Essays on Pharmaceutical and Health Insurance Markets

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A dissertation presented

by

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to

The Committee on Higher Degrees in Health Policy

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

in the subject of

Health Policy (Economics)

Harvard University

Cambridge, Massachusetts

April 2020

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Abstract

Pharmaceutical policy must balance two objectives: promoting new drug development and pricing drugs to ensure access. Though pharmaceutical innovation has made significant contributions to health and social welfare, drug costs are rapidly increasing. This combination makes it essential to understand how both regulation and market dynamics shape pharmaceutical innovation, coverage, and prices.

Chapter One studies pharmaceutical firm decisions on the timing of follow-on product introductions. Follow-on drugs, termed line extensions, receive a fixed exclusivity period that starts upon approval. 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 their 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 this prediction 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 in the 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. Delays in the introduction of new products can create welfare losses for consumers and payers, and I consider implications for optimal innovation policy.

Chapter Two (with Thomas McGuire) develops a diagrammatic model of the static and dynamic tradeoff in pharmaceutical markets. Using this framework, we examine the role of different health care financing institutions, specifically, health insurance for drugs and pharmacy benefit management firms (PBMs) on both static and dynamic efficiency. Insurance can help on both margins by decoupling the price paid by the consumer and the price received by the pharmaceutical firm. In what we refer to as a "competitive" PBM, discounts are fully passed on to health plans. In this case, the PBM has no effect on the tradeoff between dynamic and static efficiency but may affect the equilibrium. By contrast, a PBM with market power keeps some or all discounts, degrading the tradeoff. If PBM profits come from pharmaceutical firms, these firms have less incentive to invest in innovation. If PBM profits come at the expense of higher prices to consumers, efficient drug consumption is curtailed. Our framework emphasizes how prescription drug policy reforms can have effects, either intended or unintended, on both innovation and access.

Chapter Three studies variation in Medicare Part D prescription drug coverage. Part D was designed to increase drug competition by allowing plans and PBMs to selectively contract with drug manufacturers. Though Part D plans must be at least actuarially equivalent to an annual "standard benefit," PBMs and plans have flexibility on what products they include in their benefit and at what cost sharing levels. To compare plan coverage, I define three measures of class-level drug insurance generosity. Using Part D plan benefit data 2016 and novel data on the PBM each plan was associated with, I describe Part D coverage for ten therapeutic classes, including protected classes, classes with no generics, and classes where products are more likely to be close substitutes. I discuss findings through the lenses of coverage generosity, clinical adequacy, and PBM differences.

Table of Contents

Acknowledgements

The six years I have spent at Harvard have been some of the most enriching and intellectually fulfilling of my life. Many people have supported me as I set out to become a Health Economist. First, I am grateful to my dissertation committee: Thomas McGuire, David Cutler, Michael McWilliams, and Ariel Stern. They are very much a dream team of mentors. Each has pushed me to be a better researcher—more rigorous and precise in my thought, more confident and convincing as I frame and present my work—and to tie my research to real-world implications. To my committee: thank you for your support, encouragement, wisdom, sense of humor, and time.

I am also grateful to Debbie Whitney, Colleen Yout and Jessica Livingston for everything they have done to support the Health Policy PhD program and its students. I always knew that I could rely on my program's administration, which has given me immense peace of mind. I am glad to have gotten to know Debbie and Colleen over the past few years, and they are resourceful, competent, and caring. Health Policy faculty members have also been helpful and influential in my tenure as a graduate student, in particular Joe Newhouse and Amitabh Chandra, who I taught for, and David Grabowski and Haiden Huskamp, who were co-authors on my first peer-reviewed piece, and who guided me and encouraged me through that process. Three of my undergraduate professors at Middlebury College, Paul Sommers, John Maluccio, and Casey Rothschild, have also been wonderfully supportive years after I was their student.

Other staff members across Harvard University and the National Bureau of Economic Research have been extraordinarily organized, helpful, and patient with me as I have scheduled meetings, worked with data, configured computers, and applied for jobs. I would like to thank Sarah Chambers, Mary Hurley, Kim McDougall, Liz Haak, Vanessa Azzone, Steve Rabideau, Young Sul, Kenny Lau, Kelsey Robinson, Jean Roth, Mohan Ramanujan, and many others. I also want to acknowledge support from the National Institute of Aging of the National Institutes of Health

under award P01AG032952, and support from the Value of Medical Research Pre-Doctoral Fellowship via the National Institute of Aging of the National Institutes of Health through grant R24AG058049 and via the Economic and Social Research Council through grant ES/M008673/1.

Another big thank you goes to more senior students of our program, as well as post-docs at the Department of Health Care Policy. Daria Pelech, Hannah Neprash, Katherine Donato, Caitlin Carroll, Jeannie Fuglesten Biniek, Eric Roberts, and Brian McGarry were especially generous with their advice, perspective, and time.

And of course, graduate school would not have been the same had it not been for my friends and our memorable moments. My cohort-mates Julia Dennett, Adrian Garcia Mosqueria, and Vidit Munshi have been encouraging, supportive, and hilarious at all the right times. As a graduate student, I also had the pleasure of getting to know Alicia DeSantola, Hanna Katz, and Natasha Patel-Murray. They are some of my dearest friends and have listened to practice seminar talks, helped me prepare for the job market, and made my life as a student a lot of fun. Meeting Erik Sand during graduate school was serendipitous and magical, and I look forward to our next chapter.

I would not be where I am now without my loving family. My parents, Adrian and Narcy Fowler, taught me to dream big, work hard, and keep grounded. My uncle, Tony Stanford, has been encouraging and supportive throughout my life, and especially during my PhD. He has been my biggest academic champion and has shared helpful insights on graduate student life. My sister, Rachel Fowler, inspires me every day with her policy-relevant work and broad perspectives. My grandmother, Josephine Fowler, enriched my life in countless ways, and my grandparents, Raquel and Ricardo Duran, continue to do so. Finally, though I never met him, I often think about my grandfather, Frank Fowler. Frank was a doctor who made important contributions to the UK National Health Service as an administrative medical officer. This dissertation is in his honor.

Chapter 1

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

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1.1 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 United States market, 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 entry, 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 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.

[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.

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 NMEs 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. Second, once a LE enters the market, some consumers may switch from the OF to the LE because 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

[3] Appendix A provides a set of illustrative examples of LE products vis-a-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

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

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 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

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

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 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

[8] "Cannibalization" in this context refers to OF sales that are lost when OF consumers switch to the 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 OF patients, those who switched to the LE will pay higher branded prices (rather than generic prices) for duration 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 LE 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 losses due to each of these mechanisms is similar in magnitude: rough calculations place it at roughly $4,000 per product-patient. However, the incidence of this loss can vary. 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 decoupling exclusivity periods from approval, which need not decrease incentives for innovation.

This paper contributes to various literatures. First, it joins a body of work in economics, law and business that documents "life-cycle management" strategies in pharmaceutical markets.[10] This

[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.

[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)

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 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.

1.2 Background and Regulatory Context

1.2.1 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

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.

grant pharmaceutical firms time-limited monopolies on NMEs 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] Patent validity can be challenged in court by potential generic entrants, creating uncertainty for firms on when patent protection will effectively expire (i.e., when generics will enter). Pharmaceuticals can have additional patents that cover other attributes of the drug and methods of use, but primary drug substance patents are harder for generic manufacturers to successfully challenge in court (Hemphill and Sampat, 2012). The United States Hatch-Waxman Act, signed into law 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 temporary monopolies 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: NMEs approved for the first time receive five years, drugs that treat orphan conditions receive seven, and drugs that are not NMEs but required new clinical trials receive three. Exclusivity and patent periods can run concurrently, but though the validity of a drug's

[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.

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.

1.2.2 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 firms 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 States. Because of 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

[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 to the indication, which means that generics can be approved under other unprotected indications.

[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.

other factors, such as drug insurance plans encouraging the use of generics over brands, once a generic drug enters, 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 therapeutic classes like lipid regulators and calcium channel blockers (Berndt and Aitken, 2011).

1.2.3 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 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 1.1 for more detail on each of these categories).[19]

[16] In some cases, generic penetration takes less time. Vasotec, a drug 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.

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

Table 1.1: Types of Line Extensions

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.
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 or Delayed Release	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 flipped or 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.

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, flavors, or vitamins.

FDA regulations require generics to be bio- and pharmaceutically equivalent to a reference branded drug. Since a LE is not bio- and pharmaceutically equivalent to its OF, a generic to the OF

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

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 design 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 the switch). In this sense, LE introduction can be strategic, and in 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 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 with Ambien instead of seven years later, consumers would have a welfare gain of $723M. The caveat concerns innovation: if Ambien CR's exclusivity had not existed, the drug may not have been developed.

1.3 Conceptual Framework: Timing of a Line Extension 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 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 expands 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

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

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. 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 1.1 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 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.

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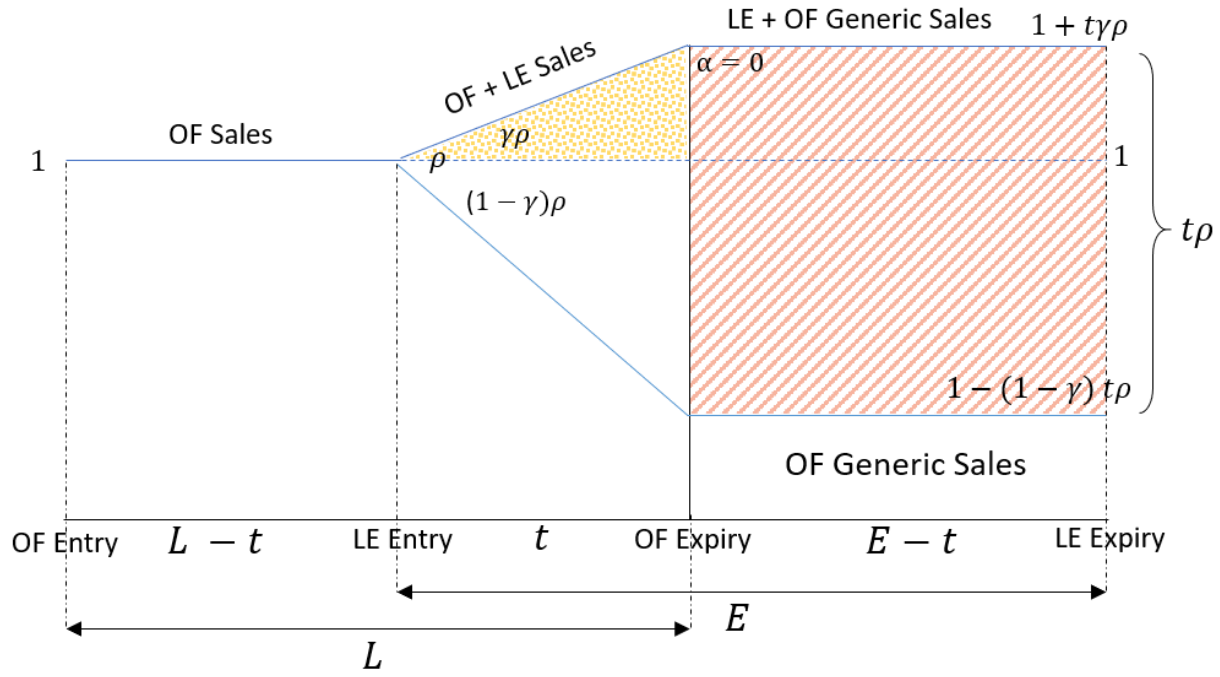
[22] LEs and OFs may be differentiated in a variety of ways that may drive market expansion. For example, a LE may be approved for an indication that an OF was not approved for, or a LE may treat the same condition as an OF, but for a different population. However, market expansion is not merely a clinical 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 firm quote on Namenda, a drug 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 a 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 A.1.

Figure 1.1: 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 (usually 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.

In Figure 1.1, 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, increasing post-OF Expiry sales and the area of market expanding sales when $\gamma > 0$. However, a longer t reduces the time in which sales are achieved post-OF Expiry.

The incremental profit from LE introduction is the shaded area in Figure 1.1. The total profit of the OF and LE franchise is the sum of the profits across each of the three periods:

$$L + \frac{1}{2}t(t\gamma\rho) + t\rho(E - t) \tag{1.1}$$

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

$$t\gamma\rho + \rho E - 2t\rho = 0 \tag{1.2}$$

The profit maximizing t^* in the base case is

$$t^* = \frac{E}{2-\gamma} \tag{1.3}$$

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, the share of sales that is market expanding versus cannibalizing 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 A, Figure A.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 possible.

As described earlier, strategic delay leads to welfare loss. Though this model holds prices constant, 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 must 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

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

the firm's marketing efforts), will pay brand prices instead of generic prices after OF Expiry.

This framework can be used to assess other, more complex decisions on LE introductions. For example, a firm may decide to launch multiple LEs for a 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 LE 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 aggregate or "chain". The model is more complex, but the framework applies.[27]

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.

1.4 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. To construct the data, I (1) identified OFs and potential LEs, (2) matched OFs and LEs, and (3) calculated 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 and key dates: OF and LE approval dates and calculated OF Expiry dates.

[27] This framework could be used to model OF discontinuation following LE entry, 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 capture all OF sales. In practice, this strategy is risky due to regulatory scrutiny, which could be modeled. This framework may also be useful when the first decision on LE timing is based on expected values of ρ and γ, and the decision to discontinue the OF is based on the realized values and cost of doing so.

1.4.1 Data Construction

The data used in this paper come from nine sources that are described in detail in Table 1.2. 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 approval. NDAs may include different strengths of one drug.[28]

Appendix A, Table A.1 provides detail on how I arrive at the sample of 710 OFs, 444 without a LE and 266 OFs that map to 525 OF-LE pairs. Of these, 341 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. I return to a subset of these as a comparison group. As noted above, 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 use the drugs@FDA data and National Drug Code Directory to identify NDAs approved from 1985 through 2016. I exclude biologics, over-the-counter drugs and medical gases, as they do not face generic competition the way small-molecule prescription drugs do. I exclude tentative approvals, as these never entered the market. This leaves a set of 2,562 NDAs. To obtain OFs, I restrict NDAs to Type 1 approvals[29] plus six NDAs in which a NME was paired with a long-time generic.[30] I exclude diagnostic classes like radiopharmaceuticals, breath tests and contrast agents, leaving an OF sample of 710 NDAs.

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[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)

Table 1.2: Data Sources and Descriptions

Source	Description	Timeframe	Availability
Drugs@FDA Database	Data on all FDA prescription and over-the-counter branded and generic drug approvals since 1939.	Through 12/27/2017	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 the products that are therapeutic equivalents 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 pharmaceutical 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 Publications and Peer-Reviewed Publications	Best-Selling Drug Lists from sources like MedScape, Axios, Drugs.com, and PharmacyTimes.	Top 100 lists for 2001, 2003-15. Top 12 list as of 1991, Top 20 as of 2017. 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 publishes annual lists of top 50 pharmaceutical firms by revenue, starting 1999.	1999-2019	Accessed through Harvard University Libraries

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 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 prefixes (e.g., levo-, etc.), and account for other forms of active ingredients (e.g., "hydrochloride" is a water-soluble version of an active ingredient).

I 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. 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

[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).

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] 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 (for detail on these categories, see Table 1.1, above). 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.

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

- **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.
- **Other:** All remaining LEs, which can be classified broadly into:
    - **Innovative:** 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.

1.4.2 Original Formulation 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 that 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.

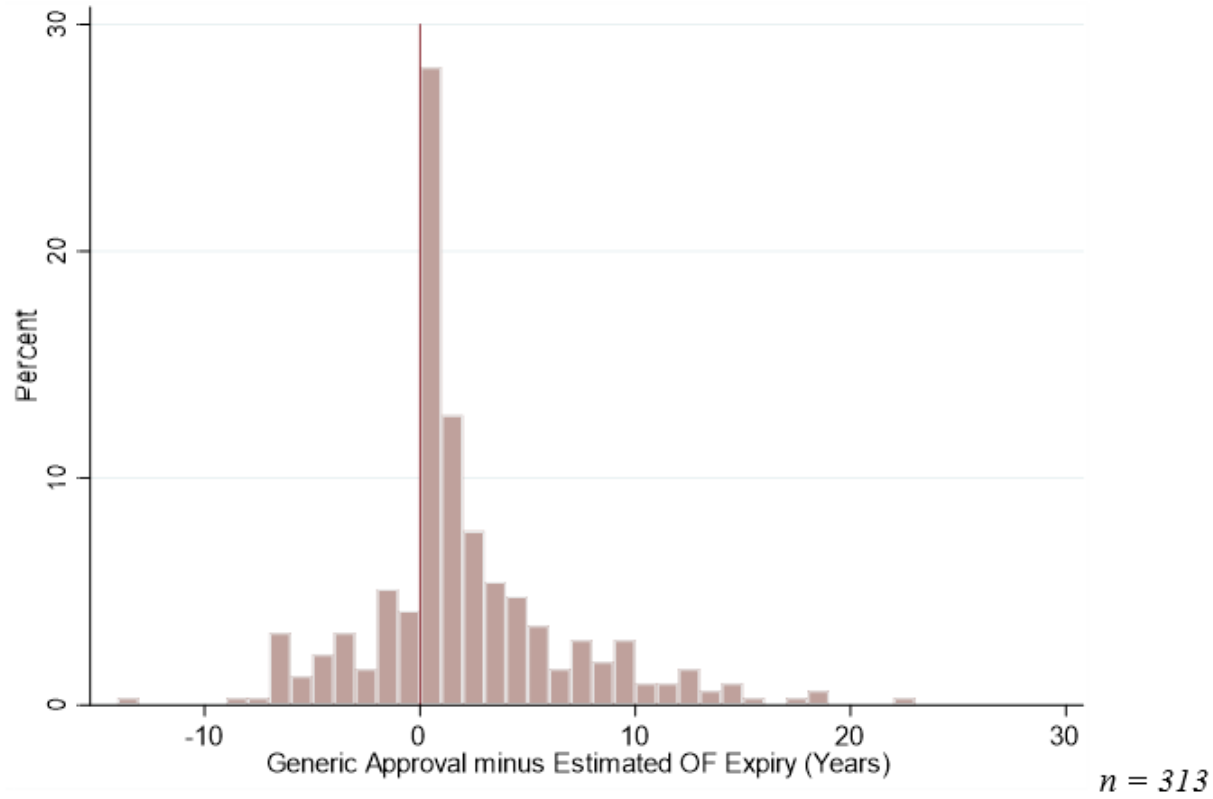
I then turn to the FDA Orange Book and flag all NDA patents that included a drug substance claim. Using the US Patent and Trademark Office data, I obtain the filing dates for each of these drug substance patents. For each NDA in the Orange Book, I record the expiration date of its first drug substance 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). 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 NMEs 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 the 710 OFs in my sample. Figure 1.2 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.

Figure 1.2: Distribution of Difference between Estimated OF Expiry and Actual First Generic Entry



Note: OF stands for Original Formulation. This graph shows 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.

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 often they must make do with ranges. My OF Expiry measure is replicable and a reasonable proxy for generic entry that errs on the early side.[37]

1.4.3 Original Formulation Descriptive Statistics

Table 1.3 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. 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 in my analysis are at the OF level and are summarized in Table 1.3. 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 to 35% of those that did. 27% of

[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.

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 is the total number of patents on a OF, including its drug substance patent. 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, see 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 1.3. 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 classes had fewer than 10% of OFs in my sample.

Table 1.3: Summary Statistics: Original Formulations

	All OFs			OFs Without LEs			OFs with at least one LE		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
OF 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

Table 1.3: Summary Statistics: Original Formulations (Continued)

	All OFs		OFs Without LEs		OFs with at least one LE	
	N	%	N	%	N	%
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%
Total	710	100%	444	100%	266	100%
Route of Administration						
Dermal	33	5%	19	4%	14	5%
Inject/IV	182	26%	146	33%	36	14%
Ophthalmic	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%
Total	710	100%	444	100%	266	100%
1st Level Therapeutic Class						
A: Alimentary Tract	82	12%	44	10%	38	14%
B: Blood	37	5%	33	7%	4	2%
C: Cardiovascular System	79	11%	44	10%	35	13%
D: Dermatologicals	29	4%	15	3%	14	5%
G: Genito Urinary System	27	4%	17	4%	10	4%
H: Systemic Hormonal	14	2%	10	2%	4	2%
J: Anti-infectives	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 System	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%
Total	710	100%	444	100%	266	100%

Note: Vintage refers to the year in which an original formulation was approved by the FDA.

1.4.4 Line Extension Descriptive Statistics

Table 1.4 shows the breakdown of LEs by technological category, overall and separately for those

that did and did not have drug substance patents other than 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. Because of the changes they make relative to their OFs, dose change and extended release LEs are potentially more cannibalizing than other LE types.

Table 1.4: Original Formulation-Line Extension Pairs by Technological Category

		All OF-LE Pairs		Pairs with LE Drug Substance Patent		Pairs without LE Drug Substance Patent	
LE Type	**Description**	**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	Minimal change and innovative LEs	32	6.1%	7	3.8%	25	7.3%
Total		525	100.0%	184	100.0%	341	100.0%

Note: Drug substance patents are on the active ingredient or molecular entity, per the FDA Orange Book. LEs with these patents have a drug substance patent not originally associated with the OF.

Figure 1.3 and Figure 1.4 show histograms of $L - t$ and t for the set of non-simultaneous OF-LE pairs. These 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.

