been shown to have an effect in innovation for the therapeutic classes used by this population [Blume-Kohout and Sood, 2013, Dranove et al., 2014]), and as pharmacy benefit managers (PBMs) refine their business model starting roughly in 2010.

There are five OF aggregate routes of administration in the data: dermal (5%), injectable (26%), ophthalmic (4%), oral (61%), respiratory (4%), and other (1%). There are also 14 general-level therapeutic classes, as shown in Table 3. The top classes, with more than 10% of OFs each, are Alimentary Tract (12%), Cardiovascular System (11%), Anti-infectives (13%), Antineoplastics (16%) and Nervous System (15%). The remaining nine classes had fewer than 10% of OFs in my sample.

4.3 Line Extension Descriptive Statistics

Table 4 shows the breakdown of LE in the sample by technological category, overall and separately for those that did and did not have LE drug substance patents separate from the OF's. I do not have an exogenous measure of which LEs are cannibalizing versus market expanding, but argue that these technological categories can be used as proxies. In particular, because of

the changes they make relative to their OFs dose changes and extended release LEs are likely to be on average more cannibalizing than other LE types.

Figure 3 and Figure 4 show histograms of $L - t$ and t for the set of non-simultaneous OF-LEs. The distributions show how LEs with and without drug substance patents have similar overall patterns of entry time relative to OF Approval ($L - t$), but quite different ones in terms of OF Expiry (t), with patented LEs entering earlier and in many cases prior to OF Expiry.

An interesting observation is that about 9% of OF-LE pairs correspond to a LEs that was approved in the first 90 days after OF approval. Given typical approval times, the FDA was reviewing both the OF and LE's applications simultaneously in these cases for at least some time, and the firm was not certain when the OF would be approved when it submitted the LE's application. I call OF-LE pairs where the LE entered within 90 days "simultaneous," and consider firm decisions for simultaneous approvals separately from a firm's decision on strategic delay.

I examine the firm's decision on the types of LEs that are approved simultaneously. Given the conceptual framework in Section 3, we would expect these to be market expanding. I estimate the probability of an OF having a LE approved within 90 days of OF approval as a function of the OF being from a top 20 pharmaceutical firm, if the OF had orphan exclusivity, the OF's NDA product count, the OF's patent count, the OF's vintage, route of administration and therapeutic class, and LE Type. However, none of the technological categories are statistically significant predictors of early entry. Including data on product indications and competition in future analyses will allow for a potentially more robust measure of market expansion.

5 Empirical Approach

5.1 Firm Timing of Unpatented LEs

I start by considering a firm's decision to launch a LE that did not have drug substance patents using the entire sample of OFs. Specifically, I model the firm's decision on the timing of subsequent unpatented LEs beyond the initial 90-day period from OF Approval. I use semi-parametric survival analysis, where a "failure" is a LE approval.[38] Survival models like this one are nonparametric for elapsed time but parametrize the effect of covariates, and have been used to study a number of duration-related outcomes, including, for example, the timing of finding work relative to unemployment benefits expiring.[39] Since an OF can have multiple LEs, I allow for multiple failures. This type of model also accounts for right-censoring from lack of data availability after December 31, 2016. In fact, because I consider multiple LEs for each OF, and in theory OFs could continue to have LEs in perpetuity, all OFs in the sample are right-censored at December 31, 2016. In contrast to survival analyses in clinical settings, which might look at one-time failures such as death or hospital discharge, OFs do not drop out of the analysis after having a LE approved to enter the market.

The hazard function is the instantaneous rate of failure, denoted $h(t) = \lim_{\Delta t \to 0} \frac{Pr(t+\Delta t > T | T > t)}{\Delta t}$ where T is a non-negative random variable denoting the time to a failure.[40] I estimate the effect of proximity to OF Expiry on the hazard rate of LE approval as follows:

$$h_i(t) = h_0(t) * \sum_{k=-3\,to\,-1\,Years}^{1+Years} \beta_k * \mathbb{1}(Period\,around\,OF\,Expiry = k)_{it} + \gamma X_{it} \tag{4}$$

In this estimating equation, $h_i(t)$ is the hazard of LE approval for OF i at time t from

[38] OLS allows for controls, but assumes the error term is distributed normally, which is not right for LE approvals.

[39] See, for example, Katz LF, Meyer BD.(1990) The Impact of the Potential Duration of Unemployment Benefits on the Duration of Unemployment. Journal of Public Economics. 1990;41 (1) :45-72.

[40] For more detail, see Cleves, M., Gould, W., Gutierrez, R., & Stata Corporation. (2010). An introduction to survival analysis using Stata (3rd. ed.). College Station, Tex.: Stata Press.

OF approval plus 90 days, and $h_0(t)$ is the baseline hazard at time t. The model makes no assumptions about the shape of the baseline hazard, which varies over time and can be interpreted as the effect of science (i.e., innovation due to the pace of the R&D process) and variables not captured in the covariates on the hazard rate. As noted above, I exclude failures that occurred in the first 90 days from OF Approvals, as those are governed by the firm decision on simultaneous launches rather than timing in response to OF Expiry.

Values of covariates in the vector X_{it} scale the baseline hazard rate. I control for the OF's market life, defined as the time from approval to expiry, as well as covariates that are likely associated with different R&D processes, and are described in Section 4 and in Table 3. These include whether the firm was among the top 20 pharmaceutical manufacturers based on revenue, if the OF is a top-selling drug, if the OF received orphan drug exclusivity, the OF's product and patent counts, the OF's vintage as measured in five-year increments, its route of administration, and the OF's broad therapeutic class.

The coefficients of interest are β_k, which capture the time-varying effect of proximity to OF Expiry on the hazard rate of getting a LE, relative to the omitted reference period of three or more years prior to OF Expiry. Specifically, these periods are from OF approval to 3 years before OF Expiry (the reference period), 3 years before OF Expiry to 1 year after, and 1 or more years after OF Expiry. These periods were chosen to balance a few considerations: first, the exclusivity period for over 90% of LEs in the sample is 3 years, and as such one would expect strategic delay to lead to LE approvals in the 3 years prior to OF Expiry. Second, given the way OF Expiry is calculated and the fact that in the validation of the measure shown in Figure 2 the measure is off by less than a year for 30% of OFs that actually had a generic, I include one year post OF Expiry. Finally, I trade off some degree of granularity for statistical power by grouping LE approvals in these periods. Robustness checks include different period groupings.

A $exp(\beta_k) > 1$ indicates that LEs were approved at a higher rate in time period k relative

to the reference period of three or more years prior to OF Expiry. I estimate the model for all OFs, considering different subsets of LEs as failures in each iteration. The baseline hazards and coefficients vary across specifications, as R&D processes may be different across LE types. I first consider all types of LEs without own drug substance patents as failures. As a falsification test, I estimate the model using LEs that had their own drug substance patents as failures. The intuition is to look at LEs that are similar in type to those that only had exclusivity, but that were granted a drug substance patent. To make samples more comparable, I exclude LEs that likely required a different scientific process (identified as those approved designated as innovative in my data, as well as those designated as "Type 1/4," combinations that include new molecular entities), and were not comparable to the LEs that did not have their own drug substance patents. The LEs in the falsification test do not have the same incentive for delayed introduction, as the end of their exclusivity period is fixed regardless of approval time. Thus, one would not expect their β_k coefficients to be significantly larger than 1 in the years around OF Expiry.

The conceptual framework suggests that firm responses will be different depending on the degree to which their LEs cannibalize sales of their previous products. To test for this I estimate the model separately for the following sets of LE types as failures: combination, route expansion, any formulation change, only formulation change, any dose change, only dose change, and extended release. In these specifications, I include more granular periods around OF Expiry to compare firm timing across LE types with more nuance. In these specifications, the baseline period is 4 or more years prior to OF Expiry, and I estimate β_ks for $k = (-4\,to\,-2), (-2\,to\,0), (0\,to\,2), (2+)$ years to/from OF Expiry.

5.2 Simulations to Quantify Strategic Delay

To quantify strategic delay in units of time, I require counterfactual LE entry times in a world where all else was equal except for the incentives for strategic delay. Because this counterfactual is not observable, I quantify the average length of strategic delay by running Monte Carlo simulations to compare observed LE approval times in the presence of incentives to delay with times that might be expected based on another plausible scenario.

I first predict the risk score for each OF i of type j and interval around OF Expiry k. The risk score is defined as $exp(\sum_k \hat{\beta}_k * \mathbb{1}(Period\,around\,OF\,Expiry = k)_{ijt} + \hat{\gamma} X_{ijt})$. The ks here correspond to the same periods used in the survival analyses above. I use the risk scores (up to five different ones per OF-LE type, corresponding to each period k), the date of OF i's Expiry, and the baseline cumulative hazard for LEs of type j to calculate the transition probabilities of OF i getting a LE of type j in the year leading up to t, for t in $[1, 32]$. I use these transition probabilities to simulate LE approvals for every OF in the sample, from approval to 32 years. More detail on this set-up is described in Appendix Section A.

I then compare actual LE entry times to LE entry times from a plausible comparison scenario. An ideal counterfactual would capture a world where firms did not have an incentive to strategically delay LEs. Because I do not observe this counterfactual, I simulate LE entry eliminating the time-varying component of the hazard rate, which is captured by the β_k coefficients. As a result, the total number of counterfactual LEs after 32 years will be less than the true LEs over that time, as there is no time-varying boost in the hazard rate around OF Expiry. I assign "missing" LEs proportionally to the years prior to OF Expiry for all OFs. I then calculate the average delay per LE by comparing the actual to the counterfactual scenario.