Figure 1.3: Distribution of LE Entry Relative to OF Approval ($L - t$)

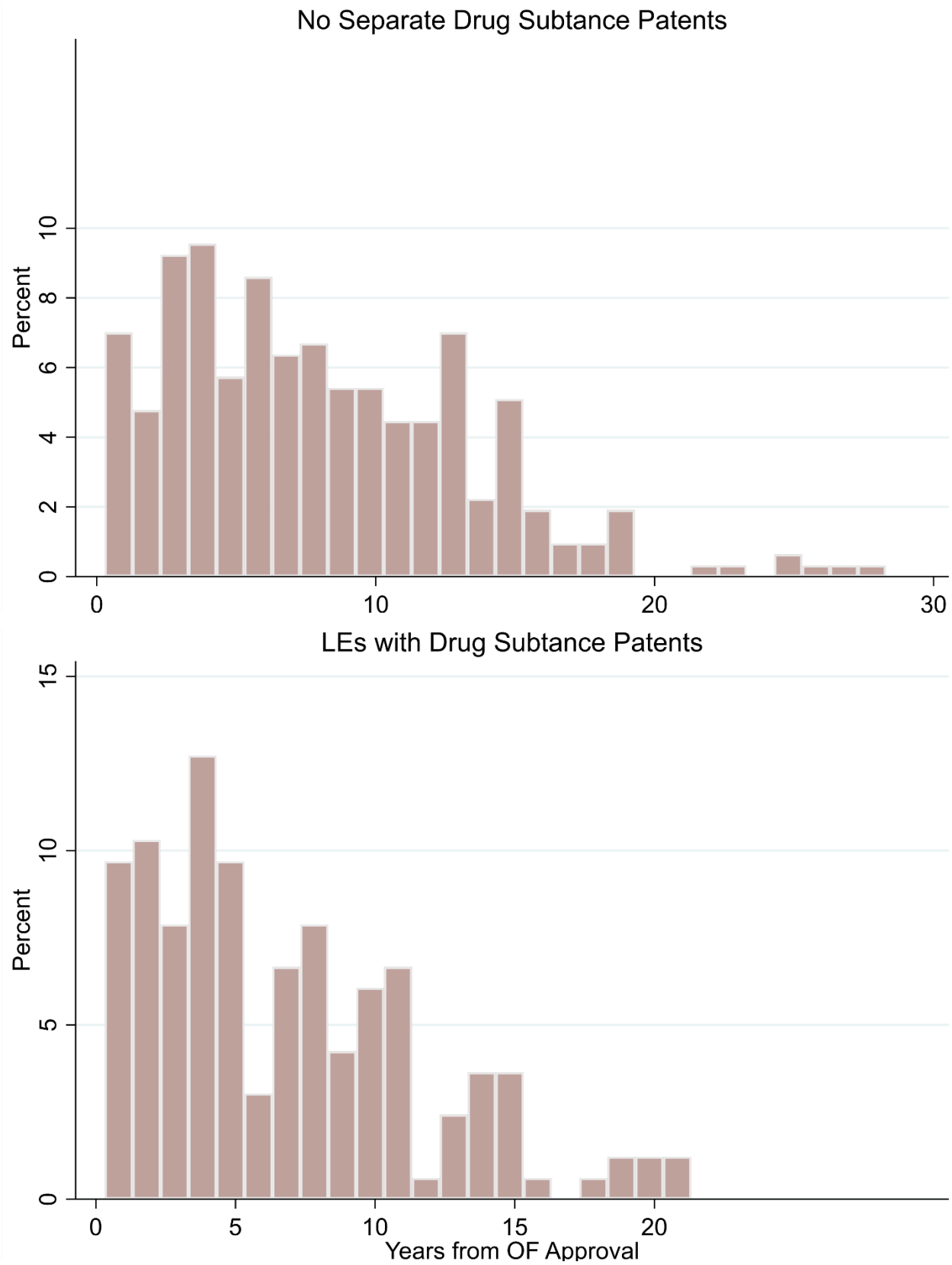
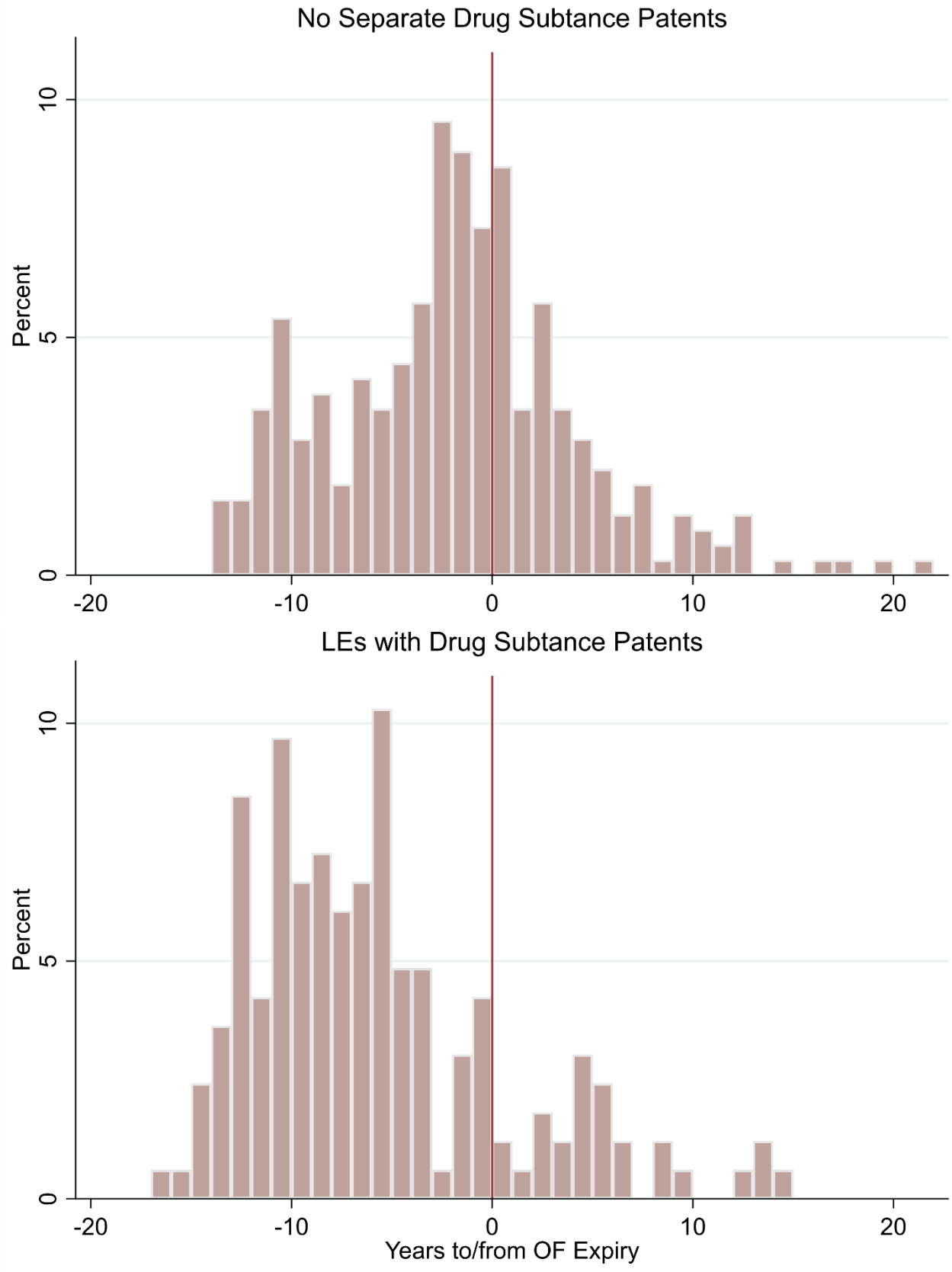


Figure 1.4: Distribution of LE Entry Relative to OF Expiry (t)



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 above, 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.

1.5 Empirical Approach

1.5.1 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

[38] Ordinary Least Squares allows for controls but assumes the error term is distributed normally.

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 $h(t) = \lim_{\Delta t \to 0} \frac{\Pr(t+\Delta t > T \mid T > t)}{\Delta t}$, 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:

$$h_i(t) = h_0(t) * \sum_{k=-3 \text{ to } -1 \text{ Years}}^{1+\text{Years}} \beta_k * \mathbf{1}\left(\text{Period around OF Expiry} = k\right)_{it} + \gamma X_{it} \qquad (1.4)$$

In this estimating equation, $h_i(t)$ is the hazard of LE approval for OF i at time t from 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. The identifying assumption is that the baseline hazard captures the rate of scientific innovation, and we would not expect bunching in the rate of

[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.

innovation at the times when drugs are approaching patent and exclusivity 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. These are described above and 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 having a LE approved, 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 Figure 1.2. 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 LEs approved in these periods. Robustness checks include different durations of groupings.

A $exp(\beta_k) > 1$ indicates that LEs were approved at a higher rate in 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 NMEs), 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 behavior, 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 $k = (-4\ to\ -2)$, $(-2\ to\ 0)$, $(0\ to\ 2)$, and $(2+)$ years to/from OF Expiry.

1.5.2 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, LE of type j, and interval around OF Expiry k.

The risk score is defined as $\exp\left(\sum_k \widehat{\beta_k} * \mathbf{1}\left(Period\ around\ OF\ expiry = k\right)_{ijt} + \hat{\gamma} X_{ijt}\right)$. The ks 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 the Monte Carlo Simulation set-up is described in Appendix 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.

1.5.3 Comparison of Patented and Unpatented LEs

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

Comparing the entry 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 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 timing 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 than a comparable LE that did not get a drug substance patent. I also assume that firms did not file more patents 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 receiving a patent is uncorrelated with 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 except that one had a drug substance patent and the other did not (i.e., as if patents were assigned randomly), and attribute the difference to firm responses to incentives created by 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. More specifically, I exclude LEs that were combinations that involved a never-approved NME. I also drop LEs that are categorized as innovative or as Type 2 (i.e., a new chemical entity). I exclude extended release LEs that allowed for weekly or monthly doses if their OFs were daily doses. Finally, I drop LEs that had drug substance patents when their OFs did not.[41]

[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 few LEs were awarded drug substance patents despite the existence of the OF.

I further restrict the data to exclude OFs approved in 2007 or later to allow for at least ten post-market years to observe LE approvals. I am left with 288 unpatented LEs and 97 patented LEs. I estimate average adjusted and adjusted differences across these groups in t, 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. for a given OF), the OF's vintage, if the firm was in the Top 20 by revenue, if the OF was a best seller, if 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 administration route and therapeutic class, and LE type. I cluster standard errors at the OF level, since some OFs have multiple LEs which are unlikely to be independent. Summary statistics of the covariates for the sample of LEs used in this analysis are described in Table 1.5.

Table 1.5: Summary Statistics for Subset of LEs Used in Unpatented to Patented Comparison

	LEs without Drug Substance Patent (N = 288)		**LEs with Drug Substance Patents (N = 97)**		
	Mean	**SD**	**Mean**	**SD**	**Difference**
LE Approval relative to OF Expiry (years)	-1.80	6.21	-7.17	4.71	5.36***
OF Approval to OF Expiry (years)	9.76	4.05	13.92	1.74	-4.16***
LE Order per OF	2.05	1.44	2.25	1.78	-0.2
Top 20 Firm	0.51	0.50	0.59	0.49	-0.08
OF is a Best Seller	0.34	0.47	0.57	0.50	-0.23***
OF had LE approval in 1st 90 days	0.10	0.30	0.09	0.29	0.01
OF Patent Count	2.81	3.10	5.48	4.29	-2.68***
OF Number of Products	2.22	1.48	3.05	1.86	-0.83***
OF Had Orphan Drug Exclusivity	0.09	0.29	0.16	0.37	-0.07*
OF Approval Year	1992.96	5.21	1999.11	4.14	-6.15***

Note: *** p<0.01, * p<0.1.

1.6 Results

1.6.1 Firm Timing of Unpatented LEs

Table 1.6 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 1.7 shows results for the different samples of LE types. Each specification includes all OFs and does not cover the first 90 days after OF Approval.

Figure 1.5 plots the coefficients of interest for the overall model (column 1 in Table 1.6) and for the falsification test with patented LEs (column 2 in Table 1.6). 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 1.5 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 1.6 and Figure 1.5, the β_k coefficients in the falsification test are statistically significantly less than one or statistically indistinguishable from one, 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.

Table 1.6: 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 years	1.964***	0.358***
	(0.404)	(0.157)
+1 and after	1.239	1.107
	(0.396)	(0.546)
OF Admin Route	Y	Y
Therapeutic Class	Y	Y
Number of Subjects	691	691
Number of Failures	312	145

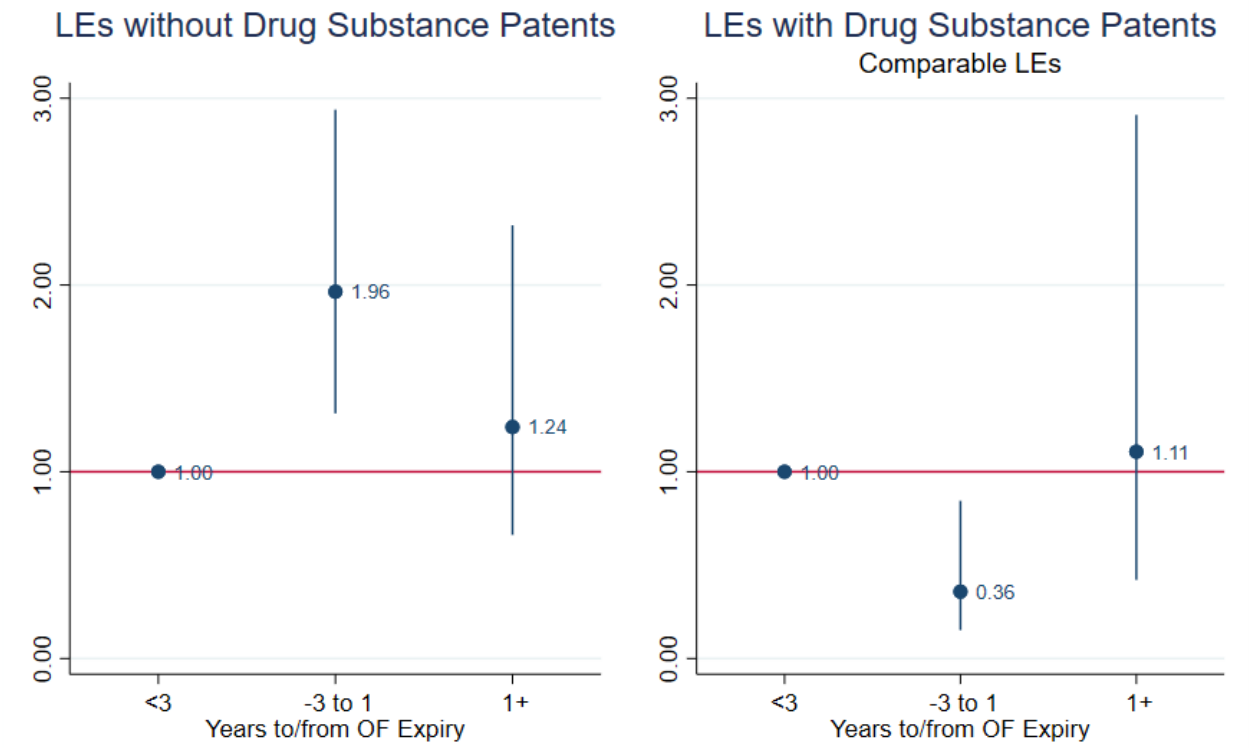
Note: Standard errors in parentheses, clustered at the OF level. *** p<0.01, ** p<0.05, * p<0.1. Coefficients are hazard ratios.

Table 1.7: Survival Analysis Results for LEs 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)	(0.083)	(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)	(0.063)	(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**	0.085***	0.634
	(0.188)	(0.350)	(0.339)	(0.524)	(0.147)	(0.0657)	(0.409)
LE in first 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: Standard errors in parentheses, clustered at the OF level. *** p<0.01, ** p<0.05, * p<0.1. Coefficients are hazard ratios. Combo is combination. XR is Extended Release. Orphan Drug Exc. is Orphan Drug Exclusivity.

Figure 1.5: Coefficients on Periods k Around OF Expiry



Note: Graphs display hazard ratio coefficients that represent the time-varying effect on the hazard rate of an OF having an LE approved at different periods leading up to and beyond OF Expiry. The left panel shows hazard ratios for LE approvals where the LE was subject to exclusivity (i.e., the firm had an incentive for strategic delay). The right panel is a falsification test that uses comparable LEs that had drug substance patents, and where the firm did not have an incentive for strategic delay.

Other covariates have an effect on the hazard rate of an OF getting a LE. Across both columns in Table 1.6, 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 1.7 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, though 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 1. 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 βk 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 most 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 A, Figure A.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.

[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.

Taken together, my results show that firms make strategic decisions on when to launch their products, with differences across LE types. A limitation is that there is large heterogeneity within LE categorizations and small sample sizes. Another 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.

1.6.2 Simulations to Quantify Strategic Delay

I use Monte Carlo simulations to interpret hazard ratios in units of time. 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.

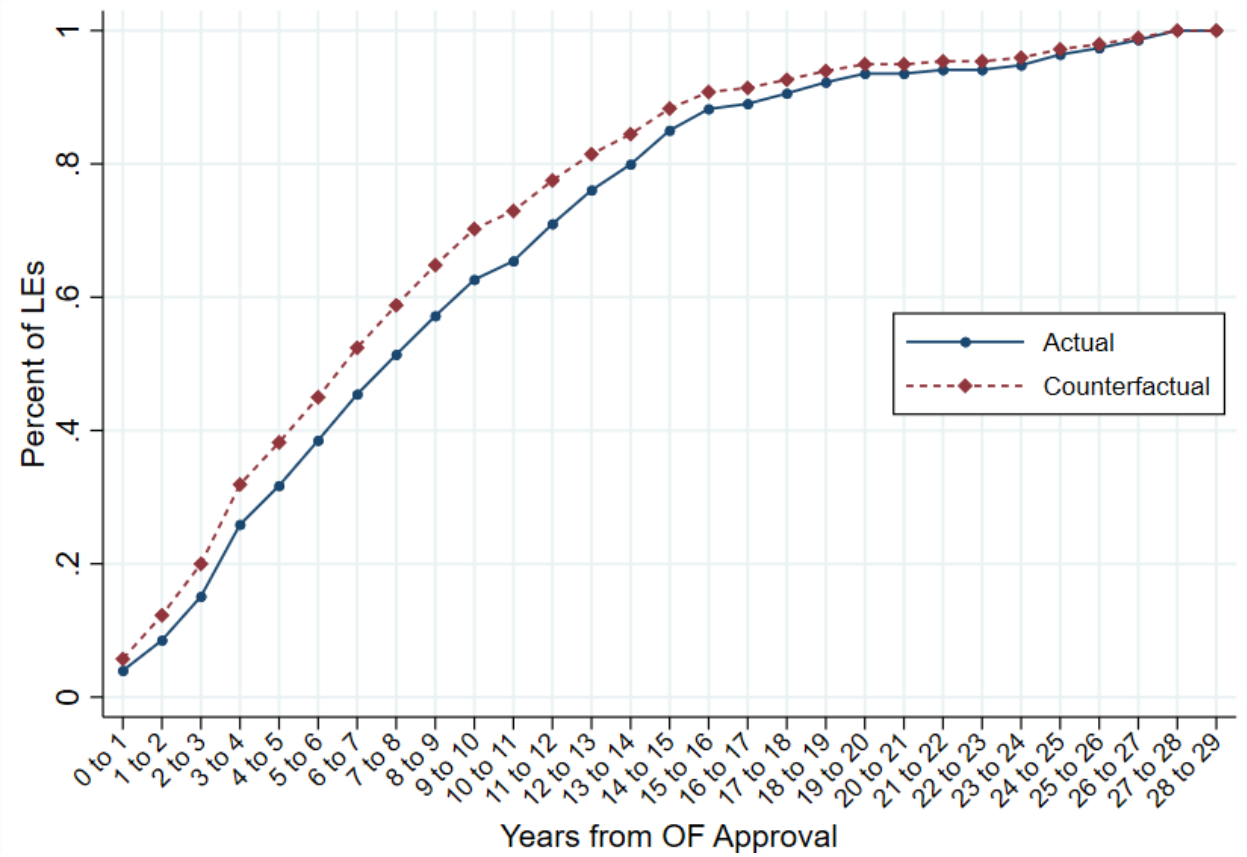
Table 1.8 details these estimates. I find that overall, introductions of LEs are delayed by 1 year on average. The cumulative percentage of LEs in the actual and counterfactual scenarios is graphed in Figure 1.6, showing the gap between actual and counterfactual LEs, due to the increase in the hazard 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.

Table 1.8: Average Delay per Line Extension by Line Extension Types

Type of LE (without drug substance patents)	Average delay per LE (months)	Average delay per LE (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: Estimates of delay are an interpretation of the hazard ratios shown in Table 1.6 and Table 1.7.

Figure 1.6: Percent of Simulated Line Extensions Approved by Elapsed Year



Note: The simulation depicted accounts 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 account for the control variables used in the survival analysis.

1.6.3 Comparison of Patented and Unpatented LEs

Table 1.9 shows the mean difference in LE approval timing relative to OF Expiry for LEs with drug substance patents relative to comparable LEs without drug substance patents. I control 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. Patented LEs enter 1.8 years earlier relative 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, suggesting that 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.

Table 1.9: Difference in Mean Approval Time for LEs With and Without Drug Substance Patents

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

Note: 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.

1.7 Discussion and Conclusion

This paper develops a conceptual framework to study firm decisions on the introduction time 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 I test for strategic delay using novel data covering United States 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 interpret the delay, I use Monte Carlo simulations and find that LEs that do not have their own drug substance patents are strategically 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 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 document heterogeneity in delay across LE types, with the LE types revealed to be cannibalizing entering with 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 brand 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 OF, 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 drug as an example, I estimate that the loss due to delayed generics is similar in magnitude. LEs that were 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 brand 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 for just one product, and is borne largely by insurers.

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

[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

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 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

[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).

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 a clear-cut example of a low-value LE that ought to receive fewer marketing protections.

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. However, changes to regulatory exclusivity periods are likely have general equilibrium effects on innovation, but such effects can be complex. If, for example, exclusivity for LEs is fixed in the way I describe above, there may be incentives for pharmaceutical firms to introduce many low-value LEs early, crowding out more valuable innovation.

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 runs counter to the goals of regulators and public policy makers. There is likely a welfare improving role for revising regulatory exclusivity periods for follow-on drug products such that they do not start at the time of drug approval.

Chapter 2

Dynamic and Static Efficiency Effects of Pharmacy Benefit Management in Health Insurance: A Diagrammatic Approach

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2.1 Introduction

Regulation of prescription drug markets balances two objectives: promoting investment in the development of new drugs and pricing drugs for the efficient level of utilization. The goals of what are referred to as "dynamic" and "static" efficiency often conflict.[1] Tradeoffs stem from the fact that higher profits for firms generally imply higher prices for consumers. If the discovery of a new drug

[1] The tradeoff between these two objectives is an overarching theme of general discussion of the economics of pharmaceutical markets. See, for example, Berndt, E. (2002). Pharmaceuticals in U.S. Health Care: Determinants of Quantity and Price. Journal of Economic Perspectives, 16 (4): 45-66., and Goldman, D., & Lakdawalla, D. (2011). Intellectual Property, Information Technology, Biomedical Research, and Marketing of Patented Products. In Handbook of Health Economics. Vol. 2, pp. 825-872. Elsevier B.V.

is made more profitable (e.g., by allowing its manufacturer a longer period to sell as a monopolist) this will encourage investment in research and development (R&D). However, the manufacturer's higher profit comes alongside higher prices to consumers, restricting output and delaying the transfer of surplus from firms to consumers. The balance between dynamic and static efficiency takes special forms in consideration of public policy for the pharmaceutical industry.

Some regulatory policies, like patent and market exclusivity policies, intend to balance dynamic and static efficiency. Yet other regulations and market institutions that affect pharmaceutical profits and pricing may also have the unintended consequence of affecting this balance. This paper introduces a framework to evaluate the economic impact of some aspects of health care financing, such as the presence of health insurance for drugs, which can affect the dynamic and static tradeoff.[2] A second health care financing institution in drug markets are Pharmacy Benefit Management (PBM) firms, which intermediate between drug sellers and buyers. This paper focuses on PBMs, their effect on profits and prices in drug markets, and their impact on the working of incentives for dynamic and static efficiency in drug markets. We use a simple diagrammatic model to depict the tradeoff between static and dynamic efficiency, and to show the effect of health insurance and PBMs on this tradeoff and on market outcomes.

Section 2 provides background on drug markets, with a focus on the role of PBMs and policies that affect the balance between dynamic and static efficiency. Section 3 presents our diagrammatic model of dynamic and static efficiency as well as how the tradeoff between the two is mediated by institutions of health care finance. Section 4 concludes.

The main result of our analysis can be stated simply. Lakdawalla and Sood (2009) explained that health insurance for drugs, by partly decoupling the price manufacturers receive from the price

[2] Our work is similar in spirit to Lakdawalla and Sood (2009), which we discuss below. See particularly footnote 28 where we discuss some of the similarities and differences in the modelling approaches.

consumers pay, can improve the dynamic-static tradeoff. Health insurance subsidizes demand, counteracting the output-restriction inefficiency caused by monopoly pricing. We show that the health care financing institution of a PBM is different. In our paper, PBMs negotiate discounts from manufacturers and pass some discounts on to buyers. In what we refer to as a "competitive" PBM, discounts are fully passed on. In this case, the PBM has no effect on the tradeoff between dynamic and static efficiency but may affect the equilibrium. By contrast, a PBM with market power keeps some or all discounts. In this case, the PBM degrades the tradeoff and may affect the equilibrium. By keeping some profits that might otherwise go to manufacturers or passed on to buyers in the form of lower prices (as would be the case in a competitive PBM market), a PBM with market power restricts output on one or both margins. If PBM profits come from manufacturers, firms have less incentive to invest in R&D. If PBM profits come at the expense of higher prices to consumers, efficient drug consumption is curtailed.

2.2 Background

2.2.1 Drug Markets and PBMs

PBMs intermediate between drug manufacturers, who invest in R&D, and insurers, who pay for drugs on behalf of consumers. PBMs play a large role in drug procurement in the United States, and one of their central function is negotiating drug prices with manufacturers on behalf of health plans.[3] More specifically, PBMs engage in selective contracting with drug manufacturers, building formularies (i.e., tiered networks of drugs). In exchange for price concessions known as rebates, PBMs place drugs on preferred tiers of their formularies. Health plans cover drugs on preferred

[3] Depending on their contracts with insurers (which include commercial, managed Medicaid, and Medicare Part D plans), PBMs can provide services like managing claims, designing drug benefits, and building pharmacy networks.

formulary tiers more generously, which increases the sales of those drugs. Rebates are usually set as a percentage of the drug's list price, which is set by the manufacturer.

In the United States, PBMs administer prescription drug plans for over 266 million people[4] and the PBM industry is dominated by several large firms. As of 2018, the top three PBMs (CVS Health, Express Scripts, and OptumRx) managed over 75% of prescription drug claims, and the top six over 95% of claims.[5] PBMs have significant bargaining power. Because PBMs can represent multiple health plans and their beneficiaries, PBMs increase the price elasticity of demand for drugs (from the manufacturer's point of view). As a result, PBMs can negotiate are lower prices than a health plan could negotiate on its own.

High consumer drug prices, an issue of static efficiency, are an important policy issue. Growing list prices hurt the uninsured and those in insurance plans with high deductibles or where cost sharing is tied to list price. A Kaiser Family Foundation poll in February 2019 found that 30% of Americans had not taken drugs as prescribed due to their cost.[6] There is debate on whether increases are due to pharmaceutical manufacturers, who directly control list prices, or due to PBMs. The argument for the latter is that manufacturers have to offer ever higher rebate percentages to PBMs to obtain favorable formulary placement, and as a result, manufacturers must raise list prices.[7]

Though list prices are observed, net prices are confidential, which makes the effects of PBMs difficult to study. Two recent papers, Sood et al. (2020) and Kakani et al. (2020) use rebate estimates from SSR Health LLC, a private data aggregator, to study the relationship between list and

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[4] Pharmaceutical Care Management Association. "What is a PBM?" https://www.pcmanet.org/the-value-of-pbms

[5] The 4th through 6th PBMs in 2018 were Humana Pharmacy Solutions, MedImpact Healthcare Systems, and Prime Therapeutics. See Fein, A. "CVS, Express Scripts, and the Evolution of the PBM Business Model", Drug Channels. May 29, 2019. Available at https://www.drugchannels.net/2019/05/cvs-express-scripts-and-evolution-of.html

[6] See Kaiser Family Foundation, "Public Opinion on Prescription Drugs and Their Prices," November 20, 2019. Available at https://www.kff.org/slideshow/public-opinion-on-prescription-drugs-and-their-prices/

[7] See Shepherd, J. "Pharmacy Benefit Managers, Rebates, and Drug Prices: Conflicts of Interest in the Market for Prescription Drugs". Yale Law & Policy Review, Vol. 38, 2019.

net prices. Sood et al. (2020) find that from 2015-2018, a $1 increase in rebates is associated with a $1.17 increase in list prices. Though their paper is descriptive, they conclude that intermediary market power is at least a partial driver of increases in list prices. Kakani et al. (2020) find that from 2012-2017, list prices grew by 12% per year, but net price growth was 3% per year. They show that over that time, the change in average rebates, or the ratio between list and net prices, increased from 32% to 48%, driven by increases in rebate levels for the same drugs over time. In theory, PBMs in a competitive market would pass rebates on to health plans and consumers, but high concentration in the PBM market makes it unlikely that PBMs fully pass rebates on to consumers.

Concentration in the PBM market and secrecy around rebates have led policy makers to consider regulatory reform. In 2019, the Trump Administration proposed eliminating rebates in Medicare Part D and Medicaid and replace them with discounts for consumers at the point of sale,[8] but it did not move forward after the CMS Office of the Actuary said the policy would lead to higher costs for insurers, consumers, and the government. Other stakeholders call for rebate transparency, but disclosure could lead some insurers to demand low prices from manufacturers who offered them to other insurers, creating an incentive for manufacturers to raise prices overall.[9] Regulation and public policy for PBMs is often considered through the lens of static efficiency. Though the potential effect of PBMs on incentives to invest in R&D has been recognized,[10] it has not been directly addressed.

[8] See the Feb. 2019 Proposed Rule, "Removal of Safe Harbor Protection for Rebates Involving Prescription Pharmaceuticals and Creation of New Safe Harbor Protection for Certain Point-of-Sale Reductions in Price on Prescription Pharmaceuticals and Certain Pharmacy Benefit Management Service Fees." Available at https://www.federalregister.gov/documents/2019/02/06/2019-01026/fraud-and-abuse-removal-of-safe-harbor-protection-for-rebates-involving-prescription-pharmaceuticals

[9] See Cutler, D., & Dafny, L. (2011). Designing Transparency Systems for Medical Care Prices. New England Journal Of Medicine, 364(10), 894-895.

[10] In the context of price negotiations in Medicare Part D, Frank and Newhouse (2008) state "if prices are driven too low to satisfy today's budget concerns, there is a real risk that the supply of future innovative drugs will be reduced, leading to considerable tension and controversy around drug pricing." More recently, Kakani et al. (2020) state that "to

2.2.2 Tradeoff Between Dynamic and Static Efficiency in Drug Markets

The Drug Price Competition and Patent Term Restoration Act, enacted by Congress in 1984, is the cornerstone of regulation of small-molecule (non-biologic) pharmaceutical markets in the United States. Commonly known as the Hatch-Waxman Act, it had two main objectives: to incentivize pharmaceutical innovation, and to make new products accessible more quickly by streamlining requirements for generic entry. In attempting to balance innovation and competition across branded and generic products, Hatch-Waxman recognized and addressed both static and dynamic efficiency as central policy issues.[11]

Hatch-Waxman increased incentives for innovation by awarding longer periods of market exclusivity to new branded products. Under Hatch-Waxman, newly approved drugs with a novel active ingredient receive five years of exclusivity, and drugs that require new clinical trials (other than for bioavailability trials) receive three. As with patents, generics cannot enter during exclusivity periods. Though exclusivity and patents can run concurrently, only patents may be challenged by generic manufacturers. Hatch-Waxman also allows branded manufacturers to recoup up to five years of patent time lost during regulator review, though total time post-approval cannot exceed 14 years.[12] The goal of increased time on the market without competition is to raise the manufacturer's expected profits, which increases the incentive to innovate.

In parallel, Hatch-Waxman aimed to decrease drug prices by increasing generic entry and competition via a streamlined process for generic approvals. Instead of requiring that generic

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the extent that savings are being retained as profit by intermediaries who are not responsible for innovation, they reduce incentives for innovation without improving affordability."

[11] See Troy, D. "Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)." Statement of D. Troy, Chief Counsel, FDA. August 2003. Available at https://www.judiciary.senate.gov/imo/media/doc/troy_testimony_08_01_03.pdf.

[12] See "Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act)," Public Law 98-417, 98th Congress, 1984, available https://www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/STATUTE-98-Pg1585.pdf.

manufacturers conduct fresh clinical trials to demonstrate safety and efficacy, Hatch-Waxman created Abbreviated New Drug Applications as a pathway for generic approval, which only require that a manufacturer prove that its proposed generic is both bio- and pharmaceutically equivalent to a branded drug. Hatch-Waxman also created incentives for generic manufacturers to challenge patents on branded products and, if successful, enter prior to the patent's expiration. The first generic manufacturer to successfully challenge a patent receives 180 days of exclusivity during which no other generic competitors can enter.[13] In the absence of a patent challenge, a generic drug can enter the market only after the patent and exclusivity periods on a branded drug expire. Overall, Hatch-Waxman reduced the cost of generic entry in the United States and increased generic competition.[14]

Discussion of drug regulation often considers its effects both on current drug consumers and on pharmaceutical innovation. For example, in 2000, David Balto, a former Assistant Director of the Office of Policy and Evaluation, Bureau of Competition of the Federal Trade Commission (FTC), wrote that Hatch-Waxman had been effective in promoting both static and dynamic efficiency in pharmaceutical markets.[15] Others have questioned whether pharmaceutical firm responses to Hatch-Waxman has undermined the policy goal of improving welfare.[16]

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[13] These challenges are known as "Paragraph IV" certifications. See Grabowski, H.G., and M. Kyle. 2007. "Generic Competition and Market Exclusivity Periods in Pharmaceuticals." Managerial and Decision Economics 28: 491–502.

[14] Grabowski H, Vernon JM. Brand Loyalty, Entry and Price Competition in Pharmaceuticals After the 1984 Drug Act. Journal of Law and Economics. 1992; 35(2):331–350.

[15] "Both of these objectives seem to have been fulfilled to a significant degree […] the added protections and exclusivity term for innovator firms have accompanied a tremendous increase both in the investment in, and the success of, pharmaceutical innovation […] the industry also has seen an increase in the percentage of branded drugs that have a generic competitor on the market […] the generic share of prescription drug volume has increased by almost 150% since enactment of the Hatch-Waxman Act in 1984." D. Balto, "Pharmaceutical Patent Settlements: The Antitrust Risks," Food and Drug Law Journal, 55, 2000. The figure for the generic share of prescriptions is from a 1998 CBO report titled "How Increased Competition from Generic Drugs has Affected Prices and Returns in the Pharmaceutical Industry."

[16] For branded firm strategies to delay generic entry, see Feldman, R., & Frondorf, E. (2017). Drug wars: How big pharma raises prices and keeps generics off the market. New York, NY: Cambridge University Press. Others argue that Hatch-Waxman undermines dynamic efficiency by creating too strong of an incentive for Paragraph IV challenges, leading to uncertainty for innovators. Grabowski, H., Kyle, M., Mortimer, R., Long, G., & Kirson, N. (2011). Evolving brand-name and generic drug competition may warrant a revision of the Hatch-Waxman Act. Health Affairs, 30(11), 2157-2166.

Other legislative initiatives could also change the balance between dynamic and static goals. For example, H.R. 3, The Elijah E. Cummings Lower Drug Costs Now Act, aims to reduce consumer spending on prescription drugs via price negotiation, out-of-pocket price caps in Part D, and drug inflation provisions for Medicare Part B and Part D drugs.[17] The Congressional Budget Office evaluated potential effects of H.R. 3 in December 2019, and their report touches on the tradeoff between access and innovation. The Congressional Budget Office found that though H.R. 3 would lead to lower spending on prescription drugs, 38 fewer new drugs would be introduced over the next twenty years (a 12.7% reduction).[18] The Congressional Budget Office's model of pharmaceutical innovation is based on a literature review of the relationship between future revenue and innovation, and of estimates of R&D costs required to bring a drug to market. To sum up, pharmaceutical public policy has the task of maintaining a delicate balance across two policy goals that are often at odds with each other, and different attempts remind us of the difficulty of designing policy that strikes the right balance.

Perspectives on optimal pharmaceutical policy and welfare analysis can change if both dynamic and static efficiency are considered. Finkelstein (2004) shows that policies that aim to increase static efficiency can also have unintended dynamic efficiency effects. She studied three policies to increase vaccine utilization for six diseases, which had the unintended consequence of increasing the return on investment in those vaccine areas. She estimated that as a result of access policies, clinical trials for vaccines for those diseases increased by a factor of 2.5. Though in five of the six disease the innovation was "me-too" or business stealing, in one case the dynamic benefits were larger than the static benefits.

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[17] The full text of H.R. 3 can be viewed at https://www.congress.gov/bill/116th-congress/house-bill/3/text.

[18] "Under current law, the Food and Drug Administration approves, on average, about 30 new drugs annually, suggesting that about 300 drugs might be approved over the next 10 years." See Congressional Budget Office, letter to the Honorable Frank Pallone concerning the Budgetary Effects of H.R. 3, the Elijah E. Cummings Lower Drug Costs Now Act (December 10, 2019). Available at https://www.cbo.gov/publication/55936.

Though the papers above considered both static and dynamic impacts of policy changes in pharmaceutical markets, much of the research on incentives for investment in R&D and incentives for efficient consumption has proceeded independently. There is a broad literature on the determinants of pharmaceutical innovation, assembling evidence that innovation responds to profit incentives (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; Lictenberg and Waldfogel (2009) for the effect of the Orphan Drug Act; Grabowski and Vernon (2000) and Budish et al. (2015) for the effect of effective duration of patents and market exclusivity; and Berndt et al. (2005) for the effect of regulatory review duration). Lakdawalla (2018) summarizes this literature.

The literature on the relationship between prescription drug prices and utilization has largely found that increases in prescription drug cost sharing are associated with decreases in drug utilization. In a review of papers published from 1985 through 2006, Goldman et al. (2007) find that a 10% increase in prescription drug cost sharing is associated with between a 2% and 6% decrease in spending on drugs. This review preceded Gaynor et al. (2007), who used commercial claims and benefit design data to study demand response to changes in drug copayment levels. In accordance with the literature they find that increased copayments lower utilization and reduce spending. They estimate an elasticity of -0.6 in the first year and -0.8 in the second year after a copayment increase, and also find 35% of the savings on prescription drugs are offset by consumers substituting to medical care. Other papers summarized in Goldman et al. (2007) have found similar offset effects for chronic conditions like diabetes, congestive heart failure, and schizophrenia.[19] Finally, Chandra et al. (2010) exploit staggered copayment changes put in place by the California Public Employees

[19] For example, Mahoney JJ. Reducing patient drug acquisition costs can lower diabetes health claims. Am J Manag Care. 2005; 11(5): S170-6; Cole JA, Norman H, Weatherby LB, Walker AM. Drug copayment and adherence in chronic heart failure: effect on cost and outcomes. Pharmacotherapy. 2006; 26(8):1157-64; Soumerai SB, McLaughlin TJ, Ross-Degnan D, Casteris CS, Bollini P. Effects of a limit on Medicaid drug-reimbursement benefits on the use of psychotropic agents and acute mental health services by patients with schizophrenia. N Engl J Med. 1994; 331(10): 650-55.

Retirement System to study the price sensitivity of prescription drug utilization among the elderly and offset effects of drug copay changes. They estimate arc-elasticities of drug utilization of -0.08 for PPO enrollees and -0.15 for HMO enrollees.

Value-based insurance design (VBID) for prescription drugs is based on demand response– the idea that utilization of and adherence to drugs increases if their cost sharing decreases – and that inefficient utilization of high-value drugs can be corrected with more generous coverage, with savings stemming from offsets in medical care or elsewhere.[20] Agarwal et al. (2018) conducted a systematic review of 21 experimental and quasi-experimental papers on the effect of VBID on drug adherence, finding improvements that ranged from 0.1%-14.3%. Yeung et al. (2018) estimate the price elasticity of demand of pharmaceuticals in a VBID setting at -0.16 for pharmaceuticals overall, and that the particular VBID design studied (which took into account drug-specific incremental cost-effectiveness ratios to pick copayment amounts) was welfare improving. Taken together, there is strong evidence that consumers respond to changes in the prices of drugs, and it follows that changes in these prices can have a significant effect on levels of utilization and static efficiency.

An area of controversy with respect to static efficiency is the entry of "authorized generics," which are generics that are approved as branded products and are marketed or licensed by a branded firm alongside its own branded drug. Authorized generics are often introduced to compete with a generic that has been awarded a 180-day exclusivity following a successful patent challenge. The FTC noted that because authorized generics decrease the value of 180-day exclusivity for potential generic entrants, there may be fewer generics that challenge patents, with generics entering later as a result.[21] Berndt el al. (2007) argue that on balance authorized generics benefit consumers and are

[20] See Baicker, K., Mullainathan, S., & Schwartzstein, J. (2015). Behavioral Hazard in Health Insurance. The Quarterly Journal of Economics, 130(4), 1623-1667.

[21] Federal Trade Commission. "Authorized Generic Drugs: Short-Term Effects and Long-Term Impact." August 2011, Available at https://www.ftc.gov/sites/default/files/documents/reports/authorized-generic-drugs-short-term-effects-

good for static efficiency because they increase generic competition and lower prices. The debate on authorized generics has focused primarily on static efficiency. Yet to the extent that authorized generics lead to more profits for branded drugs, they will affect incentives to invest in R&D.