5.3 Comparison of Patented and Unpatented LEs

To verify the magnitudes of strategic delay that the Monte Carlo simulations yield, I examine entry times for LEs without drug substance patents relative to a set of comparable LEs that had drug substance patents. This is a useful comparison because, as described in Section 2, there are two separate regulatory regimes that provide protected market periods for LEs: patents, in which firms have the incentive to introduce the LE as soon as possible, and exclusivity upon approval, in which firms would be subject to the delay incentives discussed in Section 3. All else equal, given the incentives faced by the firm, patented LEs should enter earlier than their unpatented counterparts. Of course, a limitation of this comparison is that estimated differences could be confounded if patented and unpatented LEs are different in unobservable ways that affect drug development times.

Comparing the introduction timing of patented versus unpatented LEs to discern the effect of incentives on firm decisions hinges on two assumptions. First, that firms do not strategically delay patent applications, and second, that development times are the same for patented and unpatented LEs. A corollary to the second assumption is that LEs that failed to get a patent and never came to market do not have differential development times. It is possible that patented LEs are more market expanding, which would contribute to some of the difference in approval times across patented and unpatented LEs. However this is mitigated by the fact that if a LE had a drug substance patent then it was "novel and nonobvious" and may have required more R&D efforts than a comparable LE that was not awarded a drug substance patent.

Second, I assume that firms were not submitting patent applications for drugs that were more likely to be market expanding. The analysis conditions on a LE entering the market, regardless of whether it received a patent, and that the existence of associated patents is uncorrelated with the degree of market expansion.

To evaluate the effect of the regulatory environment on LE entry times, one would ideally

compare the entry times of LEs that are identical in all ways except that one had a drug substance patent and the other did not (i.e., as if patents were assigned by coin toss), and attribute the difference to firm responses to incentives created by the regulatory regimes. However, LEs in the data are not identical, and some LEs with drug substance patents are different from LEs without. Thus, I assess the comparability of the LEs that are patented and unpatented, and exclude patented LEs that are clearly different than their unpatented counterparts in ways that would affect the duration of R&D. As a result, I exclude LEs that were combinations that involved a never-approved new molecular entity. I also drop all LEs that are categorized as innovative, or as being a Type 2 approval (i.e., a new chemical entity). I exclude extended release LEs that allowed for weekly or monthly doses if their OF allowed only for daily doses. Finally, I drop LEs that had drug substance patents when their OF did not.[41]

I further restrict the data to exclude all OFs approved in 2007 or later to allow for at least ten post-market years in which I can observe LE approvals. I am left with 288 unpatented LEs to compare to 97 patented LEs. I estimate average adjusted and adjusted differences across these groups in t, which is the years between LE approval and OF Expiry. The adjusted difference in t controls for subsets of the following covariates: years from OF approval to OF Expiry, LE Order (i.e., whether the LE was the 1st, 2nd, etc. LE for a given OF), the OF's vintage, whether the firm was in the Top 20 by revenue, whether the OF was a best seller, whether the OF had a LE launched in the first 90 days from OF approval, the total patent count for the OF, the number of products in the OF's NDA, whether the OF had orphan drug exclusivity, the OF's route of administration and therapeutic class, and LE type. I cluster standard errors at the OF level, since some OFs have multiple LEs and these are unlikely to be independent. Summary statistics of the covariates for the sample of LEs used in this analysis are described in Table 6.

[41] To have a drug substance patent approved the LE must have been deemed novel and non-obvious by the US Patent and Trademark Office, and these LEs were awarded drug substance patents despite the existence of the OF.

6 Results

6.1 Firm Timing of Unpatented LEs

Table 8 shows the results of the survival analysis for the set of all LEs without drug substance patents (column 1) and the falsification test using comparable patented LEs (column 2). I focus on the β_k coefficients, which show how approaching OF Expiry affects the probability that a LE will be approved. For the falsification test, one would not expect the β_k coefficients to be statistically significantly greater than one. Table 8 shows results for the different samples of LE types. Each of these specifications include all OFs in the sample and drop the time period and LEs approved in the first 90 days after OF Approval.

Figure 5 plots the coefficients of interest for the overall model (column 1 in Table 8) and for the falsification test with patented LEs (column 2 in Table 8). The results indicate that an OF is 1.96 times more likely to have a LE without a drug substance patent approved in the period encompassing 3 years before OF Expiry and one year after. This coefficient is statistically significant at the 99% level. In the period 1+ years after OF Expiry an OF is 1.2 times more likely to have a LE approved relative to the same baseline period, but this coefficient is statistically indistinguishable from 1. The pattern on the β_k coefficients shows an increase in the hazard rate of a LE being approved leading up to OF Expiry, consistent with strategic delay.

The panel on the right of Figure 5 plots the β_k coefficients for the set of comparable LEs that had drug substance patents. In this falsification test one would expect there to be no relationship with time to expiry (independent of time) in the hazard of having a LE approved leading up to OF Expiry. As seen in both Table 8 and Figure 5, the β_k coefficients in the falsification test are statistically significantly less than one or statistically indistinguishable from one, which is consistent with this set of LEs not being subject to the same delay incentive as the unpatented LEs. This result is further bolstered by the fact that LEs that had drug

substance patents may have been delayed by unobservable, more complex R&D processes.

Other covariates have an effect on the hazard rate of an OF getting a LE. Across both columns, the hazard ratio for a LE on an OF that is a best seller is roughly 2, and statistically significant at the 99% level. This means that a best-selling OF is about twice as likely to have a LE, patented or non-patented, relative to a non-best-selling OF. Orphan drug exclusivity affects the hazard rate of patented and unpatented LEs differently. Whereas an OF with orphan drug exclusivity is half as likely to have an unpatented LE ($p<0.01$), orphan drug exclusivity has no statistically significant effect on an OF having a patented LE approved. Finally, the OF's vintage matters as well. Relative to OFs approved in 1985-1989, OFs approved in 1995 and later are much less likely to have a non-patented LE approved than a patented one. "Patent proliferation," another pharmaceutical firm strategy that may be used to protect revenues by attempting to file for more patents, has increased over time [Jacobo-Rubio, 2019] and could help to explain this result.

Table 9 shows results of hazard model estimations considering different subsets of LE types as failures. Conditioning on LE type reduces the number of failures in the analysis, so standard errors are large in each of the specifications. Still, the magnitude of coefficients and patterns of the effect of approaching OF Expiry on the hazard rate are informative on firm decisions about the timing of introduction.

The β_k coefficients for combination LEs follow a pattern consistent with strategic delay, with a β_k of 2.25 ($p<0.1$) in the two years leading up to OF Expiry, however these coefficients are not statistically significant. Route expansion and form change LEs do not have statistically significant β_ks either.

Dose change and extended release LEs have β_ks that are statistically significantly different from one. The β_k of 8.12 ($p<0.01$) for extended release in the 2 years leading up to OF Expiry is particularly striking: it tells us that in this period, an OF is over 8 times more likely to have an extended release LE approved, relative to baseline of four or more years before OF Expiry.

All dose change LEs (which include LEs in which both the formulation and the dose changed) as well as dose change only LEs have statistically significant coefficients after OF Expiry. The β_k on all dose changes and dose changes only in the period two years directly after OF Expiry are roughly 3 and 5.6 ($p<0.05$). In the period of 2+ years after OF Expiry, these values increase further for dose changes only. The β_k on dose changes only in the period of 2+ years after OF Expiry is 10.83 ($p<0.05$).

This pronounced increase in the hazard rate of LE introduction after OF Expiry and not before might be due to several factors. First, it is possible that the OF Expiry date in the dose change cases is measured with more error than other LE types. Recall that OF Expiry is a proxy for the expected timing of the first generic entry. To examine this hypothesis, I first looked at the dose change only LEs that were approved after OF Expiry, and compared their OF Expiry dates to the date of the first generic entry for OFs that had one. There were a total of 13 dose change only LEs that entered two or more years after OF Expiry. Of these, only 9 had a generic enter. Those 9 had LEs that entered an average of 4.3 years after calculated OF expiry, but 0.5 years on average before first generic entry. More specifically, 7 of the 9 had the dose change LE approved before the actual generic approval date, suggesting that in the vast majority of cases, firms were able to preempt generic entry with the introduction of a new LE.

Estimating the model for the subset of dose change only LEs for which actual generic entry was within three years of the OF Expiry measure ($n = 21$) yields a pattern more consistent with strategic delay, but standard errors are large and indistinguishable from 1 across β_ks, as seen in Appendix Figure C.3.

It is also possible that the OF Expiry measurement error that is driving the dose change results stems from the "chaining" of multiple LE exclusivities. A pharmaceutical firm may have had multiple LEs for the OF previously, and each LE would have its own exclusivity, which taken jointly would constitute a "chaining" or "cascading" of new exclusivity periods. To examine this, I computed the average order of dose only LEs compared to other LE types.

I find that on average, the order of dose change only LEs is 2.15, which is above the average across the LE types studied of 2.02, and is exceeded only that of combinations (2.46),[42] yet it is not clear if this difference can account for patterns seen in the data. Anecdotally, it is possible that firms consider a dose change as a LE "of last resort," which could be developed quickly if a generic failed to enter when expected. It is also possible that the pharmaceutical firm intended to have the LE approved prior to OF Expiry, but the approval process took longer than expected.

Taken together, my results show how that firms are making strategic decisions on when to launch their products, with differences across LE types. A limitation of my study is that there is large heterogeneity within LE categorizations and small sample sizes. A further limitation is that I capture competition only at the general therapeutic class level, and I do not account for firm marketing due to data limitations.

6.2 Simulations to Quantify Strategic Delay

I use Monte Carlo simulations to interpret the results described above in units of time instead of hazard ratios. Monte Carlo simulations allow me to estimate the average delay per LE, given firm decisions to strategically delay LE entry. After confirming that the simulation of actual LEs matches observed LEs I extend the simulations to run for 32 years for each OF. I report results of average delay per LE in both days and years, separately for all LEs and for each of the two groupings of LE types identified in the survival analysis: extended release and dose change, versus route change, form change, and combinations.