Decoupling the manufacturer's reward for investment in R&D from the price that consumers pay can work around the tradeoff between static and dynamic efficiency.[22] For example, Kremer (1998) proposes patent buyouts, which would reward innovators with a cash transfer instead of with on-patent time during which to sell as a monopolist. Without monopoly pricing, static efficiency increases, but the getting the value of the buyout right is challenging. Others propose prizes,[23] Advanced Market Commitments,[24] and Medical Innovation Prize Funds[25] as ways to decouple the pharmaceutical firm's margin from the consumer's.[26] Lakdawalla, Sood and coauthors contribute the insight that health insurance decouples supply and demand prices and creates an opportunity to improve dynamic and static efficiency in drug markets. In the first of these papers, Lakdawalla and Sood (2009) show how a public prescription drug benefit can increase static and dynamic efficiency. An insured price between the monopolist's price and marginal cost improves static efficiency. Because manufacturers sell more and receive higher profits when consumers pay the insured price, insurance subsidies can stimulate innovation. Lakdawalla and Sood did not consider the effect of PBMs, but previewing the results of this paper, they observe that market

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and-long-term-impact-report-federal-trade-commission/authorized-generic-drugs-short-term-effects-and-long-term-impact-report-federal-trade-commission.pdf

[22] For more detail see Lakdawalla, D., & Sood, N. (2012). Incentives to Innovate. The Oxford Handbook of the Economics of the Biopharmaceutical Industry.

[23] Ridley et al. (2006) propose the fast-track review voucher to incentivize orphan drug R&D. The prize for bringing an orphan drug is a voucher that guarantees faster regulatory review on a different drug. The voucher may be used or sold.

[24] Kremer and Glennester (2004) propose Advanced Market Commitments for vaccines, which guarantees a market and price once a product that meets certain specifications is developed.

[25] Love and Hubbard (2009) propose Medical Innovation Prize Funds, which differ from Advanced Market Commitments in that they do not incentivize just one particular technology.

[26] See Kremer and Williams (2010) for an overview of tools to incentivize innovation that go beyond intellectual property rights, and thoughts on how to design and implement them.

power can cause problems: "unchecked exercise of insurer market power may become harmful, since inframarginal increases in [the discount] may eventually lower profits and thus innovation." In simulations, Gailey, Lakdawalla and Sood (2010) estimate that Medicare Part D decreases static welfare loss by over $5 billion annually and adds over $3 billion of value via innovation incentives.

Even taken in isolation from the static tradeoff, designing incentives to get the level of investment in R&D "just right" is not easy for a host of reasons, and it is unclear whether regulatory policy sets incentives at the optimal level. Even if consumers accurately assess value, a drug's social value could be larger or smaller than the profits received by the manufacturer, and there can be under- or over-investment in innovation notwithstanding the tradeoff with static efficiency. The primary reason that social value can exceed profits is that sellers cannot appropriate all consumer surplus. The primary reason profits can exceed social surplus is that profits of an innovator might come at the expense of profits from a rival, and thus represent a social transfer. In other words, even before considering static efficiency, there is a "first-best" set of incentives for investment in R&D which is not equal to setting incentives to maximize R&D. Once we consider static efficiency, we move into a second-best world in which some incentives for investment are sacrificed to achieve some gains in static efficiency. Our model includes a diagrammatic representation of both the first-best and second-best incentives for investment in R&D that take static efficiency into consideration.

2.3 Model

2.3.1 First-Best Investment in R&D and Drug Consumption

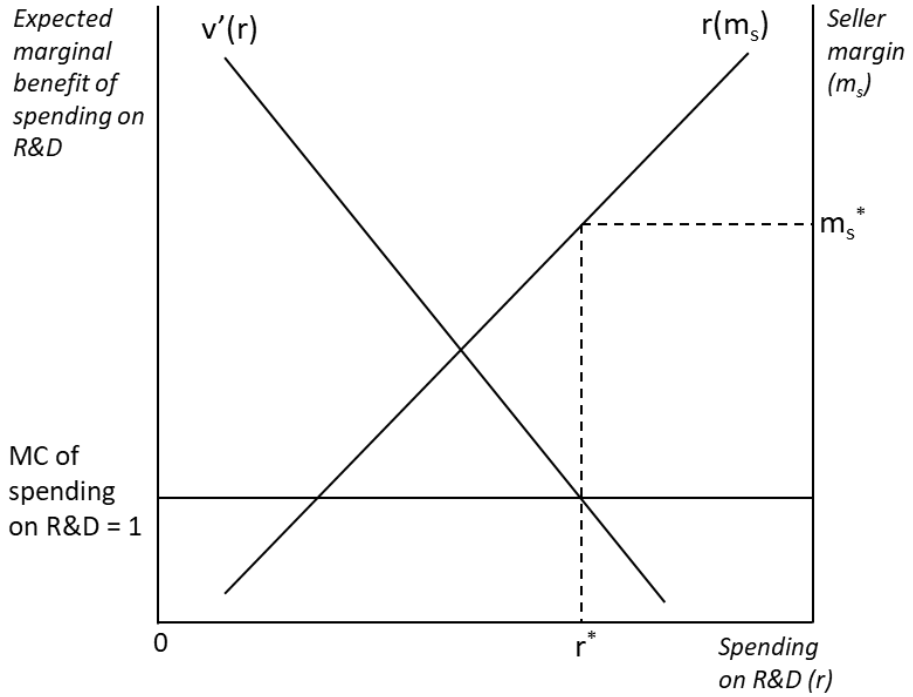
Firms invest in R&D to discover drugs that, if found "new and useful" (patent worthy), can be sold with partial protection from competition. Let the production cost of drugs be c. Patents or other protection from competition allow the firm to set a price $p_s > c$. Patents are time-limited, so a firm

might sell at a high price for that time but sell at a much lower price after protection ends. Price p_s represents the constant price equivalent to the short-term higher/long-term lower selling price.[27] Firms profit maximize, so p_s is the price the firm sets in the presence of regulator policy. The firm margin, m_s, is the difference between seller price and cost, $m_s = p_s - c$. The margin m_s generates the incentives to invest in R&D.

Spending on R&D, measured in dollars, is r, a function of m_s: $r(m_s)$ with $r(m_s) > 0$ and $r'(m_s) > 0$. R&D spending is beneficial because it leads (stochastically) to new discovery. We represent the expected benefit of spending on R&D as $v(r)$ with a declining marginal benefit of spending $v'(r)$: $v' > 0$, $v'' < 0$. The "cost" of spending on R&D is 1.

The first-best margin can be described simply. The efficient level of spending r^* is the solution to $v'(r^*) = 1$. The supply-side margin that induces this level of spending is $r(m_s^*) = r^*$. Figure 2.1 shows these results diagrammatically, depicting both $r(m_s)$ and $v'(r)$.

Figure 2.1: Supply-Side Margin Leading to Efficient Levels of Spending on R&D

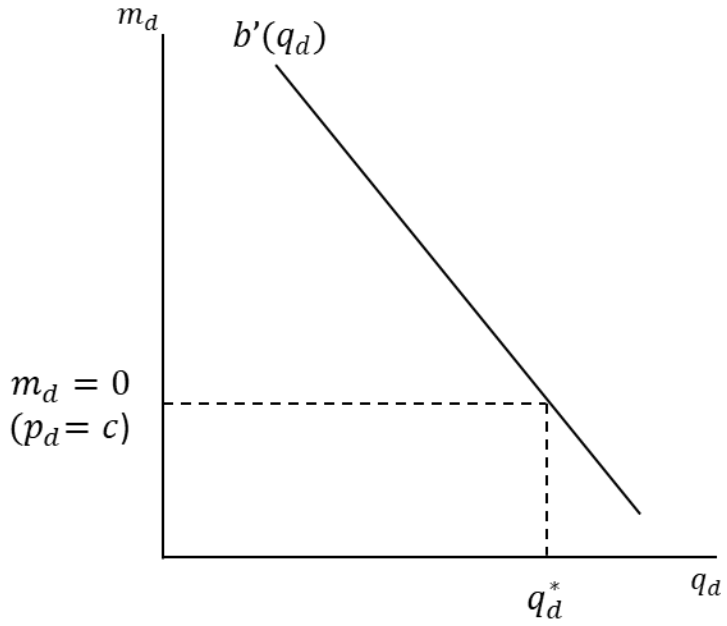


[27] For example, a longer exclusivity period increases the time a firm sells at a high price, increasing the average price, p_s.

Figure 2.1 can be used to show the m_s that leads to the efficient level of R&D spending, r^*. $v'(r)$ equals the marginal cost of spending on R&D at r^*, the level spending on R&D for dynamic efficiency. This r^* is induced by the "first-best" m_s, which we will refer to as m_s^*.

Turning to drug consumption, we define p_d as the price paid by the consumer with an associated margin $m_d = p_d - c$. The "consumer" here is the patient, recognizing that the clinical decision-making around drugs, like other medical therapies, is heavily influenced by physicians and possibly insurers. The quantity of drugs consumed is q_d. We express the benefit of drug consumption as $b(q_d)$ with $b'(q_d) > 0$ and $b''(q_d) < 0$. Figure 2.2 shows drug consumption as a function of p_d, or alternatively, m_d. The first-best on the demand side can be described simply as well. The demand-side margin leading to efficient consumption is $m_d = 0$, as shown in Figure 2.2.

Figure 2.2: Demand-Side Margin Leading to Efficient Levels of Consumption

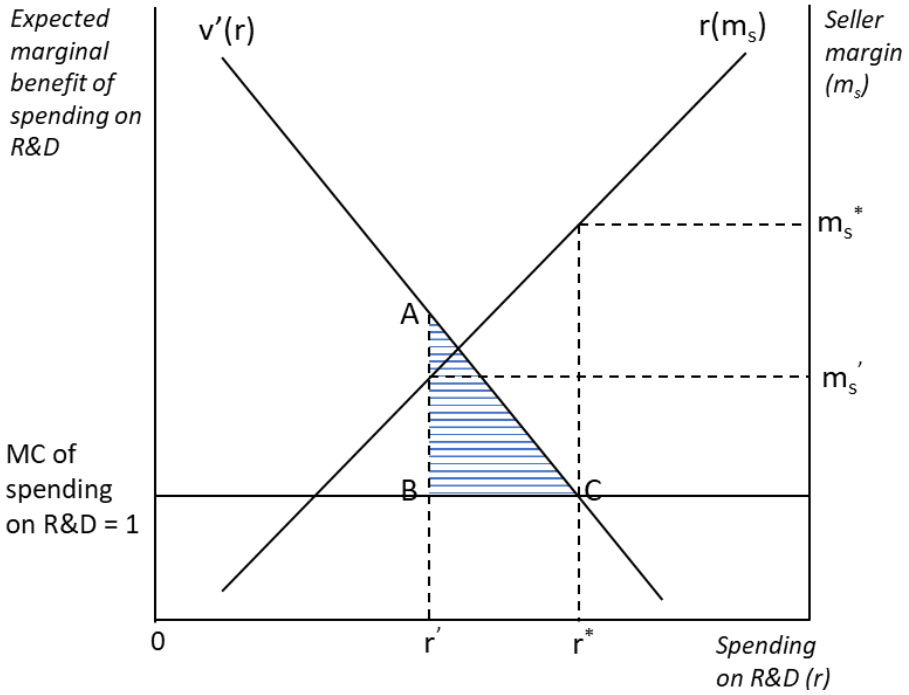


Thus, the first-best combination of the supply-side and demand-side margins is m_s^* and $m_d = 0$. m_s^* leads to "dynamic" efficiency in drug discovery and $m_d = 0$ to "static" efficiency in current drug consumption.

2.3.2 Welfare Loss in Drug Markets

Welfare loss in drug markets arises when m_s and m_d deviate from the first-best values.[28] We start by describing welfare loss in relation to dynamic efficiency. For any supply-side margin above/below m_s^*, the level of investment in R&D will be too high/low in relation to the first-best value and generate a welfare loss. Figure 2.3 shows that for an arbitrary supply-side margin m_s', the spending on R&D is r' and the associated welfare loss is equal to triangle ABC, which measures the expected benefit lost, net of the cost of the spending on R&D.

Figure 2.3: Dynamic Welfare Loss from Moving to m_s' from m_s^*



[28] Our welfare framework differs from Lakdawalla and Sood (2009) (L&S) in important ways. One of the margins they consider is the effect of drug firm prices on insurance premiums and the number of insured and uninsured. We, in effect, assume everyone has insurance. Demand response in L&S comes from consumers. With PBMs, we assume that it is the heightened demand response from PBMs that motivates drug firms to discount, and that this motivation is unaffected by demand-side prices. Another difference is one of emphasis rather than substance. On page 542 L&S argue, "there are always gains to leveraging insurer market power against pharmaceutical manufacturers, to obtain price concessions on the margin." The reason is that drug firms maximize profits with respect to their pricing and a small decrease in price has a first-order effect on static efficiency but only (by the envelope theorem) a second-order effect on profits and incentives for R&D. This is not true in our framework. Our orientation is to the regulations in the background that influence drug firm profit. Generally, any single firm may be maximizing, but changes in the supply-side margin can have first-order dynamic effects. L&S in not inconsistent here. On page 544 they say that the current level of R&D investment might be "excessive or insufficient." Translating this point about insurer market power into a world with PBMs, it is not true that a PBM with market power extracting some discount can always improve welfare. Finally, in common with L&S, we ignore financial risk protection differences among demand-side pricing alternatives.

The expression for the magnitude of loss associated with dynamic efficiency and the supply-side margin m_s' is:

$$WL_{dyn} = \frac{1}{2}\frac{v''(r)}{r'(m_s)^2}(m_s' - m_s^*)^2 \tag{2.1}$$

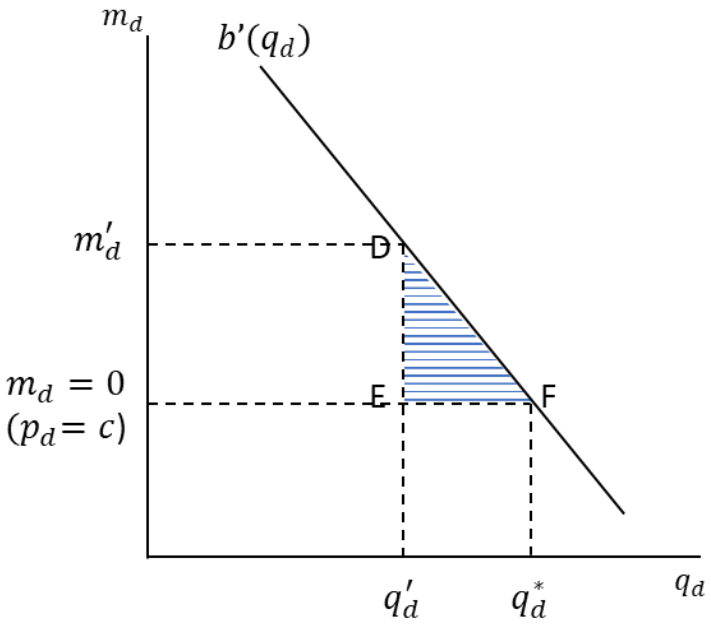
This expression for welfare loss is exact when the $v'(r)$ and $r(m_s)$ functions are linear, and otherwise the expression can be interpreted as a linear approximation to the loss.

We take a similar approach to static efficiency and depict welfare loss as a function of the demand-side margin, m_d. Any $m_d > 0$ leads to inefficient levels of drug utilization. Figure 2.4 shows the familiar static welfare loss associated with a demand-side margin $m_d > 0$ as triangle DEF. The expression for the magnitude of this loss is:

$$WL_{static} = \frac{1}{2}\frac{m_d^2}{b''(q_d)} \tag{2.2}$$

where $b''(q_d)$ is the slope of the (linear) marginal benefit (demand) curve. Welfare loss is defined to be a negative value.

Figure 2.4: Static Welfare Loss from Moving to m_d' from $m_d = 0$



Combining the expressions for static and dynamic welfare loss, the total welfare loss associated with a pair of demand and supply-side margins can be written

$$WL = \frac{1}{2}\frac{m_d^2}{b''(q_d)} + \frac{1}{2}\frac{v''(r)}{r'(m_s)^2}(m_s' - m_s^*)^2 \tag{2.3}$$

From (3), it is obvious that if m_d and m_s can be chosen independently, welfare loss is minimized at $m_d = 0$ and $m_s = m_s^*$, the first best combination of margins. Health care financing institutions alter the connection between m_d and m_s, and in so doing, determine the nature of the tradeoff between dynamic and static goals.

To proceed with our diagrammatic analysis, we simplify the expression to

$$WL \sim {m_d}^2 + \alpha(m_s' - m_s^*)^2 \tag{2.4}$$

where $\alpha = \frac{b''(q_d)v''(r)}{r'(m_s)^2}$ (2.5)

Here, α is a function of model parameters and can be interpreted as the relative importance of incentives to invest in R&D in relation to the importance of efficient consumption.

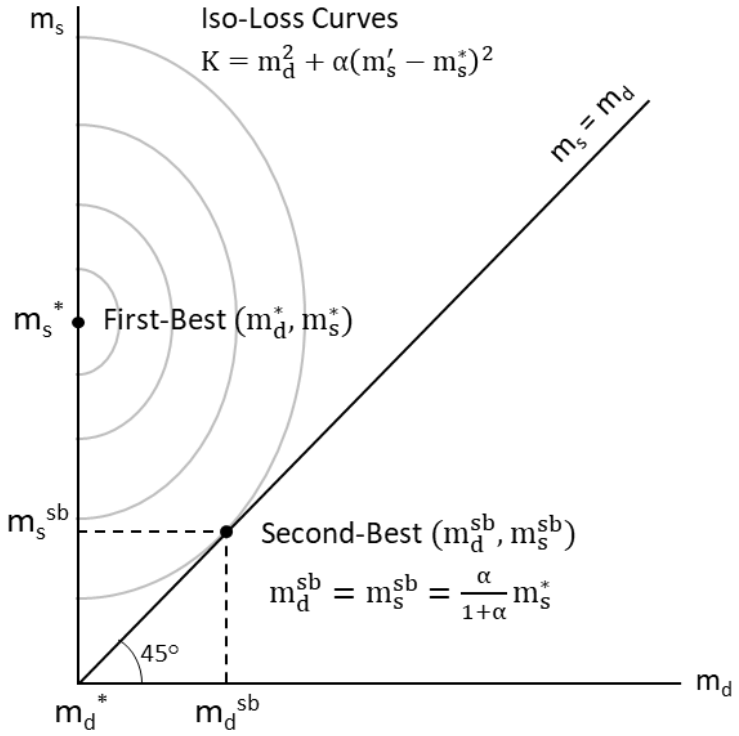
The expression for welfare loss allows us to determine pairs of m_s and m_d that lead to the same welfare loss. These pairs can be depicted diagrammatically as iso-loss curves, where each curve consists of m_d and m_s pairs that yield the same magnitude of welfare loss. The expression for an iso-loss curve is $K = m_d^2 + \alpha(m_s - m_s^*)^2$, where K is a constant. When $K = 0$, the "curve" is a point characterizing the first-best combination of margins. As K increases, the iso-loss curves take the form of ellipses around the first-best point.

For a typical consumption good, the price received by the seller must be the same as the price paid by the consumer, with $p_s = p_d$ and $m_d = m_s$. Under this constraint, the first-best combination of margins is unattainable. The second-best combination of margins minimizes welfare loss subject to $m_d = m_s$ leading to inefficient levels of investment in R&D and/or consumption.

Figure 2.5 depicts both the first-best and the second-best when $p_s = p_d$. Combinations of supply- and demand-side margins fall on a coordinate plane, with m_d assigned to the horizontal axis and m_s to the vertical axis. Figure 2.5 shows $m_s^* > 0$, the efficient dynamic margin, as well as $m_d^* = 0$, the efficient static margin. Together, point (m_d^*, m_s^*) is the first-best combination.

Figure 2.5 also shows the elliptical iso-loss curves, which are a function of both margins and are centered at the first-best point. As these curves get further from the first-best, welfare falls. The second-best combination is the tangency point between the $m_s = m_d$ line and an iso-loss curve.

Figure 2.5: Second-Best with No Insurance



In terms of our model parameters, the second-best combination of margins (m_d^{sb}, m_s^{sb}) is the point at which iso-welfare loss is minimized subject to $m_s = m_d$:

Min $m_d{}^2 + \alpha(ms - m_s^*)^2$ subject to $m_s = m_d$

Min $m_s{}^2 + \alpha(ms - m_s^*)^2$ with respect to m_s

FOC: $2m_s + 2\alpha m_s - 2\alpha m_s^* = 0$

$$m_s^{sb} = m_d^{sb} = \frac{\alpha}{1+\alpha}\, m_s^* \tag{2.6}$$

The second-best m_s^{sb} can be expressed as a simple function of the first-best m_s^*. Regardless of the value of α, m_s^{sb} is always less than m_s^*. With a larger α, the closer the second-best is to the first-best. Recall that α is the relative importance of incentives to invest in R&D versus in static efficiency.

2.3.3 Insurance Coverage for Drugs

Before turning to effects of PBMs on static and dynamic efficiency, we can illustrate how the model works by considering its application to the institution of health insurance for drugs, drawing on the insight from Lakdawalla and Sood (2009) that by decoupling consumer prices from the returns to innovation, public insurance can increase both static and dynamic efficiency.

Health insurance for drugs introduces a wedge between the price paid by consumers and the price received by sellers. In the usual context in health policy, this is regarded as problematic, creating incentives for overconsumption or moral hazard. The context is modified for prescription drugs in which the price the consumer pays without insurance is above marginal cost because of seller market power. Reducing the consumer price can improve welfare. The observation that health insurance can counteract the welfare loss from monopoly dates back to Crew (1969).