Table 10 details these estimates. I find that overall, introductions of LEs are delayed by 1 year on average. The cumulative percentage of LEs in the actual and counterfactual scenarios is graphed in Figure 6, showing the gap between actual and counterfactual LEs, due to the

[42]Combinations may face a different kind of delay: waiting for another molecule to go off-patent before being able to have a combination approved by the FDA.

increase in the hazard rate around OF Expiry. When examining LE types separately, dose change only and extended release LEs are delayed by almost 2.5 years on average, and route changes, form changes and combinations have an average shorter delay per product of five months.

6.3 Comparison of Patented and Unpatended LEs

Table 7 shows the mean difference in LE approval timing relative to OF expiry for LEs with drug substance patents relative to comparable LEs that did not have drug substance patents, controlling for the length of the OF's market life from approval to expiry, the OF's vintage, and the order in which the LE entered. The difference in approval time is 1.8 years earlier for patented LEs than for LEs without patents, which all else equal can be interpreted as evidence of delay in the introduction of unpatented LEs. After including controls on OF characteristics, the adjusted difference remains stable, which suggests it is the regulatory regime that is driving the difference. The coefficients are also statistically significantly different from zero at either the 1% or 5% level, depending on the specification.

7 Discussion and Conclusion

In this paper I develop a conceptual framework to study firm decisions on the timing of pharmaceutical LEs in response to regulatory exclusivity periods, which start upon LE approval. I show that when a larger proportion of LE sales cannibalize an OF, there is an incentive for the firm to strategically delay LE introduction, and test for strategic delay using novel data covering US drug approvals from 1985-2016.

Using semi-parametric survival analysis, I show that an OF is almost twice as likely to have a LE without a drug substance patent approved in the period surrounding OF Expiry relative to three or more years prior to OF Expiry. These results are consistent with strategic delay

and are bolstered by a falsification test. To estimate the extent of the delay I perform two analyses. I use Monte Carlo simulations to interpret these results, and find that LEs that do not have their own drug substance patents are delayed by roughly a year. A separate analysis that compared patented to unpatented LEs confirms this result.

An important implication of this study is that firms respond to delay incentives in nuanced ways that are consistent with economic theory. Firms may reveal which types of LEs are expected to be more versus less cannibalizing through their decisions about timing. I then document heterogeneity in delay across LE types, with these cannibalizing types having an estimated average delay of 2.5 years per LE, compared to 5 months per product for other types. This result suggests that when firms choose introduction times, they consider the extent to which their products that are already on the market will be affected by the new entrant–a sophisticated strategy in response to regulation.

The welfare effect of strategic LE delays depends on the extent to which a LE provides incremental benefits to consumers over the OF. Though I do not evaluate the value of LEs relative to OFs in this paper, one can think of LEs as adding variable amounts of value beyond the OF. In the first case, if a LE is a valuable improvement then consumers will prefer it due to its attributes. These consumers suffer a welfare loss from the delay in this product, as they would have benefited from it earlier had it not been strategically delayed.

In cases where a LE adds no value over the OF, the welfare loss does not come from foregone clinical benefits, but rather from increased prices paid by consumers and/or insurers. Consumers that switch from the OF to the LE are effectively taking the same drug but paying branded rather than generic prices in the period following generic entry. For example, Aricept 23 is cited as selling for $7.74 per pill in July 2012, versus $0.79 for OF Aricept, which had a generic at that time. As noted in the introduction, the clinical difference between the 23mg LE and the 20 or 25mg doses available via the OF was negligible. Thus, given Aricept's generic entry in November 2010, and Aricept 23's approval in July 2010 with exclusivity extending

beyond generic entry, consumers who switched to Aricept 23 were subject to higher prices (but no additional clinical benefits) until the generic of Aricept 23 enters.

Back-of-the-envelope calculations illustrate the magnitude of welfare loss due to strategic delay. For LEs that add value relative to a prior product, I estimate a loss of $3,900 per patient-product. I assume a QALY is valued at $100,000 and the incremental value of an LE is 0.1 QALYs.[43] If high value products follow the delay pattern of route change LEs, then they are delayed on average by 0.39 years. Thus, for each patient who could have used a LE that provides clinical benefit over the OF, the cost would be approximately $0.1 * 0.39 * \$100,000 = \$3,900$.

Using one product as an example, I estimate the loss due to delayed generic purchases as similar in magnitude. LEs approved prior to OF Expiry with exclusivity periods that extended beyond OF Expiry did so on average by 1.6 years. This is equivalent to OFs receiving a 17% extension on their effective market life. Generics lower branded prices by around 80%. In the case of Aricept and Aricept 23, the difference in price between the 23 mg brand and the 20 mg generic (i.e., two 10 mg pills) was roughly $6.20 in July 2012. Aricept is dosed as one pill per day. As a result, the loss is $\$6.20 * 365 * 1.6 = \$3,621$ per patient. In 2013, 1.3 million Medicare Part D beneficiaries were prescribed Aricept [44]. This would amount to over $4.5 billion in losses, borne largely by insurers, for just one product.

There are also other indirect welfare effects of strategic delay on prices. For instance, if firm behavior leads to the delay of product entry, this could lead to less competition among existing drugs in a therapeutic class in the earlier period, and possible higher prices as a result. Rigorously examining the extent of welfare loss to consumers as a result of strategic LE delay will be an important subject for future work.

A limitation of this analysis is that I assume that firms are introducing their LEs at the

[43] I examine the clinical literature for Alzheimer's Disease and chronic migraine, and find that going from moderate to mild disease states correspond to 0.08 and 0.13 QALY gains, respectively.

[44] See Medicare Prescriber Part D Public Use Files: `https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/PartD2013`

optimal time—that they know which LEs are on net more cannibalizing than market expanding, and that they introduce the cannibalizing set later. Due to data limitations, I also do not account for competition, which could change the extent to which LEs within different technological categories could be market expanding. Future work will leverage claims and indication data to examine the market expansion parameter of different LEs with more nuance. Still, this paper suggests that firms are making strategic decisions on the timing of their LEs, that they delay LEs in response to regulatory exclusivity periods that start upon approval, and that their responses are meticulously calibrated given the characteristics of their product portfolios.

Legislation is pending in Congress that would give the Federal Trade Commission antitrust authority over some pharmaceutical reformulations.[45] However, these bills do not change the underlying incentive for strategic delay, which stems from the coupling of a LE's approval date with the start of its fixed-length exclusivity period.

Policies to mitigate incentives for strategic delay may involve decoupling the expiration of LE exclusivity from LE approval. One approach would be to award LEs exclusivity that starts upon their approval, but that expires at a set date after OF Expiry (e.g., three years after OF Expiry). This is similar to how pediatric exclusivity (additional regulatory exclusivity given for manufacturers who conduct pediatric trials) adds six months to a drug product's overall exclusivity time. Under such a time-bounded regulatory regime, firms would be unable to push the expiration of the LE's exclusivity to the future by delaying LE introductions. Further, LEs of different value relative to OFs could be assigned different exclusivity periods, but objectively assessing value is difficult. Extended release formulations, which are shown here to be subject to strategic delay, may have clinical benefits and are preferred by some consumers. However, simple dose changes, like Aricept 23, are more clear-cut examples of low value LEs that ought

[45] See S.1416–Affordable Prescriptions for Patients Act of 2019 (`https://www.congress.gov/bill/116th-congress/senate-bill/1416/text`) and H.R.4398–Affordable Prescriptions for Patients Through Promoting Competition Act of 2019 (`https://www.congress.gov/bill/116th-congress/house-bill/4398/text`).

to receive fewer exclusive marketing protections.

Changes to regulatory exclusivity periods are likely have general equilibrium effects on innovation, but such effects can be complex. Exclusivity periods that are decoupled from LE approval need not reduce incentives to conduct research on and introduce LEs or reduce incentives to develop OFs in the first place.

Though the development and introduction of new pharmaceutical products have made significant contributions to health and social welfare [Cutler et al., 2006, Lichtenberg, 2019], the strategic delay in LE introductions that I document in this paper leads to welfare losses, and run counter to the goals of the regulations that spur this delay. There is likely a welfare improving role for revising regulatory exclusivity periods for follow-on products such that they do not start at the time of drug approval.

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8 Tables

Table 1: Description of Line Extension Technological Categories

LE Type	Description
Combination	A combination LE includes the OF's active ingredient together with other active ingredients, which can be on- or off-patent. A fixed dose combination is an LE that combines these active ingredients in the same medication. Co-packaged LEs include the active ingredients as separate medications, but bundles them in the same package.
Route Expansion	A LE and OF have different routes of administration. The aggregated administration routes used in this paper are oral, injectable/IV, ophthalmic, inhaled, topical, and other, which includes implant, intravesical, otic, rectal and vaginal.
Formulation Change	A LE and OF have the same route of administration, but different formulations. For example, within the oral administration route, formulations include capsules, orally dissolvable tablets, syrups, tablets and granules, among others. Within the topical route of administration, formulations include gels, creams, ointments and lotions. Formulation changes may also be dose changes (see below).
Dose Change	Within the same route of administration, a LE has at least one product with a different active ingredient strength than the OF's products. Dose changes may also be formulation changes.
Extended Release (XR)	Extended, delayed, controlled or long-acting release LEs are formulations that allow a measured amount of the active ingredient to enter the body over time. These LEs can be taken fewer times than the OF.
Enantiomers or other Molecular Changes	The molecules in a chemical compound can exist in a variety of configurations called isomers. A special type of isomer is an enantiomer, which is a rotated mirror image of the chemical compound. Some OFs can have an enantiomer stripped away, leaving a LE. These LEs do not necessarily have the same clinical properties as the OF and as such may offer advantages to patients, like fewer side effects.
Non-Active Ingredient Changes	A LE might add non-active ingredients to an OF, such as flavoring, sweetener, or vitamins.

Table 2: Data Sources and Descriptions

Source	Description	Timeframe	Availability
Drugs@FDA Database	Data on all FDA prescription and over-the-counter branded and generic approvals since 1939.	Through 2016	Current version available at https://www.fda.gov/Drugs/InformationOnDrugs/ucm135821.htm
FDA Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)	Lists all non-expired patents and exclusivities for approved drugs, as well as therapeutically equivalent products to a branded drug.	1985-2016 and as of December 2018	1985-2016 data available at https://economics.mit.edu/faculty/heidiw/data. Current month available at https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
FDA National Drug Code (NDC) Directory	NDC-level data provided by firms on all drugs currently marketed. Excludes withdrawn and discontinued products.	As of 4/4/2017	Current version available at https://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm.
USPTO Patent Grant Authority Files	Include issue dates for all USPTO patents and are updated monthly.	Through 11/4/2018	Current month available at https://www.uspto.gov/patents-application-process/patent-search/patent-document-authority-files
USPTO List of Patent Terms Extended Under 35 USC §156	Includes all patents that received Hatch Waxman patent term restoration, and the product the patent is associated with.	Through 3/3/2019	Current version available at https://www.uspto.gov/patent/laws-and-regulations/patent-term-extension/patent-terms-extended-under-35-usc-156
WHO Collaborating Centre for Drug Statistics and Methodology	Index of Anatomical Therapeutic Chemical (ATC) codes and names.	As of 11/7/2018	Available at https://www.whocc.no/atc_ddd_index/
NIH National Library of Medicine RxClass Browser	A web application that categorizes active ingredients into therapeutic classifications.	As of 11/7/2018	Current version available at https://mor.nlm.nih.gov/RxClass/
Industry and Peer-Reviewed Publications	Best-Selling Drug Lists from sources like MedScape, Axios, Drugs.com, and Pharmacy Times.	Top 100 lists for 2001, 2003-2015. Top 12 list as of 1991, Top 20 as of 2017. Supplement with Top 12 for 1988-92 cohort, and web search.	Accessed through Harvard University Libraries and via web search
Pharmaceutical Executive Archives	A monthly publication that has annual lists of top 50 pharmaceutical firms by revenue, starting 1999.	1999-2019	Accessed through Harvard University Libraries

Table 3: Summary Statistics: Original Formulations (OFs)

	All OFs			OFs without LEs			OFs with LEs		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Approval to Expiry (years)	710	9.98	3.90	444	9.58	3.79	266	10.66	4.00
Top 20 Firm	710	0.45	0.50	444	0.40	0.49	266	0.53	0.50
Best Seller	710	0.21	0.41	444	0.12	0.33	266	0.35	0.48
Orphan Drug Exclusivity	710	0.27	0.44	444	0.34	0.48	266	0.14	0.35
Patent Count	710	4.05	4.37	444	4.19	4.55	266	3.80	4.05
Products in NDA	710	2.20	1.55	444	2.05	1.54	266	2.45	1.54
	N	**%**		**N**	**%**		**N**	**%**	
OF Vintage									
1985-1989	88	12%		39	9%		49	18%	
1990-1994	108	15%		57	13%		51	19%	
1995-1999	166	23%		89	20%		77	29%	
2000-2004	112	16%		70	16%		42	16%	
2005-2009	86	12%		61	14%		25	9%	
2010-2016	150	21%		128	29%		22	8%	
OF Route									
Dermal	33	5%		19	4%		14	5%	
Inject/IV	182	26%		146	33%		36	14%	
Ophtalmic	30	4%		18	4%		12	5%	
Oral	433	61%		243	55%		190	71%	
Other	6	1%		3	1%		3	1%	
Respiratory	26	4%		15	3%		11	4%	
OF 1st Level Class									
A: Alimentary Tract	82	12%		44	10%		38	14%	
B: Blood	37	5%		33	7%		4	2%	
C: Cardiovascular	79	11%		44	10%		35	13%	
D: Dermatologicals	29	4%		15	3%		14	5%	
G: Genito Urinary	27	4%		17	4%		10	4%	
H: Systemic Hormonal	14	2%		10	2%		4	2%	
J: Antiinfectives	95	13%		46	10%		49	18%	
L: Antineoplastic	117	16%		99	22%		18	7%	
M: Musculo-Skeletal	27	4%		15	3%		12	5%	
N: Nervous System	103	15%		58	13%		45	17%	
P: Antiparasitics	14	2%		11	2%		3	1%	
R: Respiratory	23	3%		9	2%		14	5%	
S: Sensory Organs	30	4%		18	4%		12	5%	
V: Various	14	2%		9	2%		5	2%	
Missing	19	3%		16	4%		3	1%	

Note: OF stands for Original Formulation. LE stands for Line Extension Vintage refers to the year in which an original formulation was approved by the Food and Drug Administration.

Table 4: Original Formulation-Line Extension Pairs by Technological Category

LE Type	Description	All OF-LE Pairs		Pairs with LE Drug Substance Patent		Pairs without LE Drug Substance Patent	
		N	%	N	%	N	%
Combination	Co-packaged or fixed dose combination	131	25.0%	75	40.8%	56	16.4%
Route Expansion	Administration route change (e.g., injection to oral)	66	12.6%	21	11.4%	45	13.2%
Form Change Only	Within same route, formulation change (e.g., tablet to syrup; tablet to capsule)	74	14.1%	15	8.2%	59	17.3%
Dose Change Only	Within same form, quantity of active ingredient changes	66	12.6%	12	6.5%	54	15.8%
Form and Dose Change	Within same route, formulation changes and quantity of active ingredient changes	110	21.0%	39	21.2%	71	20.8%
Extended Release	Extended, delayed, controlled or long-acting release	46	8.8%	15	8.2%	31	9.1%
Other	Non-active ingredient and other chemical changes	32	6.1%	7	3.8%	25	7.3%
Total		525	100.0%	184	100.0%	341	100.0%

Note: OF stands for Original Formulation. LE stands for Line Extension. Drug substance patents refer to patents on the active ingredient or molecular entity, as flagged in the Food and Drug Administration Orange Book. Line extensions with drug substance patents are those that have a separate patent that was not originally associated with the original formulation.

Table 5: Line Extension Approvals in First Two Years of OF Approval, by Line Extension Technological Category

First LE of each Type per OF (LEs without own drug substance patent)	% in First 2 Years from OF Approval	N
Extended Release	0%	31
Other LEs	4%	23
Dose Change Only	9%	44
Combination	20%	51
Form Change Only	22%	46
Route Expansion	29%	41
Form and Dose Change	33%	58
All LE Types	19%	294

Note: OF stands for Original Formulation. LE stands for Line Extension. The table includes only unpatented LEs and only the first LE of each type per OF. As a result there are 294 LEs total. "Other" LEs is a heterogeneous group that includes those with a molecular or active ingredient change (like an enantiomer), LEs that were otherwise innovative (like those approved as "Type 2 - New Chemical Entity") and LEs that had changes to non-active ingredients.

Table 6: Summary Statistics: Line Extensions in Unpatented to Patented Comparison

	LEs without Drug Substance Patents			LEs with Drug Substance Patents			
	N	**Mean**	**SD**	**N**	**Mean**	**SD**	**Difference**
LE Approval relative to OF Expiry (years)	288	-1.8	6.21	97	-7.17	4.71	5.36***
OF Approval to OF Expiry (Years)	288	9.76	4.05	97	13.92	1.74	-4.16***
LE Order per OF	288	2.05	1.44	97	2.25	1.78	-0.2
Top 20 Firm	288	0.51	0.5	97	0.59	0.49	-0.08
OF is a Best Seller	288	0.34	0.47	97	0.57	0.5	-0.23***
OF had a LE approved in first 90 days	288	0.1	0.3	97	0.09	0.29	0.01
OF Patent Count	288	2.81	3.1	97	5.48	4.29	-2.68***
OF Number of Products	288	2.22	1.48	97	3.05	1.86	-0.83***
OF had Orphan Drug Exclusivity	288	0.09	0.29	97	0.16	0.37	-0.07*
OF Approval Year	288	1992.96	5.21	97	1999.11	4.14	-6.15***

Note: OF stands for Original Formulation. LE stands for Line Extension. The LEs with drug substance patents in this table excludes those that are innovative (i.e., enantiomers, those approved as new chemical entities, and those that are otherwise innovative) as described in the Empirical Approach section. *** $p<0.01$, * $p<0.1$.

Table 7: Difference in Mean Approval Time Between Line Extensions with and without Drug Substance Patents

OLS Regression Results LE approval relative to OF Expiry (years)	(1)	(2)	(3)
Patented LE	-1.906** (0.737)	-2.017*** (0.716)	-1.797** (0.703)
OF Market Life	-0.815*** (0.0749)	-0.798*** (0.0794)	-0.805*** (0.0788)
OF Vintage and LE Order	Y	Y	Y
Drug Characteristics		Y	Y
LE Technological Category			Y
Constant	3.731*** (0.922)	2.224* (1.319)	4.038** (1.554)
Observations	385	382	382
R-squared	0.522	0.594	0.606

Note: OF stands for Original Formulation. LE stands for Line Extension. Dependent variable is t, the time between OF Expiry and LE approval. Robust standard errors in parentheses, clustered at the OF level. *** p<0.01, ** p<0.05, * p<0.1. Drug characteristics include OF Patent Count, OF Number of Products, OF Orphan Drug Exclusivity, Top 20 Firm by Revenue, OF was Best Seller, OF had LE in first 90 days, OF Route and OF Therapeutic Class.