Let the coinsurance rate (the share of the price paid by the consumer), be β, $0 < \beta < 1$.[29] Then, with health insurance, the relationship between the demand- and supply-side margins is:

$$p_d = \beta p_s$$

$$m_d + c = \beta(m_s + c)$$

$$m_s = \frac{m_d}{\beta} + \frac{(1-\beta)}{\beta} c \tag{2.7}$$

[29] Copayments instead of coinsurance would be an easier case, because in principle there could be complete decoupling of demand and supply-side margins. As Lakdawalla and Sood point out, the general case has some coupling, as even with a formulary with a copayment structure, price set by the firm can affect tier placement. The coinsurance case here is a simple version of the more general case. Our conclusions are unaltered if insurance is in the form of copayments.

Without health insurance for drugs, $m_s = m_d$, but with insurance, the relationship changes to $m_s = \frac{m_d}{\beta} + \frac{(1-\beta)}{\beta} c$ and there is a different second-best combination than there is without insurance. To find it, we minimize the welfare loss subject to this new constraint:

Min $m_d{}^2 + \alpha(m_s - m_s^*)^2$ subject to $m_s = \frac{m_d}{\beta} + \frac{(1-\beta)}{\beta} c$

Min $(\beta m_s - (1-\beta)c)^2 + \alpha(m_s - m_s^*)^2$ with respect to m_s

FOC: $2\beta^2 m_s - 2\beta c + 2\beta^2 c + 2\alpha m_s - 2\alpha m_s^* = 0$

$$m_s^{sb} = \frac{\alpha m_s^* + \beta c(1-\beta)}{\beta^2 + \alpha} \tag{2.8}$$

$$m_d^{sb} = \frac{\alpha(\beta m_s^* - c(1-\beta))}{\beta^2 + \alpha} \tag{2.9}$$

Figure 2.6 depicts the second-best combination of margins with insurance. Feasible combinations of margins are depicted as a line of slope $\frac{1}{\beta}$ that intercepts the vertical axis at $\frac{(1-\beta)}{\beta} c$. This slope is steeper than 1, the slope without insurance. We plot the iso-loss curves as above. The second-best combination is the tangency point between the constraint line and an iso-loss curve.

Figure 2.6: Second-Best Combinations of Margins with Insurance

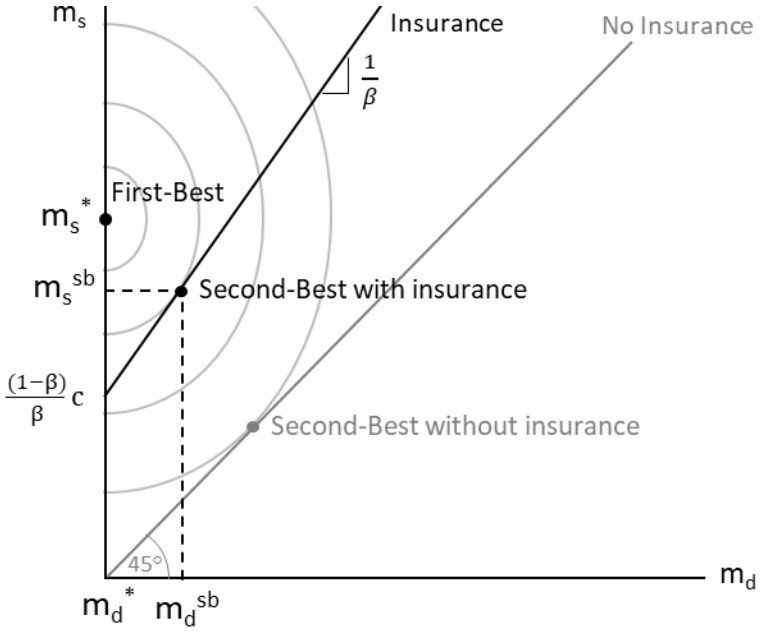
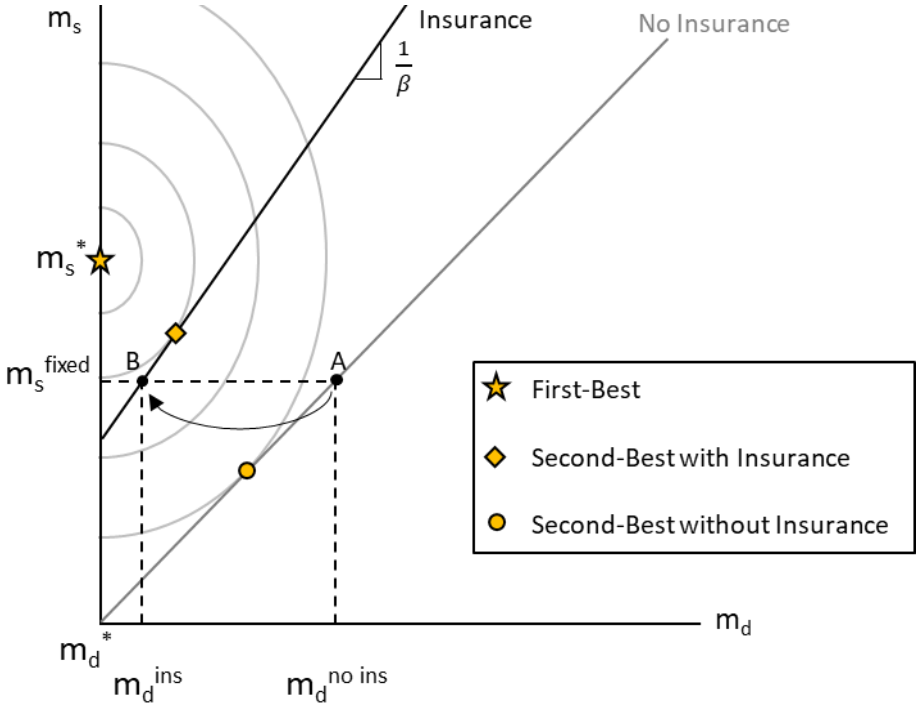


Figure 2.6 shows that health insurance improves the static-dynamic tradeoff by moving the feasible combinations of margins up and to the left, and that the second-best with insurance is on an iso-loss curve closer to the first-best and as a result better than without insurance.[30] We can also see this mathematically by comparing Equation (2.6) to Equation (2.8) and Equation (2.9).

We now turn to outcomes and consider, in the presence of a p_s fixed by regulatory policy, how the equilibria are different in the worlds with and without health insurance. Fixing p_s in both contexts is equivalent to fixing m_s. Given the expressions that govern the relationships between m_s and m_d in the worlds with Equation (2.7) and without insurance ($m_s = m_d$), given β, it is clear that at any fixed m_s, the corresponding m_d without insurance is larger than with the first-best $m_d^* = 0$, the equilibrium under insurance improves social welfare. We depict this graphically in Figure 2.7.

Figure 2.7: Welfare Improvement from Insurance Relative to No Insurance, Given a Fixed m_s



[30] There are cases where insurance does not lead to an improvement in the second-best. See Figure B.1 in Appendix B for a diagrammatic example. The condition on c and β that leads to the second-best under insurance as better than the second best without insurance is $\frac{1-\beta}{\beta} c < m_s^* + \frac{m_s^*}{\sqrt{1+\alpha}}$.

In Figure 2.7, the fixed seller's margin is m_s^{fixed}. With this fixed seller's margin, the outcome without insurance is point A and the outcome with insurance is point B, since the demand-side margin with insurance is less than without insurance. Under a fixed p_s, moving from no insurance to insurance increases welfare, moving from point A to point B.

2.3.4 Pharmacy Benefit Management Firms

Here we introduce a second health care financing institution, the PBM, which intermediates between the drug manufacturer and the health insurer. Health insurance remains in place. We focus on the primary function of PBMs, to use buying power to extract lower prices from manufacturers.[31] The manufacturer now sells to the PBM and offers the PBM discounts (i.e., rebates) in exchange for favorable placement on a formulary. The PBM can extract rebates because it makes the demand for the product more elastic, from the manufacturers' perspective.[32]

We consider a competitive PBM sector and one where PBMs have market power. This second case is relevant as market power in relation to drug suppliers is a part of the PBM business model. Large PBMs with substantial market share may also exercise market power in relation to the insurers with which they contract. We capture this feature by considering different degrees to which a PBM passes on rebates to the insurer. A PBM uses market power with respect to manufacturers by extracting a rebate. A PBM exercises market power with respect to insurers by passing along only a share of that rebate. Keeping some of the rebate is analogous to a monopoly markup over cost (the PBMs acquisition cost of the drug). The markup in this case is limited by what the insurer would have to pay for the drug if it purchased the drug directly from the manufacturer.

[31] Lakdawalla and Sood (2009) consider negotiations on prices but say that transactions costs for discounts can degrade the welfare improvement from them. PBMs with market power in our context can be interpreted as a transactions cost.

[32] See Duggan, M., & Morton, F. (2010). The Effect of Medicare Part D on Pharmaceutical Prices and Utilization. American Economic Review, 100(1), 590-607.

We denote the rebate as r. Generally, the PBM keeps $(1-\gamma)r$ of the rebate, passes γr through to the health insurance plan. The relationship between the margins is now:

$$p_s - c - r = m_s$$

$$p_d = \beta(P_s - \gamma r)$$

As before, we can characterize the relationship between the demand and supply-side margins in the presence of the new intermediary:

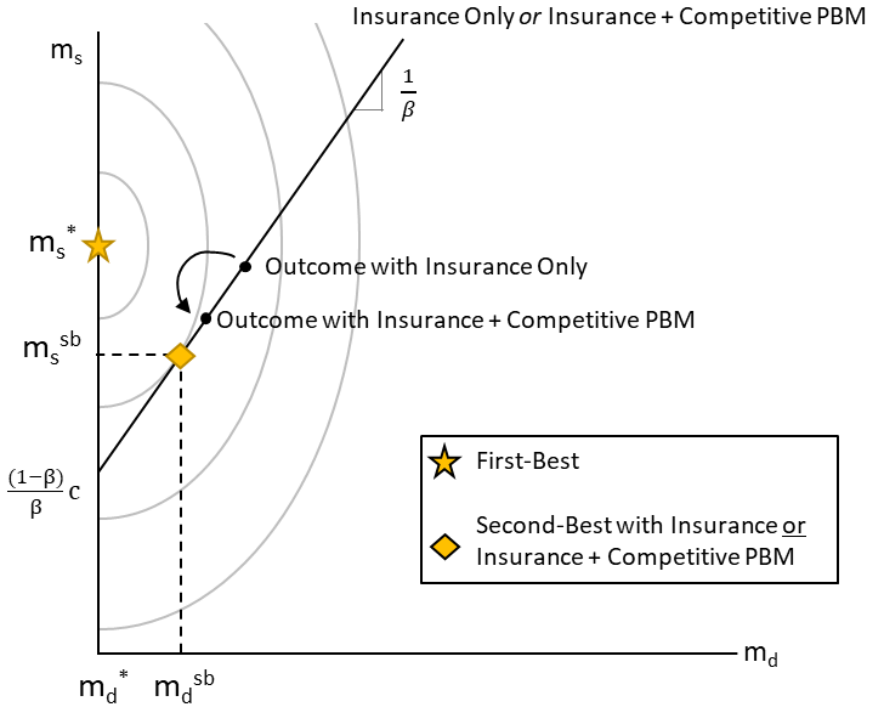
$$m_d + c = \beta(c + m_s + r - \gamma r)$$

$$m_s = \frac{(1-\beta)}{\beta}c + \frac{m_d}{\beta} - (1-\gamma)r \tag{2.10}$$

Consider first a competitive PBM where competition forces the PBM to pass the entire rebate though to the health insurer, $\gamma = 1$. In this case, the feasible combinations of m_s and m_d in Equation (2.10) are the same as in Equation (2.7) with insurance only. Adding a competitive PBM has no effect on the tradeoff between dynamic and static efficiency or on the second-best combination of margins.

How can a competitive PBM change welfare? If we regard p_s as set by regulation, the competitive PBM obtains a discount that reduces m_s and that passes on to the health plan, reducing m_d. Whether this is welfare improving depends on the starting point. If the supply- and demand-side margins were "too high" under insurance relative to the second-best, a competitive PBM would move the equilibrium down and to the left on the m_s-m_d tradeoff line, which can improve welfare. If the supply-side margin were already too low in relation to the second-best, reducing it further would reduce welfare. Figure 2.8 depicts a welfare-improving shift due to a competitive PBM.

Figure 2.8: Example of Welfare-Improving Shift from Adding a Competitive PBM to Insurance



More generally, in a world with a PBM in addition to health insurance, we can solve for the welfare-maximizing combination of margins, which is the tangency point between the constraint line and an iso-loss curve.

Min $m_d{}^2 + \alpha(m_s - m_s^*)^2$ subject to $m_s = \frac{m_d}{\beta} + \frac{(1-\beta)}{\beta}c - (1-\gamma)r$

Min $(\beta m_s - (1-\beta)c + (1-\gamma)\beta r)^2 + \alpha(m_s - m_s^*)^2$ with respect to m_s

FOC: $2\beta(\beta m_s - (1-\beta)c + (1-\gamma)\beta r) + 2\alpha m_s - 2\alpha m_s^* = 0$

$$m_s^{sb} = \frac{\alpha m_s^* + \beta c(1-\beta) - \beta^2 r(1-\gamma)}{\beta^2 + \alpha} \tag{2.11}$$

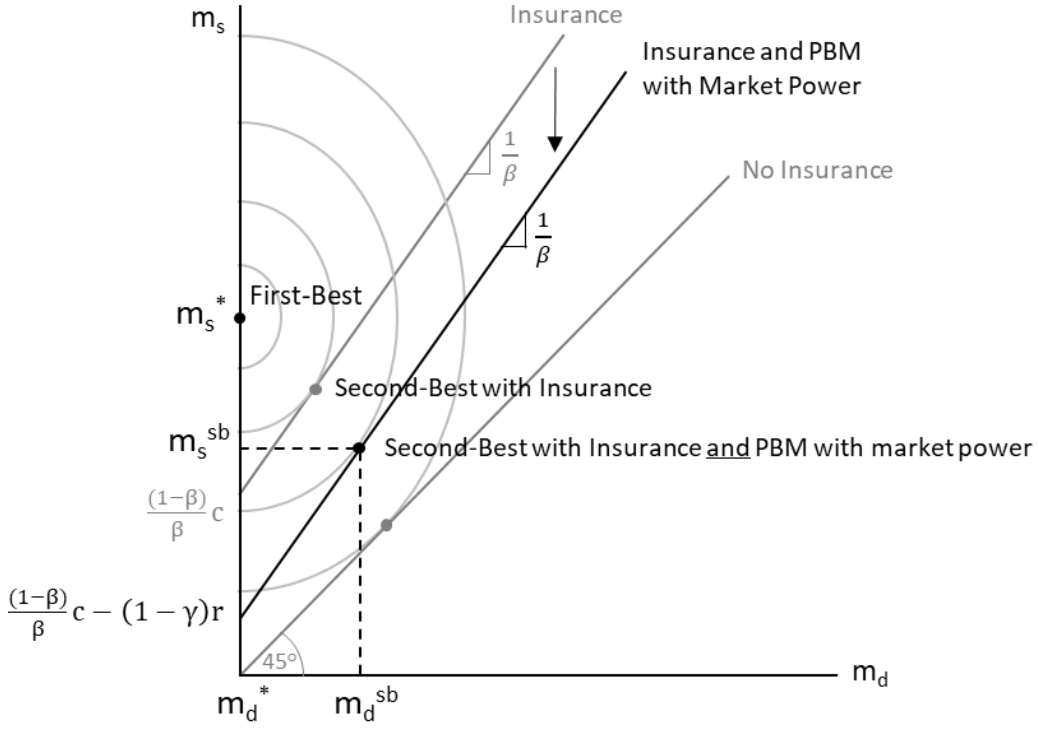
$$m_d^{sb} = \frac{\alpha(\beta m_s^* - c(1-\beta) + \beta r(1-\gamma))}{\beta^2 + \alpha} \tag{2.12}$$

The second-best seller's margin under PBM in Equation (2.11) is always less than or equal to the second-best seller's margin under insurance in Equation (2.8), because the numerator of Equation (2.11) subtracts $\beta^2 r(1-\gamma)$, a term that is either zero or positive, from the numerator of Equation (2.8). And, the second-best demand-side margin is always higher in the presence of a PBM

with market power in Equation (2.12) than with health insurance only in Equation (2.9) because the numerator of Equation (2.12) adds $\alpha\beta r(1-\gamma)$ to the numerator in Equation (2.9), and that term is positive if the PBM keeps any share of rebates. In terms of second-best comparisons then, the PBM with market power reduces efficiency on both fronts in relation to a competitive PBM sector.

Figure 2.9 shows this result diagrammatically, depicting the second best under insurance and a PBM with market power, $\gamma < 1$. Note how the constraint line has shifted down from the world with insurance by $(1-\gamma)r$, though its slope remains at $\frac{1}{\beta}$ as with insurance only. If the PBM retains any of the rebate, the second-best combination of margins is degraded.

Figure 2.9: Second-Best Under Insurance and PBM with Market Power



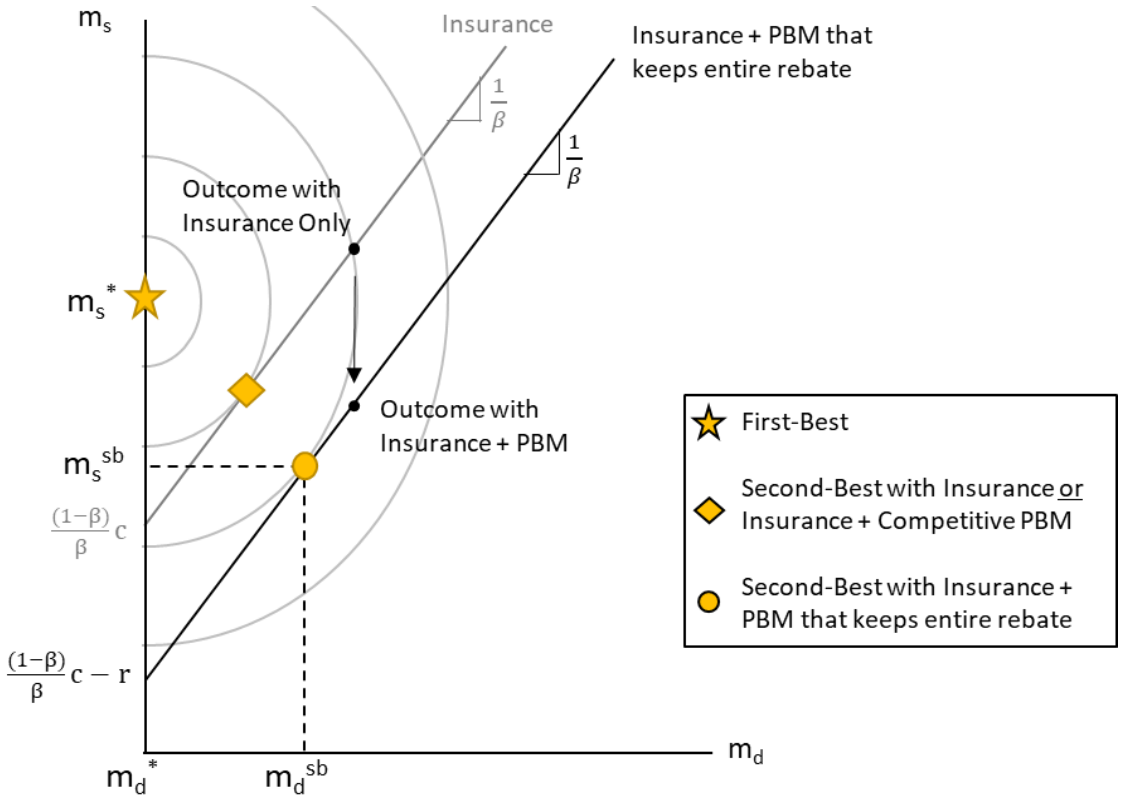
Consider now the case in which a PBM with market power passes none of the rebate through to the insurer, $\gamma = 0$, the polar opposite of the competitive PBM case. From Equation (2.10) we can see that the PBM shifts the m_s-m_d line down by r. The tradeoff between m_s and m_d has been altered by the PBM, since the discounts the PBM takes from the manufacturer are not

passed through to the health insurer or consumer, and the second-best in this world is worse than with insurance only or with insurance plus a competitive PBM.

We now consider how the introduction of a PBM with market power affects welfare. In a case where the m_s is very high and above m_s^*, then a PBM with market power improves welfare by reigning in the m_s. We depict an example in Figure B.2 in Appendix B. For a unilateral reduction in m_s to improve welfare (without changing m_d), innovation policy would have to be far from optimal.

When the PBM keeps the entire rebate ($\gamma = 0$), for any fixed set of policies affecting p_s, a discount of r reduces m_s. This is shown as a downward movement of m_s in Figure 2.10. The realized m_d is the same as in the world without a PBM. Graphically, this is depicted as a vertical shift downward. At any initial equilibrium where, in a second-best payment policy, $m_s < m_s^*$, this shift down is unambiguously welfare-reducing. Figure 2.10 shows a welfare decreasing shift in outcomes from the world with insurance only to the world that adds a PBM that keeps the entire rebate.