Table 8: Survival Analysis Results

Hazard Ratios	(1) All Unpatented LEs	(2) Comparable Patented LEs
OF Characteristics		
OF Market Life	1.001	1.158***
	(0.0252)	(0.0441)
Top 20 Firm	1.051	0.946
	(0.129)	(0.174)
Best Seller	2.066***	1.874***
	(0.315)	(0.355)
OF Patent Count	0.986	1.066***
	(0.0188)	(0.0202)
OF Product Count	1.022	1.059
	(0.0506)	(0.0637)
OF Orphan Drug Exclusivity	0.522***	1.245
	(0.112)	(0.328)
Had LE in First 90 Days	0.901	1.047
	(0.191)	(0.294)
OF Vintage		
1990-1994	0.908	1.380
	(0.148)	(0.816)
1995-1999	0.505***	3.771**
	(0.0856)	(1.995)
2000-2004	0.425***	5.201***
	(0.0900)	(2.807)
2005-2009	0.240***	4.731***
	(0.0845)	(2.657)
2010-2016	0.160***	5.441***
	(0.0847)	(3.235)
Years to/from OF Expiry		
-3 to +1	1.964***	0.358**
	(0.404)	(0.157)
+1 and after	1.239	1.107
	(0.396)	(0.546)
OF Administration Route	Y	Y
Therapeutic Class	Y	Y
Number of Failures	312	145
Number of Subjects	691	691

Note: OF stands for Original Formulation. LE stands for Line Extension. Coefficients are Hazard Ratios. Standard errors in parentheses, clustered at the OF level. *** p<0.01, ** p<0.05, * p<0.1.

Table 9: Survival Analysis Results for Line Extensions of Different Technological Categories

Hazard Ratios	(1) Combo	(2) Route	(3) All Form	(4) Form Only	(5) All Dose	(6) Dose Only	(7) XR
OF Characteristics							
Market Life	0.984	1.024	0.994	1.047	1.009	1.099	1.048
	(0.0627)	(0.0834)	(0.0459)	(0.0722)	(0.0510)	(0.0958)	(0.121)
Top 20 Firm	1.018	1.395	1.179	0.913	1.050	0.802	0.851
	(0.298)	(0.482)	(0.248)	(0.275)	(0.222)	(0.258)	(0.338)
Best Seller	2.170**	1.638	2.526***	3.017***	1.850**	1.647	2.671**
	(0.710)	(0.781)	(0.681)	(1.264)	(0.506)	(0.753)	(1.241)
Patent Count	0.964	0.961	1.015	1.022	0.964	0.912	1.011
	(0.0492)	(0.0634)	(0.0285)	(0.0409)	(0.0345)	(0.0643)	(0.0521)
Product Count	0.978	0.807	1.006	1.055	0.915	0.854	1.322**
	(0.124)	(0.129)	(0.0904)	(0.128)	(0.0937)	(0.142)	(0.167)
Orphan Drug Exc.	0.248*	0.681	1.109	1.013	0.435**	0.0849***	0.634
	(0.188)	(0.350)	(0.339)	(0.524)	(0.147)	(0.0657)	(0.409)
LE in 1st 90 Days	0.577	0.616	0.732	0.911	1.016	2.184	0.853
	(0.323)	(0.401)	(0.256)	(0.414)	(0.382)	(1.197)	(0.690)
Years to/from OF Expiry							
-4 to -2	1.755	1.984	1.636	2.090	1.877	3.020	2.519
	(0.940)	(1.249)	(0.649)	(1.151)	(0.815)	(2.041)	(2.343)
-2 to 0	2.246	1.243	1.417	1.232	2.140	3.355	8.123**
	(1.398)	(0.995)	(0.645)	(0.806)	(1.025)	(2.509)	(7.476)
0 to 2	0.914	0.658	1.660	1.146	2.984**	5.656**	3.768
	(0.728)	(0.675)	(0.857)	(0.910)	(1.614)	(4.973)	(4.263)
2+	0.813	2.166	0.881	0.708	2.762	10.83**	6.600
	(0.751)	(2.438)	(0.604)	(0.721)	(1.978)	(12.25)	(9.932)
OF Admin Route	Y	Y	Y	Y	Y	Y	Y
OF Vintage	Y	Y	Y	Y	Y	Y	Y
Therapeutic Class	Y	Y	Y	Y	Y	Y	Y
Number of Subjects	691	691	691	691	691	691	691
Number of Failures	56	39	111	54	108	51	31

Note: OF stands for Original Formulation. LE stands for Line Extension. Coefficients are Hazard Ratios. Standard errors in parentheses, clustered at the OF level. *** p<0.01, ** p<0.05, * p<0.1

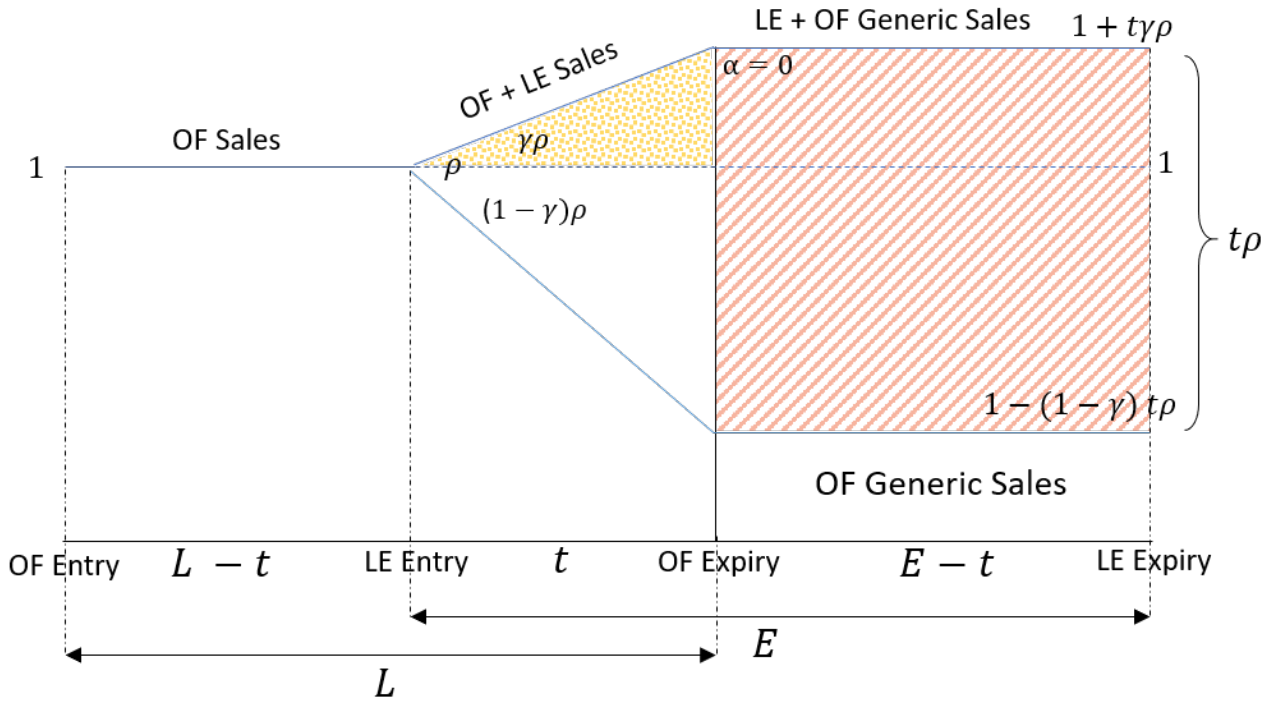
Table 10: Average Delay per Line Extension

Type of LE (without drug substance patents)	Average delay per LE In months	In years
All LEs (includes "Other")	12	1.03
Extended Release and Dose Change Only LEs	30	2.48
Route Expansion, All Formulation Change, Combination LEs	5	0.39

Note: OF stands for Original Formulation. LE stands for Line Extension. The estimates of delay per line extension shown in this table are an interpretation of the hazard ratios shown in Tables 8 and 9.

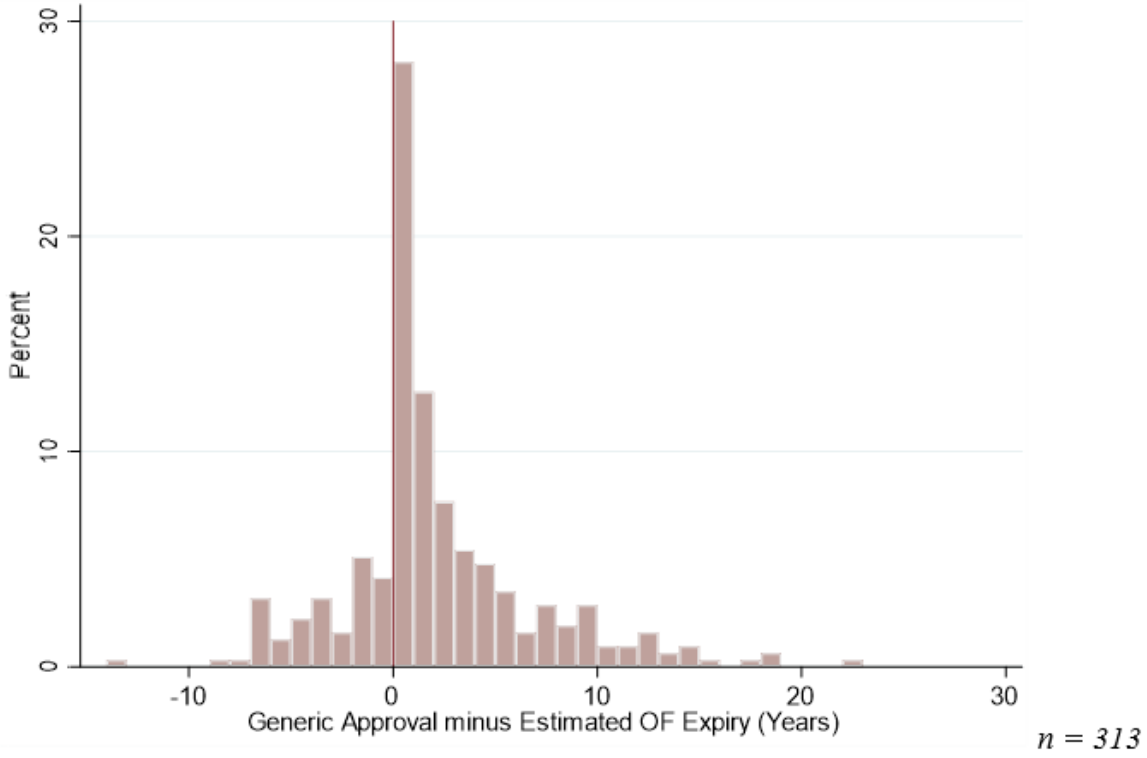
9 Figures

Figure 1: Model of Line Extension Introduction Timing (Base Case)



Note: OF stands for Original Formulation. LE stands for Line Extension. L is the OF's market life from approval to OF Expiry. E is the LE's market life from approval to LE Expiry (often three years). ρ is the LE adoption parameter. γ is the market expanding parameter or the share of LE sales that is market expanding. These values are known to the firm. α, which is zero in the base case, determines the rate of LE sales after OF Expiry.