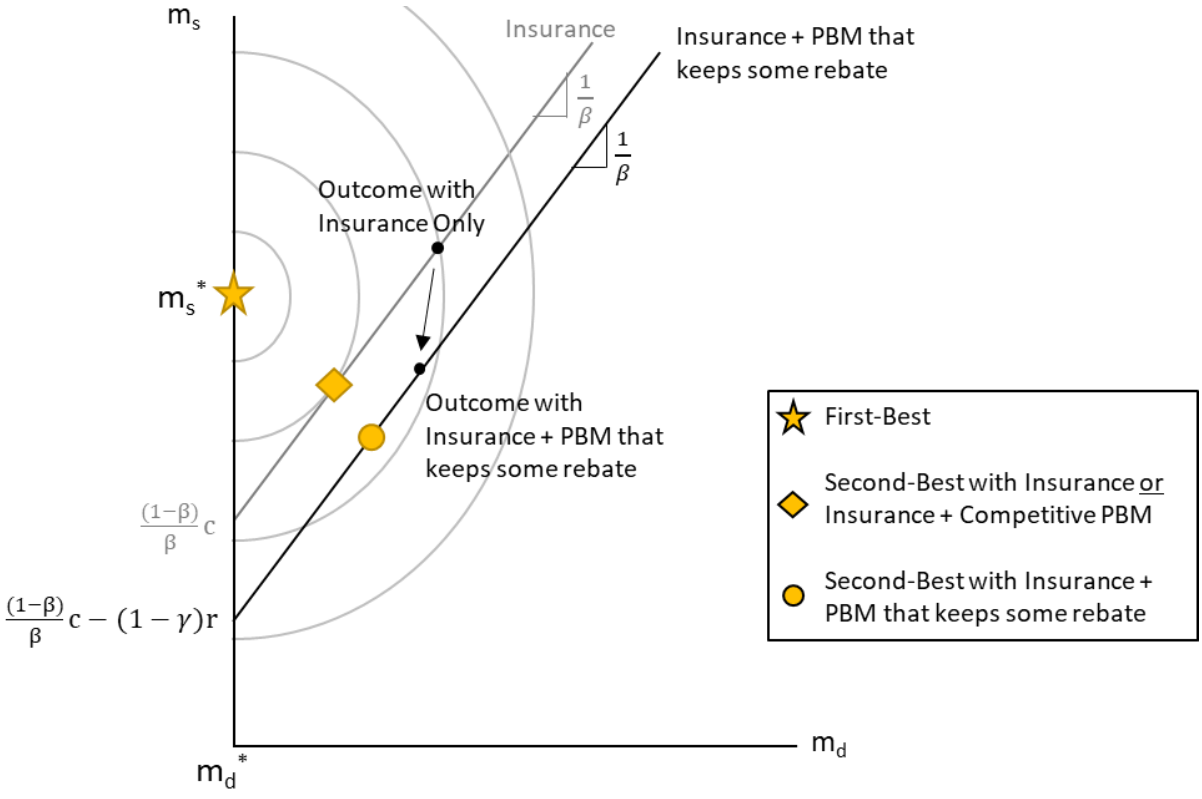
Figure 2.10: Shift from Insurance Only to Insurance and PBM that Keeps Entire Rebate



It is important to note that this equilibrium shift will not play out if the PBM takes the whole rebate and the insurance plan is no better off than it was without the PBM. Insurance plans will only contract with the PBM if the PBM makes them better off, for example by passing through some of the rebate, by attracting more enrollees to the insurance plan, or by helping the insurer compete.

In the intermediate case, with $0 < \gamma < 1$, the m_s-m_d schedule shifts downward, but not as far as when $\gamma = 0$. Thus, the second-best is worse than under insurance or a competitive PBM, and better than under a PBM that keeps all of the rebate. In terms of market outcomes, if the PBM passes on some of the rebate, the health plan can pass it on to consumers in the form of a lower m_d. There may or may not be improvement in welfare, again depending on the starting point and, on how large the rebate is, and on α. Figure 2.11 depicts a welfare-improving change in outcomes caused by going from insurance only to insurance with a PBM that keeps some of the rebate. In this example, the starting point had a supply-side margin higher than m_s^*.

Figure 2.11: Example of Welfare-Improving Change due to PBM with Market Power



2.4 Discussion

We show, in pictures, how health care financing institutions affect the static-dynamic tradeoff in pharmaceutical markets. First, we illustrate Lakdawalla and Sood's (2009) main insight: that health insurance for drugs is welfare improving. We then add PBMs to the framework. Regardless of whether PBMs are competitive or have market power, if they can extract discounts from manufacturers when prices are fixed, PBMs will always reduce the pharmaceutical firm's margin, which decreases incentives for innovation. If, in the absence of the PBM, the firm's margin was set at a dynamically optimal level, then PBMs degrade dynamic efficiency. We show that PBMs can improve static efficiency only when they do not keep all rebates. However, insurance firms will only contract with PBMs if they are better off for doing so. Thus, the scenario where the PBM keeps all the rebates may not actualize.

A main question is whether the dynamic welfare loss caused by PBMs is outweighed by static welfare gain. In most cases, a PBM that extracts rebates but does not pass any rebates through to the health plan does not help static efficiency and reduces welfare. In terms of second-bests, we show that the second-best with insurance only, or with insurance plus a competitive PBM, is better than the second-best where a PBM keeps some of the rebate. In terms of equilibria, whether a PBM increases or decreases welfare depends on the starting point and the shape of the iso-loss curves.

If prices are fixed, our model shows that a PBM that extracts rebates from manufacturers will decrease incentives for innovation. However, PBMs can provide more services than just price negotiation. Some of their markup to plans is not simply keeping the rebate, rather, it can be considered a payment for expertise in benefit design, improvements in medication adherence, management of chronic conditions, among other services, which we do not consider in our model.

A limitation of our analysis is that we cannot shed light on what the optimal margin for innovation is, and where we currently are relative to that point. In some therapeutic areas there may

be too little innovation, and in others too much. We are also unable to say what values parameters like α correspond to. As a result, when we turn to market outcomes, we are can only say that welfare gains or losses could potentially happen and depend on the starting point relative to the optimal margins, which is unknown on the dynamic side. In addition, issues of asymmetric information, agency, and others can interfere with efficient outcomes. Finally, vertical integration between insurers and PBMs has been increasing,[33] and we do not consider vertical integration in our model.

Overall, our paper highlights health care financing institutions for pharmaceuticals may affect both static and dynamic efficiency. Though health insurance is one of the few schemes to increase access to drugs that does not directly reduce incentives for innovation, the competitiveness of the combined health insurance and PBM ecosystem has the potential to improve or hurt social welfare, on both the static and dynamic dimensions. Though it can be straightforward (or politically convenient) to think about drug policy through the lens of one of our graph axes—either innovation or access—we stress that social welfare encompasses both.

[33] See Fein, A. "Insurers + PBMs + Specialty Pharmacies + Providers: Will Vertical Consolidation Disrupt Drug Channels in 2020?" Drug Channels. December 12, 2019. Available at https://www.drugchannels.net/2019/12/insurers-pbms-specialty-pharmacies.html

Chapter 3

Pharmacy Benefit Managers, Plans and Coverage in Medicare Part D: An Analysis of Ten Therapeutic Classes

Author: Annabelle C. Fowler

3.1 Introduction

The enactment of Medicare Part D in 2006 extended prescription drug coverage to elderly Americans, and the voluntary program now enrolls 45 million people.[1] Because pharmaceuticals make substantial contributions to health and social welfare,[2] encouraging access to drugs and efficient levels of utilization is an important policy goal. In Part D, private insurers contract with the Center for Medicare and Medicaid Services to provide drug coverage to beneficiaries. The

[1] Cubanski, J., Damico, A., and Neuman, T. "10 Things to Know About Medicare Part D Coverage and Costs in 2019." Kaiser Family Foundation, June 4, 2019. Available at https://www.kff.org/medicare/issue-brief/10-things-to-know-about-medicare-part-d-coverage-and-costs-in-2019/

[2] See Lichtenberg, F. (2019). How many life-years have new drugs saved? A three-way fixed-effects analysis of 66 diseases in 27 countries, 2000-2013. International Health. 11(5):403-416.

architecture of Part D coverage hinges on formularies (i.e., tiered "networks" of covered drugs), which are developed by insurers, or more commonly by Pharmacy Benefit Managers (PBMs) on behalf of insurers. Formularies are a form of selective contracting and that spurs competition among branded drugs. As a result, though each Part D plan's drug benefit must be at least actuarially equivalent to a standard defined benefit and adhere to other coverage regulations, plans have substantial flexibility in what drugs are covered and at what out-of-pocket costs for beneficiaries. As a result, comparing the generosity or "extent" of coverage across plans can be challenging.

In this paper, I describe Part D coverage through the lenses of coverage generosity, clinical adequacy, and PBM differences. To do this, I define three measures of coverage generosity and apply them empirically to describe Part D coverage across ten drug classes. The ten classes have special attributes: three have no generics, two are classes where each of the drug products are clinically substitutable, and six are "protected," which means that plans must provide some coverage for substantially all drugs in those classes. A novel aspect of this paper is that it includes data on the PBMs associated with Part D plans. PBMs have a substantial role in determining formularies, but due to limited data availability, the interaction between insurers and PBMs has been understudied.

Many factors may affect the creation of formularies and prescription drug benefits, including the clinical effectiveness or drugs in a class, therapeutic class characteristics (e.g., the number of close substitutes), disease characteristics (e.g., acute versus chronic), plan competition, the importance of offset effects (i.e., where plans that minimize cost over medical care have different incentives than those that minimize cost over prescription drugs only), selection incentives, and others. Further, regulations that determine minimum coverage levels, such as the protected drug classes in Part D, also affect formulary design. The organizational levels involved in the design of prescription drug benefits each face different incentives and market conditions that can potentially affect drug coverage decisions.

In designing a drug benefit, stakeholders must decide which drugs are on formulary, their relative "ranking" or formulary tier, utilization management levers applied to each, and cost sharing amounts. Whereas a beneficiary may be concerned about the generosity of different plans, insurers and PBMs may prioritize providing cost-effective or clinically adequate formularies, without an explicit focus on generosity. This paper is anchored around facts on Part D coverage that speak to these issues. Section 2 provides a brief background of Medicare Part D and PBMs, Section 3 describes the measures and data I use to study formulary coverage, Section 4 describes Part D coverage, and Sections 5 concludes.

3.2 Background

3.2.1 Part D and Pharmacy Benefit Managers

Part D, Medicare's voluntary prescription drug insurance program, took effect in January 2006. Unlike other federal drug insurance schemes, Part D uses private plans that compete for enrollees based on premiums, benefit design, networks of pharmacies, covered drugs, and other characteristics. The program also includes a provision that bans government price negotiations with drug manufacturers. Instead, the program allows plans and entities like PBMs to do so. The goal of this design was to increase drug competition by allowing plans to selectively contract with drug manufacturers. Manufacturers would compete against one another (by offering price concessions to plans) so that their branded products would be included on the "preferred" tier of a plan's formulary. Preferred tiers are associated with lower cost sharing than non-preferred tiers or exclusion from coverage, so utilization for preferred drugs increases. The more a plan's benefit design can steer volume to certain drugs, be it through cost sharing, utilization management, or other tools, the more leverage the plan has in the negotiation. Duggan and Scott Morton (2008)

found that Part D's structure of having plans negotiate with manufacturers to create formularies led to more than a 13% decrease in the average prices of pharmaceuticals.

Medicare beneficiaries are in either Traditional Medicare (TM) or in Medicare Advantage (MA) plans. To join Part D, TM enrollees can sign up for a standalone prescription drug plan (PDP), and MA enrollees can choose a MA plan that includes a Medicare Advantage Drug Plan (MA-PD) as part of its benefit. Medicare has a standard Part D benefit every year[3] and plans may have a different structure as long as they have at least the same average benefit (i.e., are actuarially equivalent or better). Because plans have flexibility in designing their benefit subject to this constraint, there is considerable variation in their formularies, cost sharing, pharmacy networks, and other characteristics. The majority of Part D beneficiaries are in plans that do not conform to the standard benefit, and in 2016, every PDP deviated from the standard benefit.[4] Comparisons between PDP and MA-PD are difficult because the payment structure for MA has higher rates than under TM,[5] and MA-PD plans can use some of their MA payments to supplement Part D benefits or lower Part D premiums. MA-PDs must provide the basic benefit or more but not charge for any additions, and most MA-PD beneficiaries have benefits than go beyond the standard benefit.

PBMs have a major role in Part D. PBMs construct formularies on behalf of health plans, and because they represent beneficiaries across many plans, PBMs have more negotiation leverage against drug manufacturers than if plans negotiated on their own. In the U.S., the PBM industry is dominated by several large firms. In 2018, the top three PBMs (CVS Health, Express Scripts, and

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[3] The 2016 standard benefit is a $360 deductible and 25% coinsurance up to $3,310 in total covered spending. Over that amount, there is a coverage gap up to $4,850 in out-of-pocket spending. Above that, enrollees pay 5% coinsurance. See Trish, E. Kaiser, K. and Joyce, G. "How Would Sharing Rebates at the Point-Of-Sale Affect Beneficiary Cost-Sharing in Medicare Part D?" USC White Paper, March 17, 2020. Available at https://healthpolicy.usc.edu/research/how-would-sharing-rebates-at-the-point-of-sale-affect-beneficiary-cost-sharing-in-medicare-part-d/

[4] MedPAC, Status Report on the Medicare Prescription Drug Program. Chapter 14. March 2017. Available at http://www.medpac.gov/docs/default-source/reports/mar17_medpac_ch14.pdf

[5] See Gold, M. Medicare Part D's Importance Extends Far Beyond the Drug Benefit it Provides. Health Affairs Blog. January 15, 2016. Available at https://www.healthaffairs.org/do/10.1377/hblog20160115.052694/full/

OptumRx) managed over 75% of prescription drug claims.[6] This concentration has largely been driven by consolidation. In late 2012, Express Scripts acquired Medco to create the largest PBM.[7] In March 2015, OptumRX announced it would acquire Catamaran, with the deal closing in Q4 2015.[8]

The price concessions that PBMs obtain from drug manufacturers are known as rebates and are confidential. This secrecy around discounts has led to controversy, with some blaming PBMs for failing to pass rebates through to health plans and consumers. Though this may be true in commercial insurance in Part D PBMs appear to pass through virtually all rebates. In 2018, CVS Health responded to the Trump Administration's request for information regarding a potential drug price policy reform. CVS Health said that they "return over 95% of rebates to commercial clients and their members. For Medicare Part D plans, effectively 100% of the rebates are passed through to help lower premiums, which reduce costs for both the beneficiary and the government.[9]" Express Scripts also has stated that 100% of Part D rebates are passed through,[10] and a U.S. Government Accountability Office report found that PBM rebates offset Part D spending by 20%, from $145 billion to $116 billion, and that PBMs primarily received fees from health plans instead of keeping a portion of rebates.[11] An analysis in the same report examined 20 contracts between Part D insurers

[6] See Fein, A. "CVS, Express Scripts, and the Evolution of the PBM Business Model", Drug Channels. May 29, 2019. Available at https://www.drugchannels.net/2019/05/cvs-express-scripts-and-evolution-of.html

[7] Sorkin, A., and Nicholson, C. Express Scripts to Buy Medco for $29 Billion. DealBook. New York Times, July 21, 2011. Available at https://dealbook.nytimes.com/2011/07/21/express-scripts-to-buy-medco-for-29-billion/

[8] The transaction did closed in Q4 2015. Legacy contracts for Catamaran remained in place for a transition period. See Matthews, A. and Walker, J. UnitedHealth to Buy Catamaran for $12.8 Billion in Cash. Wall Street Journal, March 30, 2015. Available at https://www.wsj.com/articles/unitedhealth-to-buy-catamaran-for-12-8-billion-in-cash-1427709601

[9] CVS Health is now vertically integrated with Aetna. See CVS Health Responds to Request for Information on Trump Administration's Blueprint to Lower Drug Prices. Press Release on July 16, 2018. Available at https://cvshealth.com/newsroom/press-releases/cvs-health-responds-request-information-trump-administrations-blueprint#footnote-1%20https://www.gao.gov/assets/710/700260.pdf

[10] See "Cigna Reiterates Support for Proposed Merger with Express Scripts." Exhibit 99.1. August 2018. Available at https://www.sec.gov/Archives/edgar/data/701221/000095015918000341/ex99-1.htm

[11] U.S. Government Accountability Office Report. Medicare Part D: Use of Pharmacy Benefit Managers and Efforts to Manage Drug Expenditures and Utilization. GAO-19-498: Published: Jul 15, 2019. Publicly Released: Aug 13, 2019. Available at https://www.sec.gov/Archives/edgar/data/701221/000095015918000341/ex99-1.htm

and PBMs in 2016, and found that for 19 of them, "the primary revenue source for PBMs from services they provided to Part D plans was (1) a volume-based fee paid by plan sponsors based on the number of paid claims that the PBM processed; (2) a flat monthly per-member, per-month fee paid by plan sponsors; or (3) a combination of the two" (GAO, 2019).

PBMs have incentives to cover generic drugs and encourage switching to generics because PBMs make four times on generics than they do on brands.[12] PBMs do not receive rebates on generics, and instead make profits by leveraging "spread pricing" – the difference between what the PBM reimburses a pharmacy for dispensing a drug and what it charges the health plan for the drug.[13]

PBM Pharmacy and Therapeutics (P&T) committees, which must meet at least quarterly and are regulated by CMS, make recommendations on Part D formulary coverage of drugs. Specifically, P&T committee members must be practicing physicians or pharmacists, they must represent specialties that are relevant to plan enrollees, and at least one physician or pharmacist must be independent and "free of conflict with respect to the Part D sponsor and pharmaceutical manufacturers" (CMS, 2016). The P&T committee evaluates the tradeoffs between price and the clinical value of different drugs, decides what the formulary should include, and deploys the PBM's negotiation team to deal with the manufacturers. When a new product enters the market, P&T committees have up to six months to review it and make a formulary recommendation. P&T recommendations generally focus on clinical effectiveness, but they are not binding (CMS, 2016).

PBMs market themselves as adding more value than price discounts. According to a March 2017 MedPAC Status report on Medicare Part D, PBMs develop and maintain formularies, build

[12] See Sood, N., Shih, T., Van Nuys, K. and Goldman, Dana. "Follow the Money: The Flow of Funds in the Pharmaceutical Distribution System." Health Affairs Blog. June 13, 2017. Available at https://www.healthaffairs.org/do/10.1377/hblog20170613.060557/full/

[13] For more on spread pricing, see Langreth, R., Ingold, D. & Gu, J. "The Secret Drug Pricing System Middlemen Use to Rake in Millions." Bloomberg. September 11, 2018. Available https://www.bloomberg.com/graphics/2018-drug-spread-pricing/

pharmacy networks and negotiate the price the insurer will pay pharmacies to dispense prescriptions. PBMs also claim to add value by offering cheaper pharmacy channels, encouraging generics and moving utilization to cheaper branded drugs, improving beneficiary adherence, and managing specialty medications.[14] Usually, PBMs set formularies but plans have flexibility in deciding the cost sharing amounts associated with each tier, and what PBM services the plan wants to use.

An emerging literature examines how drug coverage responds to financial incentives (see, for example, Carey 2017, Geruso et al. 2019, Lavetti and Simon 2018, Han and Lavetti 2016) and to changes in regulation (Andersen 2017), but formulary design is still not well understood. In addition to direct factors like therapeutic class and drug characteristics, strategic factors like selection, offsets, and competition, there may be formulary placement in response to other factors such as saliency bias, if for instance, beneficiaries pick plans based on heuristics like looking at the cost sharing for branded drugs. There are also differences in the incentives that PDPs and MA-PDs face, despite both being types of Part D plans. For instance, stand-alone PDPs have no incentive to exclude drugs that are associated with high-cost patients, whereas MA-PD plans do. Similarly, since MA-PD plans minimize costs over health care expenditures overall, but PDPs minimize costs for drug spending only, MA-PD plans may be more likely to cover drugs that offset medical care spending.

3.2.2 Part D Protected Classes

Since Part D first started in 2006, CMS has designated six "protected" therapeutic classes. Plans are required cover "all or substantially all" of the drugs in these classes, which include anti-convulsants, antidepressants, antipsychotics, antineoplastics, antiretrovirals, and immuno-suppressants.[15] These

[14] See Pharmacy Benefit Managers (PBMS): Generating Savings for Plan Sponsors and Consumers. Prepared by Visante for the Pharmaceutical Care Management Association. February 2016. Available at https://www.pcmanet.org/wp-content/uploads/2016/08/visante-pbm-savings-feb-2016.pdf

[15] From Duggan et al. (2008), "'Substantially all' means that all drugs in the protected classes are expected to be included in plan formularies, with exceptions for multi-source brands of identical molecular structure, extended release products when an immediate-release product is included, products that have the same active ingredient, and dosage forms that do

six classes were protected for two primary reasons. The first was to mitigate benefit design that would allow plans to "cream-skim" by dissuading beneficiaries with certain conditions from joining a plan.[16] For example, by limiting coverage of antiretrovirals, a plan might have fewer enrollees with conditions like HIV/AIDs. The second was to ensure that beneficiaries who were using medications in those classes and were transitioning to Medicare from other plans would not have interruptions in their treatment.[17] Legislation in 2008 and 2010 ensured that protected classes would remain in Part D. It has become politically difficult to remove them as they are viewed as necessary protection for enrollees.[18] Indeed, drugs in these six categories are weaker substitutes for each other than the "average" drug, and sometimes patients might become resistant to some of these drugs and need to switch to another within the same class (Duggan et al., 2008).

Antidepressants, which are one of the six protected classes, are known for their heterogeneous patient responses.[19] Patients respond to different drugs within the class, some are far more effective than others, but it is not the same for each patient. As a result, there is an access argument for mandating that all these drugs be included on Part D formularies. The tradeoff is that if PBMs are unable to exclude drugs in protected classes from formularies, PBMs lose negotiation

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not provide a unique route of administration." See also Federal Register, Final Rule. 70 FR 4193. "Medicare Program; Medicare Prescription Drug Benefit." Jan. 28, 2005. https://www.federalregister.gov/documents/2005/01/28/05-1321/medicare-program-medicare-prescription-drug-benefit

[16] Other provisions to mitigate formulary design for selection include risk adjustment and a requirement that CMS review and approve each formulary. If plans can predict costly beneficiaries after risk adjustment, there is still an incentive for them to design their benefits to avoid these beneficiaries.

[17] See Medicare Modernization Act Final Guidelines – Formularies. "CMS Strategy for Affordable Access to Comprehensive Drug Coverage: Guidelines for Reviewing Prescription Drug Plan Formularies and Procedures." Available at https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/downloads/FormularyGuidance.pdf

[18] See Kocot S., McCutcheon, T., & White, R. "Protected class policy can promote both patient access and competition" Health Affairs Blog. Jan. 2019. Available at https://www.healthaffairs.org/do/10.1377/hblog20190118.805215/full/

[19] The classic trials on patient responses to antidepressants are from the National Institutes of Mental Health STAR*D Study, which was a federally funded, long-term pragmatic trial. STAR*D found that patients are heterogeneous in their responses, and that even if a patient did not respond to a drug in an antidepressant subcategory, she might still respond to a different drug in that subcategory. For more detail on STAR*D, see https://www.nimh.nih.gov/funding/clinical-research/practical/stard/allmedicationlevels.shtml.

leverage and are less likely to obtain lower prices. Yarbrough (2020) finds that protected class status in Medicare Part D led to over $100 million in additional spending per drug per year, driven both by increases in price and volume.

Protected classes require drugs to be "on formulary" but there is no explicit regulation on what the cost sharing for these products must be. A drug could be "covered" by many plans, but cost sharing could vary widely across them. Cost sharing and utilization management measures (e.g., step therapy or prior authorization) for all classes are decided by the plans.

3.2.3 Evaluating Drug Insurance Plans: Consumer Choice and Public Policy

A large literature on plan choice in Medicare Part D has found that beneficiaries do not always make choices in their best interest. Heiss et al. (2013) found that only 1 of 4 beneficiaries selected a Part D plan that minimized cost (from an ex ante perspective), and that if beneficiaries had chosen the cheapest plan, they would have each saved an average of $300. Similarly, Zhou and Zhang (2012) found that only 5% of beneficiaries chose the least expensive plan given their utilization, and over 20% of enrollees spent at least $500 more than if they had picked the cheapest plan. In a review of the literature on health insurance plan choice, Winter and Wuppermann (2019) highlight three reasons why enrollees make suboptimal plan choices. The first is that insurance is complex, that beneficiaries may not understand how plan features (e.g., deductibles) work, and as a result are unable to compare plans effectively. The second is large hassle or search costs due to the choice environment being too complicated, or if there is too much variation in the plan attributes that beneficiaries must evaluate. The third reason is due to cognitive biases. For example, Abaluck and Gruber (2011) found that Part D enrollees focus primarily on premiums instead of on other costs when choosing plans. They conclude that beneficiaries do not make fully rational plan choices.

Empirically, it appears that streamlining information for Part D beneficiaries can help them make better choices. Part D has an online tool, Plan Finder, that can help enrollees choose plans by

showing them the lowest cost plan given their current medication. However, only 14% of enrollment is via the tool, and some argue that the tool is clunky and complex. McGarry et al. (2018) run a randomized experiment to test if simplified data in Plan Finder can help improve Part D choices. They found that if Plan Finder displayed more straightforward cost data, beneficiaries would select lower cost plans of equal or better quality. In another study on decision aids and Part D plan choice, Bundorf et al. (2019) conducted a randomized field experiment and found that an online tool that gave "expert recommendations" based on personalized data led beneficiaries to improved plan choices. Though many of the trial's participants engaged with the tool, they were largely high-income and had high technological affinity. In addition, participants who were looking to change plans were more likely to use the tool. Also in the context of Part D, Kling et al. (2012) found that providing beneficiaries personalized cost data on plans, including which plan would be the cheapest for them, led consumers to switch to plans that saved them money. However, the evidence on the effect of personalized information on insurance choice in other settings is mixed.[20]

Evaluating a plan's coverage is not always straightforward. Beneficiaries will likely know the drugs they took in the previous year, but if they are forward-looking, they will also consider the breadth of a formulary. A forward-looking beneficiary would have to know about the cost sharing for different drugs, their clinical value, and the odds that she would need drugs she did not take in the previous year. Risk aversion might lead to a preference for more extensive coverage and risk protection. From a policymaker's perspective, comparing drug coverage across plans might help them assess if formularies are balancing access with cost control. For these reasons, both beneficiaries and policymakers may find measures of prescription drug insurance coverage to be useful. However, most of the approaches to evaluate health insurance do not translate directly to

[20] For example, Ericson et al. (2017) did not find that a personalized information campaigns had the same effect in the context of a health insurance exchange in Colorado, but they did not include a suggested alternative plan.

drug insurance plans with tiered benefits (Glazer et al., 2012). This paper describes and implements three measures that can be used to compare coverage across Part D plans.

3.3 Data, Sample, and Coverage Measures

To study Part D coverage, I assemble a dataset of 2016 Part D plans including the PBM associated with each. I define three measures to evaluate drug coverage and apply these measures empirically with a focus on ten therapeutic classes.

3.3.1 Part D Plan Benefit Design and PBMs

Part D Plans release details on their drug coverage for the following calendar before open enrollment, which runs from October 15 to December 7 each year. I use public-use CMS Part D Formulary Files for contract year 2016, which capture the coverage data released by Part D plans in October 2015. The Formulary Files include the universe of 2016 Part D plans and data on the formulary associated with each, plan-specific cost sharing structures that correspond to each formulary tier, and data on plan characteristics like type (i.e., MA-PD or PDP). Each formulary in the data is a set of drug identifiers and their corresponding tiers. I supplement these data with public-use 2016 CMS Contract Data. CMS makes available data on Medicare contracts, from which I pull plan-level enrollment, parent insurer information, and detail on plan types (e.g., HMO, PPO, etc.). If plan-level enrollment was less than 10 and thus masked, I input an enrollment of 5.

The Part D data show three of the four organizational levels involved in Part D coverage: plans, carriers and parent insurers (but not PBMs). Of these, the most granular is the plan, which corresponds to the plan a beneficiary would see when looking to enroll in Part D (e.g. Advantra Freedom (PPO), or Aetna Medicare Rx Saver (PDP)). The level above the plan is the carrier, which is an insurance organization that contracts with CMS to offer a Part D benefit (e.g. Coventry Health

and Life Insurance Co., or Aetna Health, Inc. of Texas). Above that is the parent insurer. For example, parent insurer Aetna, Inc. includes carriers Coventry Health and Life Insurance Co., Aetna Health, Inc. of Texas, and many others. To add PBMs to the data, I turned to online research, using primarily PBM and insurer press releases, SEC filings, and media articles. This effort allowed me to map PBMs to 1,928 plans, which corresponds to 75% of the plans in the sample and over 90% of the enrollment. Table 3.1 lists PBMs and their associated lives across PDP and MA-PD plans.

This paper studies 2,467 plans—1,676 MA-PD plans and 791 PDP plans—that correspond to 431 unique carriers and 152 parent insurers. I excluded 8 plans with no enrollees, 50 plans in U.S. territories, and 41 plans with no benefit data. I also excluded Medicare-Medicaid plans and Special Need Plans (n = 628). Plans for low income beneficiaries, including people eligible for Medicare and Medicaid, must have very low cost sharing.[21] As a result, these plans are unable to use financial incentives to steer volume the way other plans can.[22] The 2,467 plans in the sample are primarily for people who do not have severe or disabling chronic conditions, are not institutionalized, and are not eligible for Medicare and Medicaid. In 2016, 41 million people were enrolled in Part D, with about 60% in PDP plans and 40% in MA-PD plans.[23] As seen in Table 3.1, the sample of plans in this paper cover over 31 million people, with 64% in PDP plans and 36% in MA-PD plans.

Though each carrier is associated with a unique PBM, parent insurers, an organizational level above the carrier, may be associated with more than one PBM. This can occur after an insurer merger or acquisition if a legacy contract remains in place. For example, parent insurer Aetna

[21] In 2016, low income Part D beneficiaries had cost sharing amounts ranging from $1.20 to $2.95 for generics and drugs on preferred tiers, and $3.60 to $7.40 for other drugs. See 2021 to 2006 Medicare Part D Standard Benefit. Available at https://q1medicare.com/PartD-The-MedicarePartDOutlookAllYears.php

[22] Duggan et al. (2008) discuss cost sharing for low-income beneficiaries. Plans that serve these beneficiaries are less able to steer utilization with different cost sharing amounts, and "might seek to influence [beneficiary] choices through requirements for prior authorization for certain drugs, step therapy, or a more restrictive formulary."

[23] See MedPAC, Status Report on the Medicare Prescription Drug Program. Chapter 14. March 2017. Available at http://www.medpac.gov/docs/default-source/reports/mar17_medpac_ch14.pdf

acquired Coventry in 2012. At the time, Aetna had an agreement with PBM CVS Caremark that preceded the acquisition and Coventry had an agreement with Express Scripts. As a result, Coventry's Part D lives remained with Express Scripts through 2015 and switched to CVS Caremark in 2016.[24] To my knowledge, my PBM research accounts for the few legacy contracts that led to carriers within parent insurers having different PBMs in 2016.

Table 3.1 Pharmacy Benefit Managers and Associated Lives

Pharmacy Benefit Manager	MA-PD Lives (thousands)	PDP Lives (thousands)	Total Lives (thousands)	Share of Lives
CVS Caremark	989	7,365	8,354	26.7%
Humana	2,414	4,714	7,128	22.8%
OptumRX	2,255	4,803	7,058	22.6%
Express Scripts	1,315	919	2,234	7.1%
Catamaran	516	1,033	1,549	4.9%
Prime Therapeutics	399	596	995	3.2%
Medimpact	893	9	902	2.9%
Envision RX Options		366	366	1.2%
MagellanRX		46	46	0.1%
Blue Shield of California		44	44	0.1%
SelectHealth Prescriptions	37		37	0.1%
National Pharmaceutical Services	8		8	0.0%
Missing	2,536	38	2,573	8.2%
Total	11,362	19,933	31,295	100.0%

Note: Does not include SNPs, Medicare-Medicaid plans, plans in US territories, or plans that do not cover at least one of the drugs in the ten classes studied.

[24] Kelly, C. "Aetna/Coventry $15B Pharmacy Spend Will Be Managed By Different PBMs Near Term." August 27, 2012. Available at https://pink.pharmaintelligence.informa.com/PS054687/AetnaCoventry-$15B-Pharmacy-Spend-Will-Be-Managed-By-Different-PBMs-Near-Term

3.3.2 Therapeutic Classes and Drug Products

This paper studies coverage for ten therapeutic classes: Proton Pump Inhibitors (PPIs), Angiotensin II Receptor Blockers (ARBs); three antidiabetics, Glucagon Like Peptide-1 Receptor Agonists (GLP-1RAs), Dipeptidyl Peptidase 4 Inhibitors (DPP-4s), and Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2s); and five antidepressants, Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclics (TCAs), Monoamine Oxidase Inhibitors (MAOIs), and "Other," which includes buproprion and mirtazapine. Table 3.2 summarizes the primary clinical use and 2015 Part D 30-day prescriptions for each of the classes.[25]

Table 3.2: Summary of Ten Therapeutic Classes Studied

Class	Acronym	Primary Use	Note	2015 Part D 30-Day Fills
Proton Pump Inhibitors	PPIs	Heartburn and Gastric Acid	High within-class substitutability	89,502,125
Angiotensin II Receptor Blockers	ARBs	Blood Pressure	High within-class substitutability	60,249,364
Glucagon Like Peptide-1 Receptor Agonists	GLP-1RAs	Antidiabetic	No generics	2,146,004
Dipeptidyl Peptidase 4 Inhibitors	DPP-4s	Antidiabetic	No generics	11,695,399
Sodium-Glucose Co-transporter-2 Inhibitors	SGLT-2s	Antidiabetic	No generics	1,492,492
Selective Serotonin Reuptake Inhibitors	SSRIs	Antidepressant	Protected Class	78,168,557
Serotonin and Norepinephrine Reuptake Inhibitors	SNRIs	Antidepressant	Protected Class	19,228,811
Other Antidepressants	-	Antidepressant	Protected Class	16,343,717
Tricyclic Antidepressants	TCAs	Antidepressant	Protected Class	10,221,345
Monoamine Oxidase Inhibitors	MAOIs	Antidepressant	Protected Class	50,534

[25] The Part D 30-day fills come from the 2015 Part D Prescriber Public Use File, which I describe below.

These ten classes were chosen to reflect variation in Part D class protections, variation in which drugs within-class are considered clinical substitutes, and the extent of generic competition.

Despite patient heterogeneity in responses to antidepressants, substantial evidence shows that the effectiveness of each of the five antidepressant classes is comparable both across and within class, and each is associated with different side effects.[26] In its guidelines for treating depression, the American Psychiatric Association states that "for most patients, a selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), mirtazapine, or bupropion is optimal." MAOIs and TCAs are older and not used as often as the other three classes. MAOIs require dietary changes and can cause severe side effects, so they are usually used by patients who do not respond to other treatments. In addition, because of the health profile of the elderly, (e.g., prone to low blood pressure when standing up, cardiac disease) the guidelines state that SSRIs, SNRIs, and other antidepressants should be used over MAOIs or TCAs, since the latter can cause cardiovascular side effects. SSRIs and SNRIs are often considered first-line treatments.

For most patients, the effectiveness of antidepressants is comparable between and within classes, so factors that determine the drug prescribed include patient preferences, anticipated side effects, other medical conditions, potential drug interactions, and cost. Patients may sometimes need to switch antidepressants. If a patient is not responding to a drug, the guidelines say they can switch to another drug from the same class or from a different one. If the patient is switching because of side effects, they should switch to a drug with a different side effect profile, which may mean switching to a different class. Side effects can also be managed by taking other drugs.[27]

[26] American Psychiatric Association. (2010) "Practice Guideline for the Treatment of Patients with Major Depressive Disorder." Available https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf

[27] Ibid. Specifically, see Table 7 of the Guidelines.

I specifically include ARBs, PPIs, and five types of antidepressants because of variation in how clinically substitutable the drug products in each of these classes are. As described above, patient response heterogeneity for antidepressants is well documented. A specific drug may work better for one person than for another or cause more side effects than for someone else. This heterogeneity in patient responses is an argument for generous Part D coverage in these classes, since even within subtypes of antidepressants, different active ingredients and drug products are not necessarily close clinical substitutes for a every patient. On the other hand, ARBs and PPIs are far more substitutable within-class, with patients responding similarly to the drug products in each of the two classes. As a result, it is less clinically important for formularies to cover all ARBs and PPIs.

I include the three antidiabetic classes because they had no generics as of October 2015 (the first was expected in 2018).[28] These classes provide a snapshot of coverage without generics, where manufacturers were likely eager to negotiate with PBMs for favorable formulary placement. Each of these classes is used as second line therapy for Type II diabetes in addition to metformin, and the 2016 American Diabetes Association Guidelines did not favor one of the three over the others.

I identified the active ingredients in each class and mapped them to products in Food and Drug Administration (FDA) databases. For antidepressants (SSRIs, SNRIs, MAOIs, TCAs, and Other), I follow Keyloun et al. (2017). Their paper studies adherence to specific antidepressants and to each of the five antidepressant classes, and includes a mapping of active ingredients to each class. For ARBs, PPIs, and antidiabetics (GLP1-RAs, DPP-4s, and SGLT-2s), I searched the World Health Organization Anatomical Therapeutic Chemical classification directory to retrieve the active ingredients associated with each class.[29]

[28] Takeda, the manufacturer of the three DPP-4s with the lowest 2015 utilization launched authorized generics of each in April 2016. Since the formulary data is from October 2015, these products were not included in initial 2016 coverage.

[29] The relevant Anatomical Therapeutic Chemical classes are C09CA (Angiotensin II receptor blockers, plain), A02BC (Proton pump inhibitors), A10BJ (Glucagon-like peptide-1 analogues), A10BH (Dipeptidyl peptidase 4 inhibitors), and A10BK (Sodium-glucose co-transporter 2 inhibitors). See https://www.whocc.no/atc_ddd_index/

I obtained the prescription drugs associated with each of these active ingredients using drugs@FDA, the FDA's National Drug Code Directory, and internet searches. I distinguish across branded and generic drug products, and excluded those approved in or after 2016. I also excluded a small number of products that were not approved for the clinical uses listed in Table 3.2.[30]

Utilization and estimated out of pocket costs for each of these drugs come from the 2015 Part D Prescriber Public Use File. This dataset is based on CMS's Chronic Conditions Data Warehouse. For every drug prescribed by providers and paid for by Medicare Part D, these data include total standardized 30-day prescriptions filled and total drug cost. The total cost figure includes "the ingredient cost of the medication, dispensing fees, sales tax, and any applicable administration fees and is based on the amount paid by the Part D plan, Medicare beneficiary, government subsidies, and any other third-party payers." I use total 30-day fills and total drug cost to estimate the out-of-pocket price a consumer would pay without insurance for one 30-day fill. This estimate is likely a lower bound of the true out-of-pocket cost that an uninsured person would incur.

A list of the products included in each class, together with their Part D 2015 utilization and estimated out-of-pocket cost, can be found in Appendix Table C.1. Some drugs are not covered by any 2016 plans but do have 2015 utilization. This is often due to discontinuations or entry in 2015, which may be too late for inclusion in the October 2015 data. Appendix Table C.2 lists these drugs.

3.3.3 Coverage Measures

I define and implement measures to compare Part D plan coverage. The extent of a prescription drug benefit's coverage can be defined (as an inverse measure) as the out-of-pocket expenditures a

[30] For example, pharmaceutical firm Novo Nordisk has launched two products with the active ingredient liraglutide, a GLP-1RA antidiabetic. Victoza (liraglutide) was approved in 2010 as an antidiabetic, and Saxenda (liraglutide), was approved in 2014 as a chronic weight management drug to treat obesity (and not for the management of diabetes). Since I am interested in GLP-1RAs that are antidiabetics, I include Victoza in the class but exclude Saxenda. See "FDA Approves Novo Nordisk's Saxenda as a Treatment for Chronic Weight Management." Diatribe Learn, December 23, 2014. Available at https://diatribe.org/fda-approves-novo-nordisk-saxenda-treatment-chronic-weight-management.

beneficiary of a given plan must make for drugs when she fills her prescriptions. Two factors contribute to this definition of coverage: (1) whether a drug is covered by a plan (i.e., if the drug is "on formulary"), and (2) if covered, the dollar amount of its associated cost sharing. A measure of drug benefit coverage must consider both components.

In a world with only one drug, studying coverage would be simple: the plan with the "best" coverage (from the consumer's perspective) would be the one that covered the drug with the lowest out-of-pocket cost sharing amount. If a plan did not cover the drug at all, then its beneficiaries would be responsible for the uninsured out-of-pocket cost at the pharmacy. This scenario is far from realistic as over three thousand different prescription drugs, corresponding to hundreds of thousands of National Drug Codes (NDCs), were prescribed for Medicare beneficiaries in 2015.[31] To at least partly relate drug benefit generosity to the demand characteristics of groups of beneficiaries, coverage measures may examine only a subset of products, such as a specific therapeutic class. For example, the extent of Plan A's coverage of ARB's could be calculated and compared to Plan B's. This measure would be relevant to beneficiaries who anticipate using ARBs, but less relevant to other beneficiaries.

For the empirical application of the measures below, I focus on the cost and coverage of 30-day prescriptions filled at non-preferred pharmacies, after deductible and before the coverage gap. Over 75% of Part D prescriptions meet these criteria. I calculate the measures at the plan-class level and aggregate to the parent organization-class and PBM-class levels, weighting by enrollment.

Measure 1: Cost Share Index

I adapt from Glazer et al. (2012) a measure of prescription drug benefit coverage based on the economic theory of price indexes. This measure considers the perspective of a "representative

[31] Part D Prescriber Data CY 2015. Available at https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/PartD2015.html

beneficiary" using drugs in proportion to the observed national distributions. In this paper, the Cost Share Index measure of plan p for a given bundle or class of drugs c, is the sum of the expected out of pocket spending of each drug d in bundle c, times the drug's utilization weight within the bundle.

$$Cost\ Share\ Index_{cp} = \sum_{d \in c} Cost\ sharing_{dp} \times weight_d$$

If a drug is not covered by a plan, it is included in the Cost Share Index and its associated cost sharing is the uninsured out-of-pocket price that a beneficiary would pay at a pharmacy. This value is listed for each drug in Appendix Table C.1, as is each drug's within-class utilization weight. To compare across classes, the measure can be divided by the maximum value of the Cost Share Index for each class, and it would then range from 0 (most generous) to 1 (least generous).