Figure 2: Distribution of Difference between Estimated Original Formulation Expiry and First Generic Entry



Note: OF stands for Original Formulation. This graph looks at the difference between my calculated OF Expiry measure (a proxy for generic entry) and actual generic entry for the 313 OFs in my sample that had a generic.For 75% of OFs, those on the right of the graph, generic entry occurred *after* calculated OF expiry. Roughly 30% of OFs in this sample had generics enter within a year of calculated OF Expiry.

Figure 3: Histograms of $L - t$

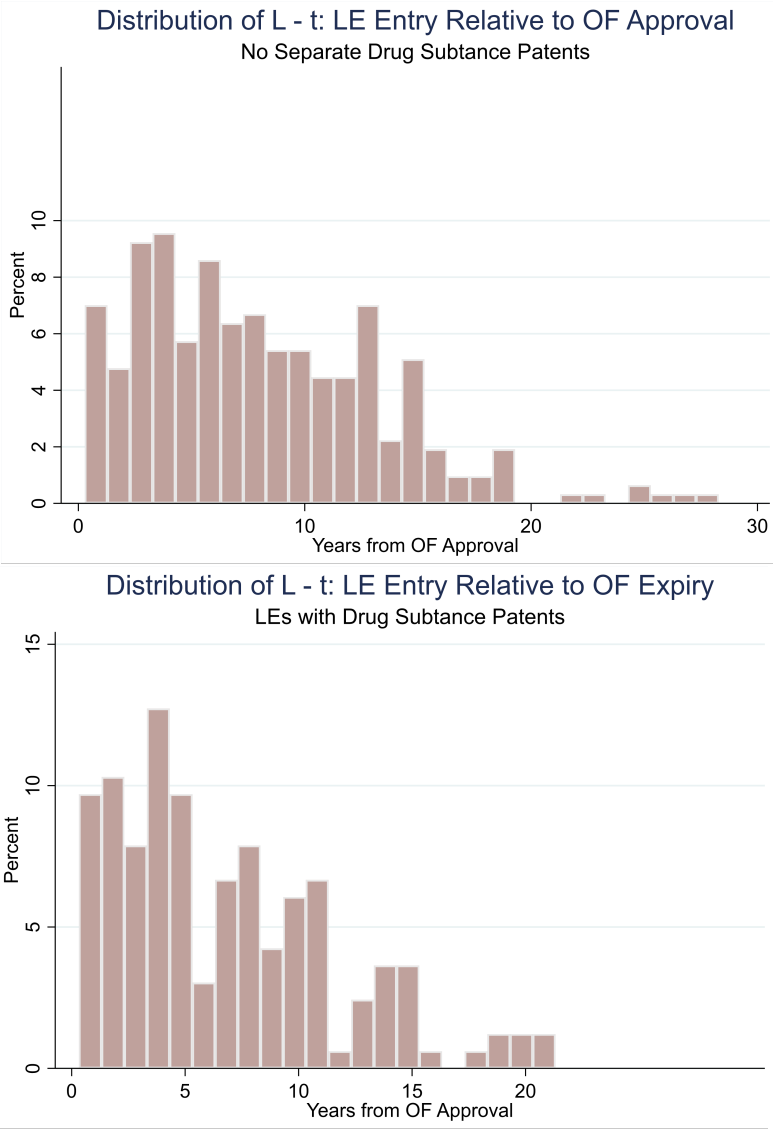


Figure 4: Histograms of t

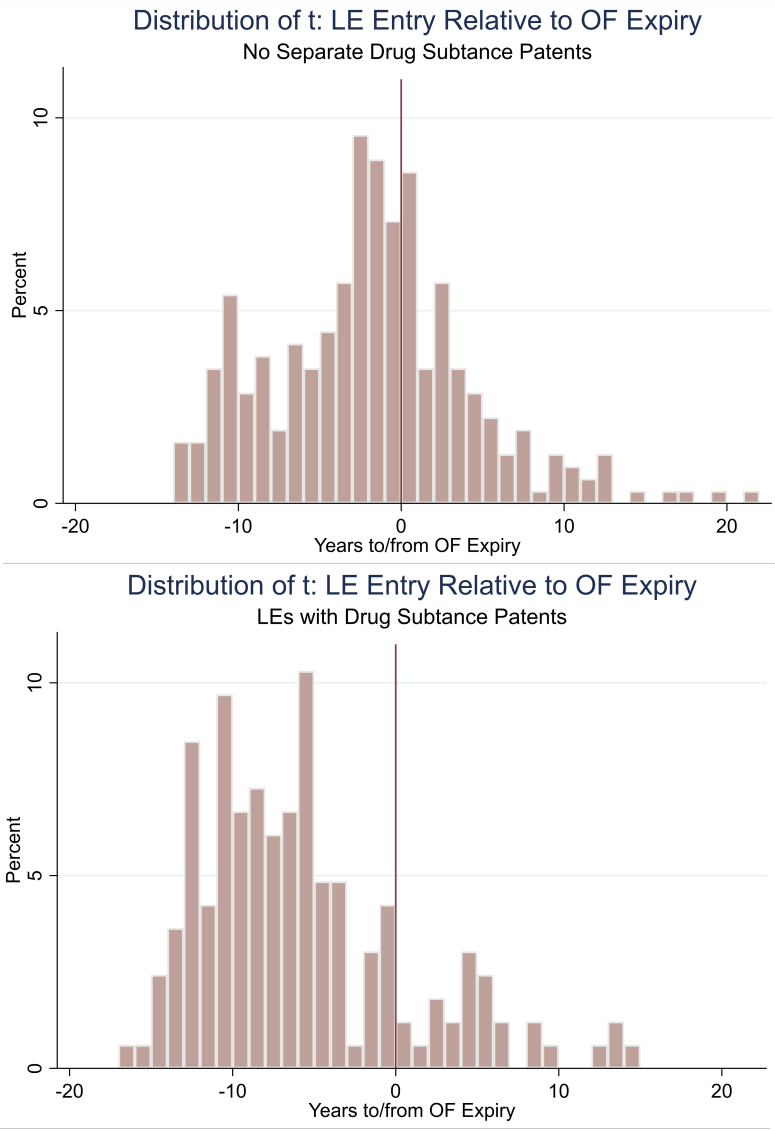
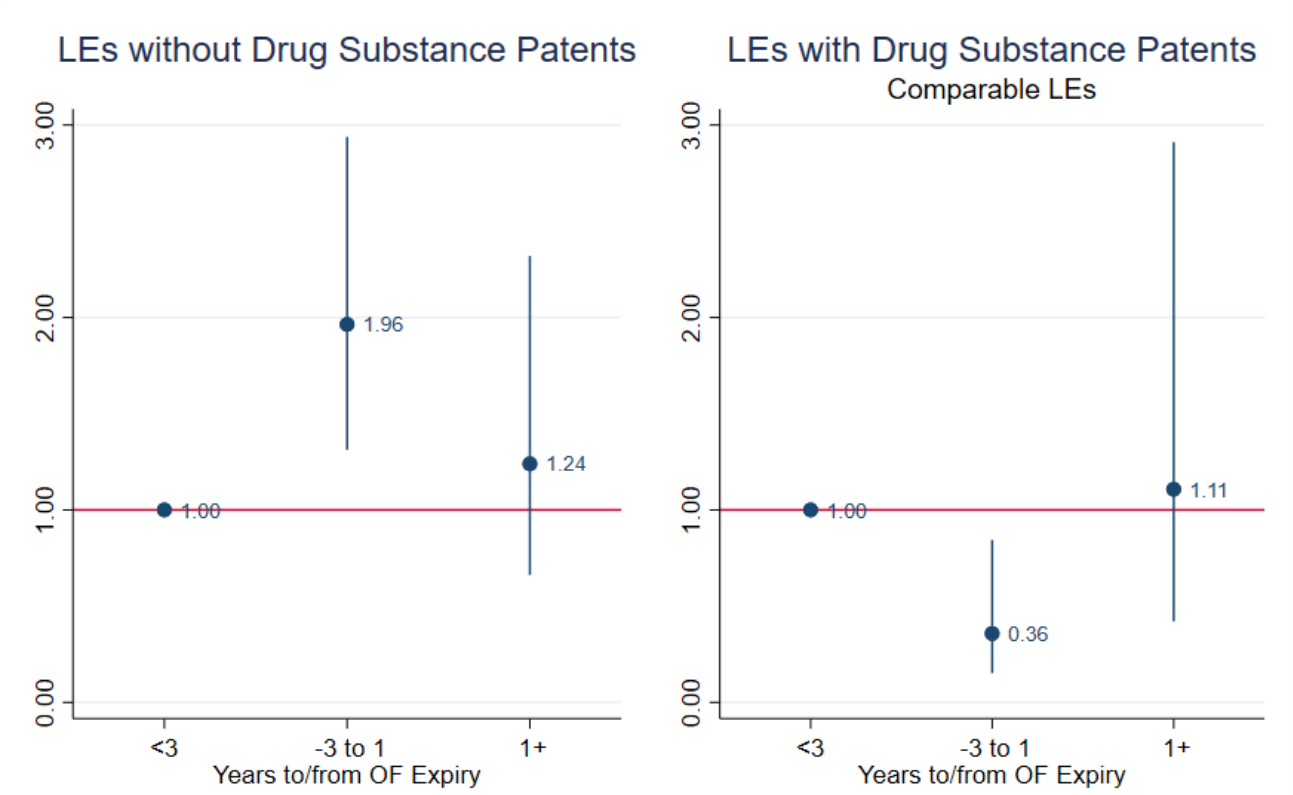
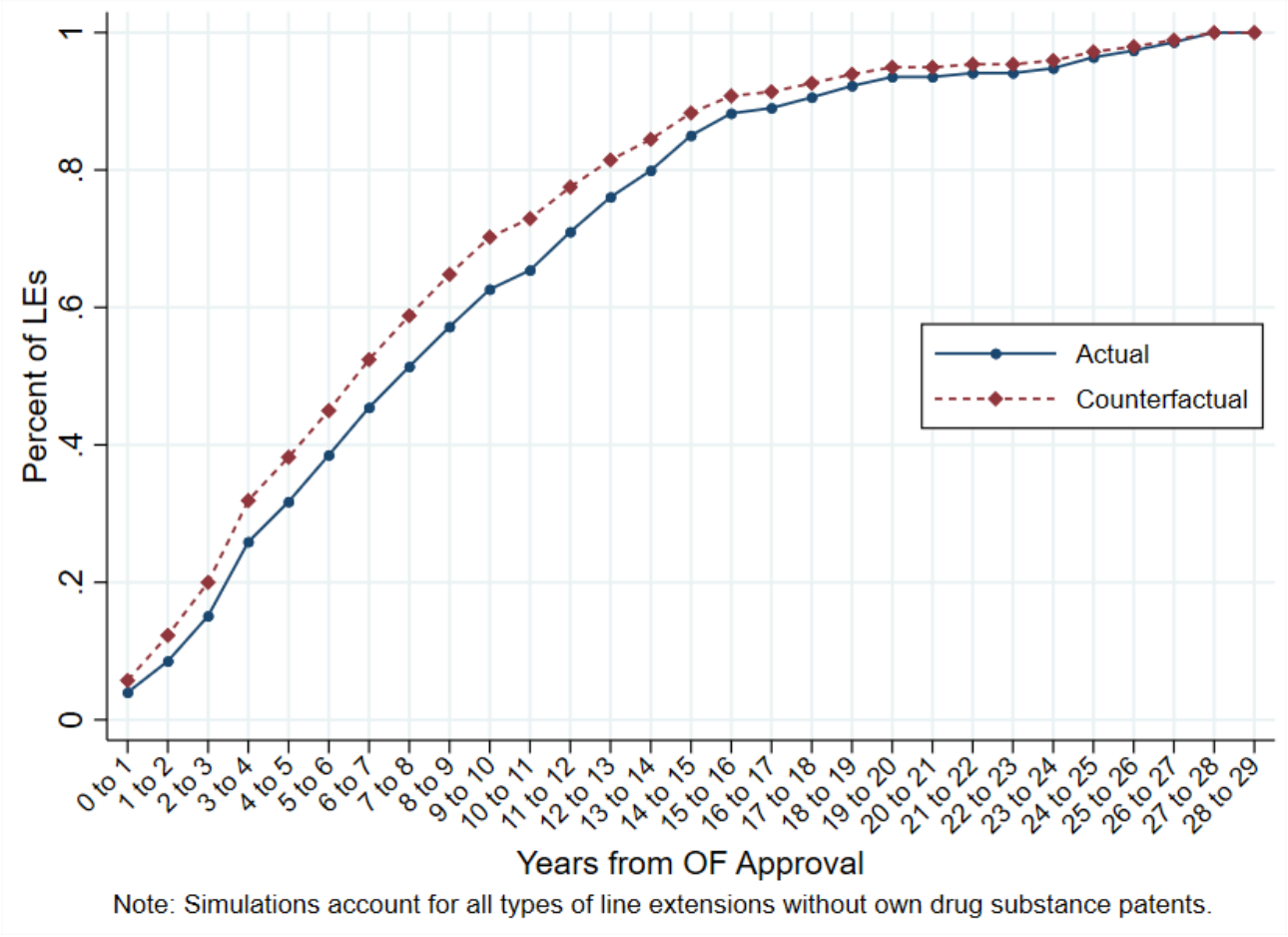


Figure 5: Coefficients on Periods k Around OF Expiry



Note: Graph shows hazard ratios that represent the time-varying effect of the hazard rate of an OF having an LE approved at different periods leading up to and beyond OF Expiry, per table 8. The left panel shows hazard ratios for LE approvals where the LE is subject to exclusivity, and as a result the firm has an incentive for strategic delay. The right panel is a falsification test that uses comparable LEs that had drug substance patents, and as such did not have a similar incentive for strategic delay.

Figure 6: Percent of Simulated Line Extensions Approved by Elapsed Year



Note: Simulations account for all types of line extensions without own drug substance patents. The counterfactual scenario assumes no time-varying changes to the hazard rate of line extension approvals in the periods around Original Formulation Expiry. The transition probabilities used in this simulation take into account the control variables used in the survival analysis.

Appendix

A Further Detail

A.1 Line Extension and Original Formulation Examples

Abilify and Abilify Maintena

Manufacturer: Otsuka

Active ingredient: aripiprazole

OF: Abilify, an oral tablet of 2 mg, 5 mg, 10 mg, 15 mg, 20 mg or 30 mg, approved as an antipsychotic in November 2002

LE: Abilify Maintena, an intramuscular extended-release suspension of 300mg or 400 mg, approved as an antipsychotic in February 2013

Namenda and Namenda XR

Manufacturer: Forest Labs

Active ingredient: memantine

OF: Namenda, an oral tablet of 5 mg or 10 mg, approved to treat Alzheimer's Disease in October 2003

LE: Namenda XR, an oral extended-release capsule of 7 mg, 14 mg, 21 mg or 28 mg, approved to treat Alzheimer's Disease in June 2010

Januvia and Janumet

Manufacturer: Merck

Active ingredient: sitagliptin

OF: Januvia, an oral tablet of 25 mg, 50 mg, or 100 mg, approved to treat type 2 diabetes in October 2006

LE: Janumet, a fixed dose combination oral tablet of stigaliptin and metformin, a generic often considered the first-line treatment for type 2 diabetes. Approved in March 2007 as 50 mg sitagliptin/500 mg metformin or 50 mg sitagliptin/1000 mg metformin to treat type 2 diabetes.

Norvasc, Lipitor and Caduet

Manufacturer: Pfizer

Active ingredients: amlodipine besylate, atorvastatin.

OF: Norvasc (amlodipine besylate), an oral tablet of 2.5 mg, 5 mg and 10 mg, approved to treat hypertension in July 1992

OF: Lipitor (atorvastatin), an oral tablet of 10 mg, 20 mg, 40 mg and 80 mg, approved to lower cholesterol in December 1996

LE: Caduet, a fixed dose combination oral tablet of amlodipine besylate/atorvastatin in 5/10 mg, 10/10 mg, 5/20 mg, 10/20 mg, 5/40 mg, 10/40 mg, 5/80mg and 10/80 mg, approved to treat cardiovascular disease in January 2004

A.2 Monte Carlo Simulations

The cumulative hazard function at time t is denoted H_t. It is calculated as the risk score for each observation times the baseline cumulative hazard function evaluated at time t. Empirically, I first evaluate the baseline cumulative hazard function at each elapsed year 0 through 32. These values are the same for each OF.

Each OF has up to five risk scores that correspond to periods around OF Expiry, as defined by k. I map these onto elapsed time. For instance, the two-year period leading up to OF Expiry might actually correspond to elapsed years 9 to 11 from approval for a given OF. I multiply the baseline cumulative hazard values by each observation's predicted risk score for the years that correspond to the correct timeframe, and get cumulative hazard H_{it}. When risk scores for an

OF span the same elapsed year, I weight risk scores accordingly. This yields cumulative hazard values for years 0 through 32 for each OF.

For each OF, $Pr(t)$ is the probability of having a LE approved in the year leading up to t, and is equal to $H_{it} - H_{it-1}$ for integer ts from 1 to 32. I use these transition probabilities to simulate 32 years of LE approvals for every OF in the sample, running each OF 1,000 times.

B Tables

Table B.1: Original Formulation-Line Extension Data Construction

NDAs	Sample and Restrictions
2,628	Prescription NDAs approved from 1985-2016
2,565	Excluding NDAs for medical gases
2,562	Excluding NDAs listed as OTC in NDC data
767	Approved as Type 1 – New Molecular Entity or Type1/4 where a New Molecular Entity is combined with long-time generic
710	Excluding diagnostic and therapeutic radiopharmaceuticals, urea breath tests, and contrast agents [**OF Sample**]
1,664	Approved as Types 2-5 and remaining Type 1/4, and is not designated as an authorized generic [**Potential LEs**]
131	Approved as Types (6-10) or flagged as authorized generics [**Excluded**]

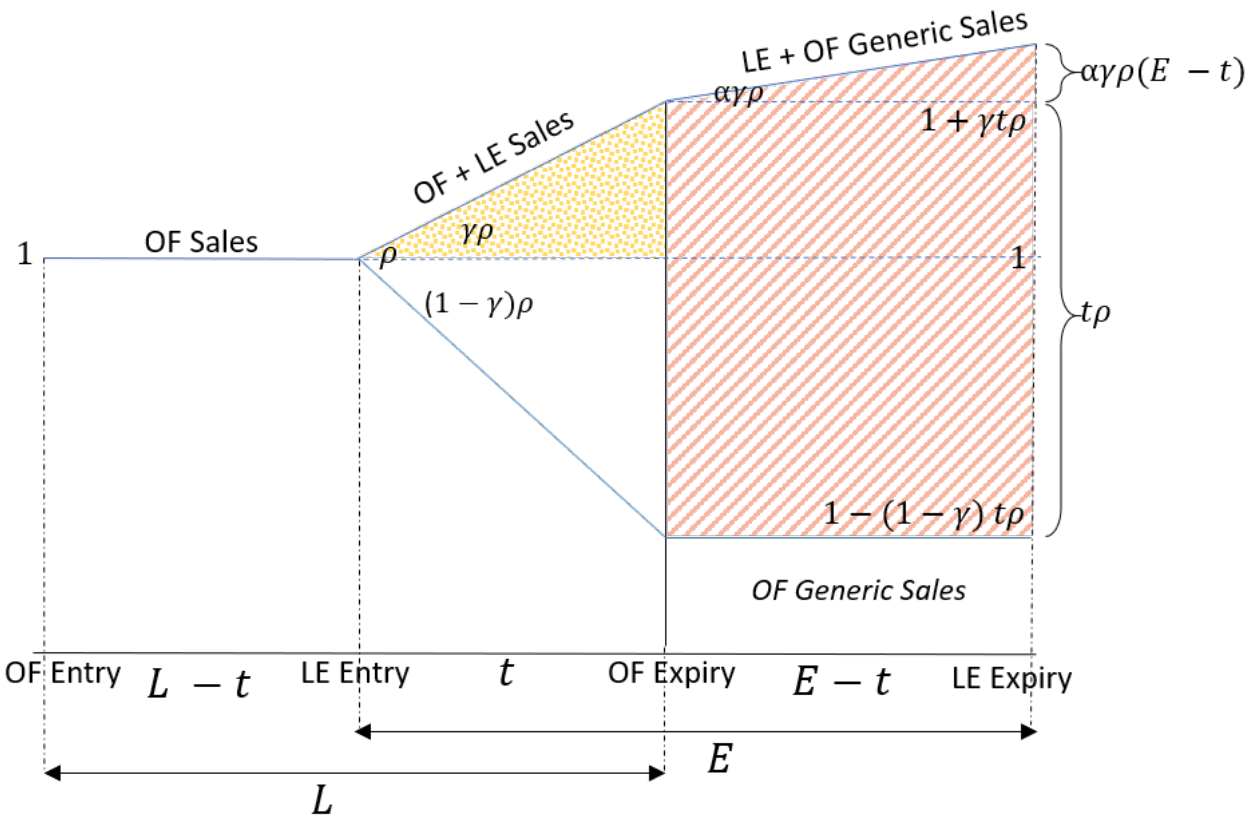
OF NDAs	
444	OF NDAs without LEs
266	OF NDAs with at least one LE
710	Unique OF NDAs in dataset

OF-LE Pairs	
341	LEs without own drug substance patent
184	LEs with own drug substance patent
525	Unique OF-LE pairs in dataset

Note: OF stands for Original Formulation. LE stands for Line Extension. NDA stands for New Drug Application, which firms must submit to the Food and Drug Administration for regulatory approval. OTC stands for over-the-counter, which are excluded because they are not affected by generic entry in the same way as prescription drugs. NDC stands for National Drug Code.

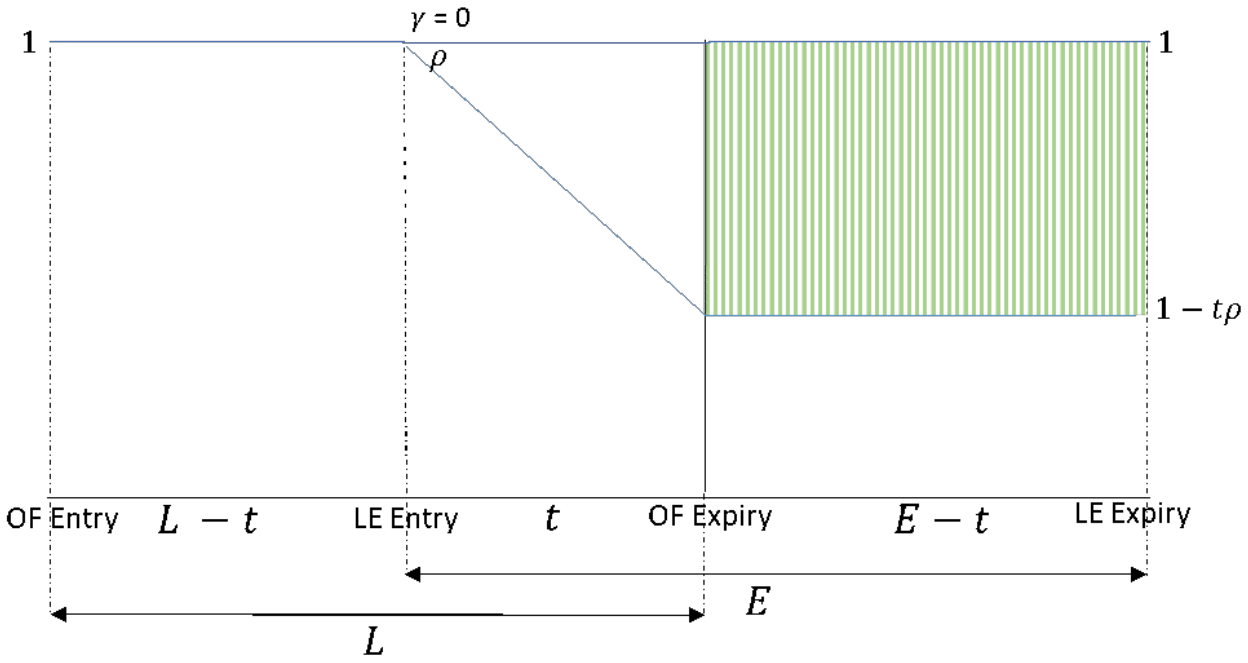
C Figures

Figure C.1: Model of Line Extension Introduction Timing (General Case)



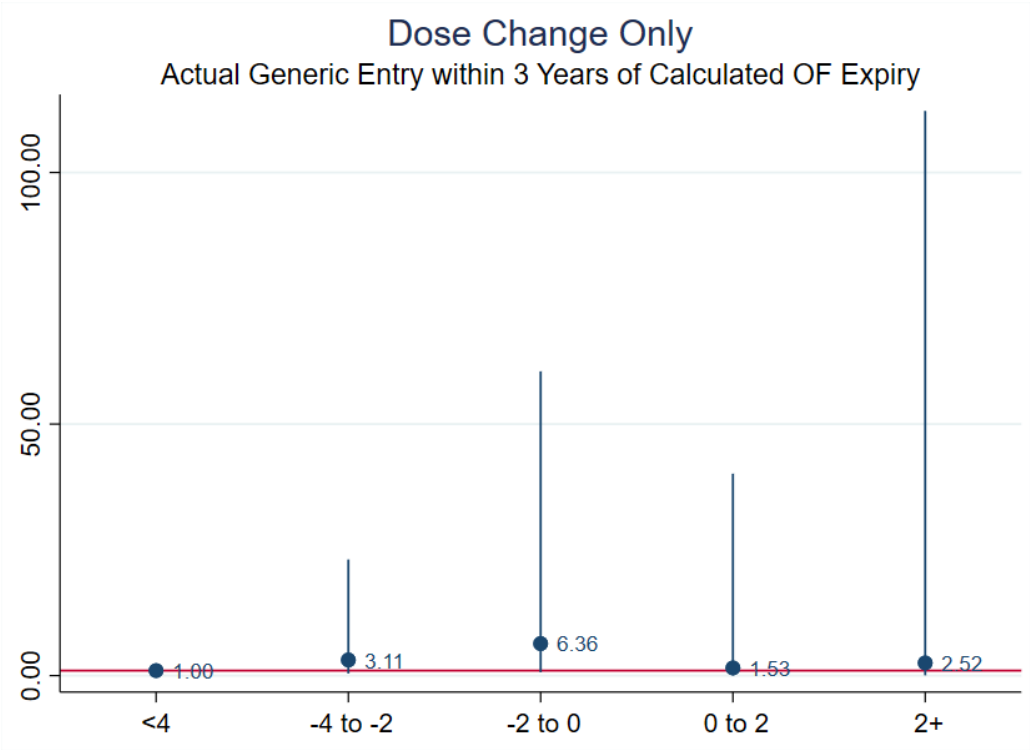
Note: OF stands for Original Formulation. LE stands for Line Extension. L is the OF's market life from approval to OF Expiry. E is the LE's market life from approval to LE Expiry (often three years). ρ is the LE adoption parameter. γ is the market expanding parameter or the share of LE sales that is market expanding. α determines the rate of LE sales after OF Expiry. These values are known to the firm.

Figure C.2: Model of Line Extension Introduction Timing (No Market Expansion)



Note: OF stands for Original Formulation. LE stands for Line Extension. L is the OF's market life from approval to OF Expiry. E is the LE's market life from approval to LE Expiry (often three years). ρ is the LE adoption parameter. γ is the market expanding parameter or the share of LE sales that is market expanding, and in this case is equal to zero. These values are known to the firm.

Figure C.3: Coefficients on Periods k Around OF Expiry for Subset of Dose Change Only LEs



Note: Graph shows hazard ratios. Sample of failures is subset to dose change only LEs where actual generic entry was within three years of calculated OF expiry.