The Cost Share Index can be thought of as a measure of "overall" class coverage, or from the consumer's point of view, the generosity of a plan's coverage for a class. However, the measure ignores substitution across products within a class because the utilization weights for each drug are fixed and reflect average utilization across Part D. Realized weights at the plan level may be different, as beneficiaries may substitute away from products that have higher out-of-pocket costs.

Measure 2: Fixed Distribution Cost Index

Though the Cost Index Measure can be used to compare coverage across plans for the same class of drugs, it is less useful to understand how plans cover different classes. The Fixed Distribution Cost Index standardizes weights across classes to make the measure more comparable. More specifically, the Fixed Distribution Cost Index only considers the four top drug products in each class by share, combining across both brand and generic versions of the product.

From the plan's perspective, if the generic is covered, then that is equally as good coverage clinically relative to covering the branded version of the drug, since generics and their branded drugs are identical. Thus, to calculate the measure, the cost share assigned to each drug for each plan is the

minimum of the drug's brand and generic cost share. This means that if a plan only covers the generic version of a drug, then the drug is still considered covered. From an insurer's perspective, branded and generic versions of a drug are very close substitutes, and there are strong incentives for them to encourage enrollees to purchase generics. In addition, pharmacists in each of the fifty states are required to dispense generics if they are available and a prescriber has not indicated that a brand is medically necessary. Similarly, if an uninsured individual is prescribed a drug, she is likely to purchase the generic rather than the branded version due to cost and to generic substitution laws. If the drug product is not covered by a plan, it is assigned the generic uninsured out-of-pocket cost.

I assigned each top-four drug product a weight based on a fixed distribution across classes. The distribution comes from the simple average of the first-ranked product share across classes, the second-ranked product share across classes, and so on. Table 3.3 summarizes the top-four drug products in each class, their minimum uninsured cost, and their fixed weights.

More specifically, the Fixed Distribution Cost Index of class c and plan p is the sum of the minimum cost sharing associated with each of its top four drugs d times the fixed weights.

$$Fixed\ Distribution\ Cost\ Index_{cp} = \sum_{d \in c\,=\,1}^{4} \min\left(Cost\ Share\right)_{dp} \times\ fixed\ weight_{d}$$

Table 3.3 also includes the share of each drug product that is generic. With few exceptions, if a generic is available, utilization for a drug product is over 90% generic. The exceptions are PPI Nexium (15% generic), SNRI Pristiq (2% generic), and MAOIs Emsam and Marplan (0% generic). ARB Benicar and the three antidiabetic classes had no generics as of October 2015.

As with the Cost Share Index, the Fixed Distribution Cost Index can be divided by the maximum Fixed Distribution Cost Index for each class, and the measure would range from 0 (most generous) to 1 (least generous).

Table 3.3: Summary of Top 4 Drug Products in Each Therapeutic Class

Class	Top 4 Drug Product (combines brand + generic)	Min OOP Cost est.	Total Class 30-Day Fills	Drug Share Class	Drug Share Generic	Fixed weight
PPIs	Omeprazole (Prilosec)	$8.34	89,502,125	60%	100%	55%
PPIs	Pantoprazole (Protonix)	$8.89	89,502,125	23%	100%	25%
PPIs	Esomeprazole (Nexium)	$195.64	89,502,125	10%	15%	15%
PPIs	Lansoprazole (Prevacid)	$35.09	89,502,125	3%	95%	5%
ARBs	Losartan (Cozaar)	$5.82	60,249,364	63%	100%	55%
ARBs	Losartan/HCT (Hyzaar)	$6.85	60,249,364	20%	100%	25%
ARBs	Ibesartan (Avapro)	$13.36	60,249,364	5%	99%	15%
ARBs	Olmesartan (Benicar)	$161.20	60,249,364	4%	0%	5%
DPP-4s	Sitagliptin (Januvia)	$316.64	11,695,399	58%	0%	55%
DPP-4s	Sitagliptin/Met (Janumet)	$309.06	11,695,399	14%	0%	25%
DPP-4s	Linagliptin (Tradjenta)	$312.99	11,695,399	14%	0%	15%
DPP-4s	Saxagliptin Tab (Onglyza)	$314.50	11,695,399	7%	0%	5%
GLP-1RAs	Liraglutide (Victoza)	$533.59	2,146,004	66%	0%	55%
GLP-1RAs	Exenatide (Bydureon)	$497.40	2,146,004	17%	0%	25%
GLP-1RAs	Exenatide (Byetta)	$483.97	2,146,004	12%	0%	15%
GLP-1RAs	Dulaglutide (Trulicity)	$533.36	2,146,004	3%	0%	5%
SGLT-2s	Canagliflozin (Invokana)	$342.28	1,492,492	80%	0%	55%
SGLT-2s	Dapagliflozin (Farxiga)	$339.44	1,492,492	10%	0%	25%
SGLT-2s	Empagliflozin (Jardiance)	$341.56	1,492,492	5%	0%	15%
SGLT-2s	Canagliflozin/Met (Invokamet)	$325.75	1,492,492	4%	0%	5%
SSRIs	Sertraline (Zoloft)	$6.09	78,168,577	23%	100%	55%
SSRIs	Citalopram (Celexa)	$4.59	78,168,577	20%	100%	25%
SSRIs	Trazodone (Desyrel)	$5.68	78,168,577	19%	100%	15%
SSRIs	Escitalopram (Lexapro)	$10.28	78,168,577	14%	99%	5%
SNRIs	Duloxetine (Cymbalta)	$72.11	19,228,811	55%	99%	55%
SNRIs	Venlafaxine XR (Effexor XR)	$18.75	19,228,811	34%	99%	25%
SNRIs	Venlafaxine (Effexor)	$26.16	19,228,811	7%	100%	15%
SNRIs	Desvenlafaxine (Pristiq)	$157.91	19,228,811	4%	2%	5%
Other Antidep.	Mirtazapine (Remeron)	$13.30	16,343,717	45%	100%	55%
Other Antidep.	Bupropion XL (Wellbutrin XL)	$29.36	16,343,717	29%	99%	25%
Other Antidep.	Bupropion SR (Wellbutrin SR)	$17.59	16,343,717	20%	100%	15%
Other Antidep.	Bupropion (Wellbutrin)	$28.98	16,343,717	5%	100%	5%
Tricyclics	Amitriptyline HCL (Elavil)	$15.21	10,221,345	55%	100%	55%
Tricyclics	Nortiptyline HCL (Pamelor)	$8.16	10,221,345	23%	100%	25%
Tricyclics	Doxepin HCL (Generic)	$24.39	10,221,345	12%	100%	15%
Tricyclics	Imipramine HCL (Tofranil)	$17.34	10,221,345	5%	100%	5%
MAOIs	Phenelzine (Nardil)	$65.18	50,534	46%	93%	55%
MAOIs	Tranylcypromine (Parnate)	$248.34	50,534	36%	94%	25%
MAOIs	Selegiline Transderm (Emsam)	$1,312.7	50,534	16%	0%	15%
MAOIs	Isocarboxazid (Marplan)	$489.15	50,534	2%	0%	5%

Note: The four fixed weights are obtained by calculating the simple average of the ten first-ranked products, the ten second-rank products, and so on.

Measure 3: Lowest Cost Share

A third measure of coverage is simply a plan's least expensive ("lowest") cost sharing amount for a drug in a bundle or therapeutic class. The lowest cost share for plan p is the minimum out of pocket cost a beneficiary would have to pay for any drug d within a bundle of drugs c.

$$Lowest\ Cost\ Share_{cp} = \min_{d \in c} OOP_{dp}$$

If a drug is not covered by a plan, it is still included in the Lowest Cost Share, and its associated cost sharing is the uninsured out-of-pocket price that a beneficiary would pay at a pharmacy, which is listed for each drug in Appendix Table C.1.

Unlike the Cost Share Index, the Lowest Cost Share assumes all drugs within the defined set are perfect substitutes. From the beneficiary's perspective, the Lowest Cost Share can be thought of as a plan's "maximum" generosity and is the value of the cheapest drug in a class.

3.4 Facts on Coverage in Medicare Part D

3.4.1 Class Utilization is Highly Concentrated, Except for SSRIs

Though there are between 4 and 17 unique drugs in each of the classes I study, utilization in nine of ten classes is highly concentrated. Of course, utilization is endogenous as formularies respond to and affect the products that enrollees consume. Nevertheless, the clustering of volume on few products in most classes is striking. Table 3.4Table 3. summarizes the concentration per class using the Herfindahl-Hirschman Index (HHI), share of the top product, and sum of the shares of the top 3 products.

Market definition affects measures of concentration and generosity that rely on product shares (like the Cost Share Index). Table 3.4 includes a row that combines the three major

antidepressant classes (SSRIs, SNRIs and Other) into one aggregate class. By expanding the market definition, antidepressant market concentration appears much lower.

Table 3.4: Market Concentration by Therapeutic Class

Drug Type	Class	N Drugs	HHI	Share Top Drug	Share Top 3 Drugs
Antidiabetic	SGLT-2s	6	0.6535	80%	96%
Antidiabetic	GLP-1RAs	5	0.4818	66%	95%
Antidiabetic	DPP-4s	10	0.3770	58%	85%
Blood Pressure	ARBs	17	0.4375	63%	88%
Gastric Acid	PPIs	12	0.4256	60%	93%
Antidepressant	SNRIs	6	0.4211	55%	96%
Antidepressant	TCAs	15	0.3770	55%	95%
Antidepressant	MAOIs	4	0.3653	46%	98%
Antidepressant	Other Antideps.	6	0.3321	45%	95%
Antidepressant	SSRIs	15	0.1726	23%	63%
Agg. Antidepressant	SSRI + SNRI + Other	27	0.1004	16%	43%

Note: Number of drugs counts unique products, combining across branded and generic versions. Agg. Antidepressant groups SSRIs, SNRIs and Other Antidepressants into one class.

Thee HHIs of nine of the ten classes, except for SSRIs, are greater than 0.2000. Since antidepressants are not particularly substitutable within class and because all antidepressants are required to be on formulary, we may expect lower market concentrations in antidepressant classes. However, only SSRIs stand out among antidepressants, with an HHI of 0.1726, and 23% of utilization on the top product in the class. SNRIs are similar in concentration to some of the other non-antidepressant classes, with an HHI close to that of PPIs.

The top product across the five antidepressant classes ranges from 23% to 55%, which is less than the 58% to 80% range across the antidiabetics, ARBs and PPIs. Shares across the top 3

products for each of the antidepressant classes (except for SSRIs) is over 95%, similar to the non-antidepressant classes. The top 3 share for SSRIs is lower, at 63%. Thus, across antidepressants there is less clustering on the top product relative to other classes, but once we look at the top three products, there is just as much and sometimes more than on the other classes.

ARBs and PPIs are mostly all available as generics. From a clinical perspective, those beneficiaries can take the cheapest drug in the class, as they are largely substitutable. If we assume that beneficiaries are switching to the least expensive product, the concentration in those classes suggests that either formularies are covering similar sets of products as low-cost, preferred generics. similarly, or there are switching costs or inertia from taking branded versions of products that persist once the products go generic.

Conditional on being on formulary, I find that a drug's average cost sharing amount is positively correlated with its share, which means that more popular drugs are also the cheapest. For low-cost drugs, this may reflect steering and demand response. However, for drugs that have small shares (e.g., some MAOIs), those beneficiaries are unable to substitute away from those drugs, and plans may be aware of that and pricing these drugs higher accordingly. A limitation of my analysis is that I do not have individual-level utilization data to test this hypothesis.

3.4.2 MA-PD is More Generous than PDP for Branded and Low-Volume Classes

How does coverage vary across MA-PD and PDP plans, from the beneficiary's perspective? For each of MA-PD and PDP, I compare the average cost share index and average lowest cost share (weighted by enrollment) across plans. Table 3.5 summarizes the measures and the difference between them across plan types. When values in the "Difference" columns are negative, then on average MA-PD plans are more generous than PDP plans for that class. Table 3.5 shows that for the average Cost Share Index, MA-PD plans are more generous than PDP plans for ARBs, Antidiabetics, and MAOIs.

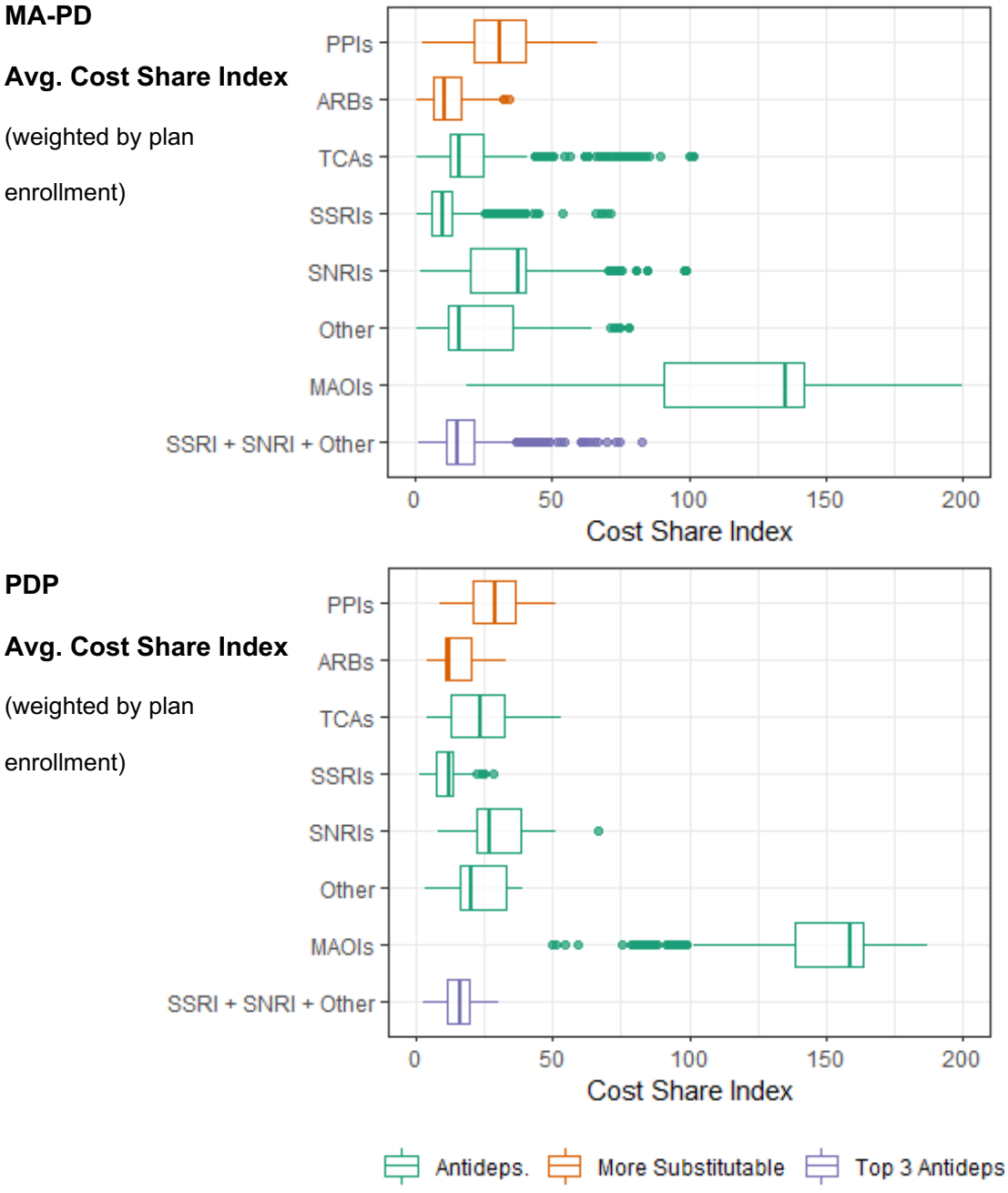
Table 3.5: Comparison of Coverage Generosity Across MA-PD and PDP Plans, by Class

Class	Avg Cost Share Index (weighted by lives) MA-PD	PDP	Difference MA-PD - PDP	Avg Lowest Cost Share (weighted by lives) MA-PD	PDP	Difference MA-PD - PDP
ARBs	$12.22	$14.59	-$2.37	$4.79	$6.04	-$1.25
PPIs	$30.93	$30.31	$0.62	$6.98	$10.25	-$3.27
DPP-4s	$66.04	$97.93	-$31.90	$49.26	$51.84	-$2.58
GLP-1RAs	$119.33	$171.72	-$52.39	$51.33	$68.23	-$16.90
SGLT-2s	$94.15	$104.05	-$9.90	$53.26	$55.66	-$2.40
SSRIs	$11.29	$10.93	$0.35	$4.49	$4.57	-$0.08
SNRIs	$34.44	$29.70	$4.75	$12.69	$16.47	-$3.79
Other Antideps.	$23.04	$22.63	$0.41	$12.80	$10.74	$2.06
TCAs	$23.19	$22.52	$0.67	$8.55	$7.51	$1.04
MAOIs	$112.78	$149.85	-$37.06	$31.04	$33.29	-$2.25
SSRI+SNRI+ Other	$18.10	$15.73	$2.37	$4.55	$4.46	$0.09

Differences between the PPI, SSRI, Other Antidepressant and TCA average Cost Share Index measures across MA-PD and PDP are less than $1, suggesting that in these classes, incentives like offsets, where we would expect different coverage across MA-PD and PDP, may not be at play. MAOIs, which are used by few beneficiaries, are not covered as generously as other antidepressants. From an access perspective this may be problematic as beneficiaries on MAOIs are likely to have tried other antidepressants and not responded to them. It is possible that since these beneficiaries are price inelastic, plans know that they can charge more for these drugs. It is also possible that beneficiaries on MAOIs are more expensive after risk adjustment, and that plans are trying to cream-skim and avoid them. That MA-PD is more generous than PDP may speak to offset effects.

Figure 3.1 shows the distributions of the average Cost Share Index (weighted by lives) for each class, separately for MA-PD and PDP for all classes except the three antidepressants. The Cost Share Index does not account for substitution and hinges on the sets of drugs in each bundle, which can appreciated by comparing the range of the SSRI+SNRI+Other average Cost Share Index to the range of the average Cost Share Index for each of those classes separately.

Figure 3.1



The average Cost Share Index for the combined class of antidepressants more closely reflects the SSRIs since SSRIs have much higher volume and utilization weights, masking the wider ranges for SNRIs and Other antidepressants. In their antidepressant coverage, plans appear to steer enrollees to SSRIs. Generous SSRI coverage suggests that plans consider SSRIs to be substitutes with other types of antidepressants. For SSRIs, MA-PD and PDP plans are generous: 75% of enrollees have a SSRI Cost Share Index of $12 or less. Average coverage for SNRIs and Other varies more widely and is less generous.

Figure 3.2 shows the distributions of the average Cost Share Index (weighted by lives) for the three antidiabetic classes, separately for MA-PD and PDP. Since all the products in these classes are branded, the range of the average Cost Share Index is larger than for the other seven classes.

Figure 3.2

Antidiabetic Avg. Cost Share Index

(weighted by plan enrollment)

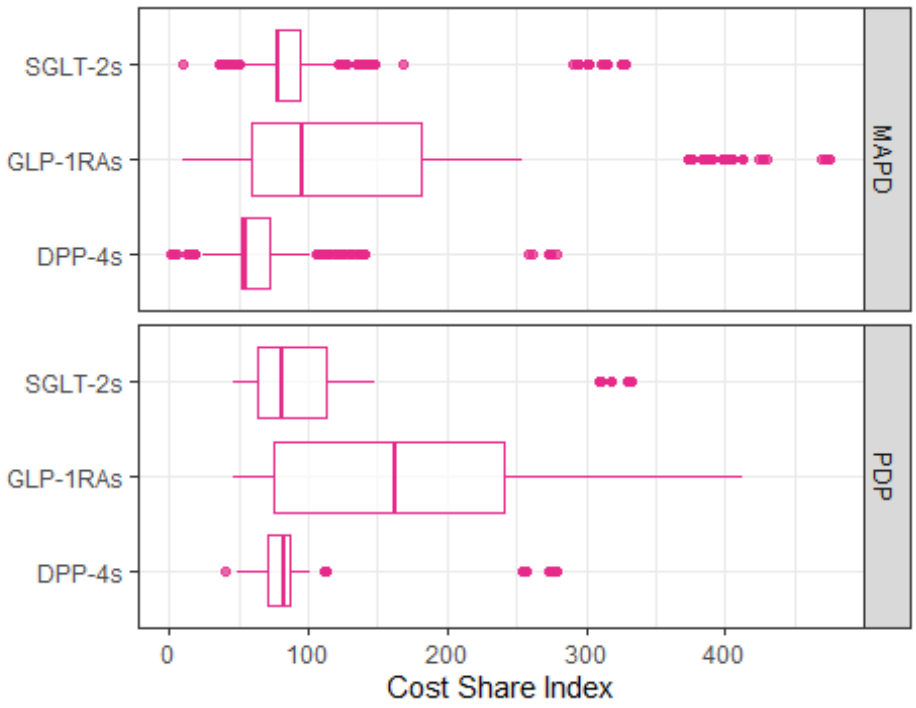
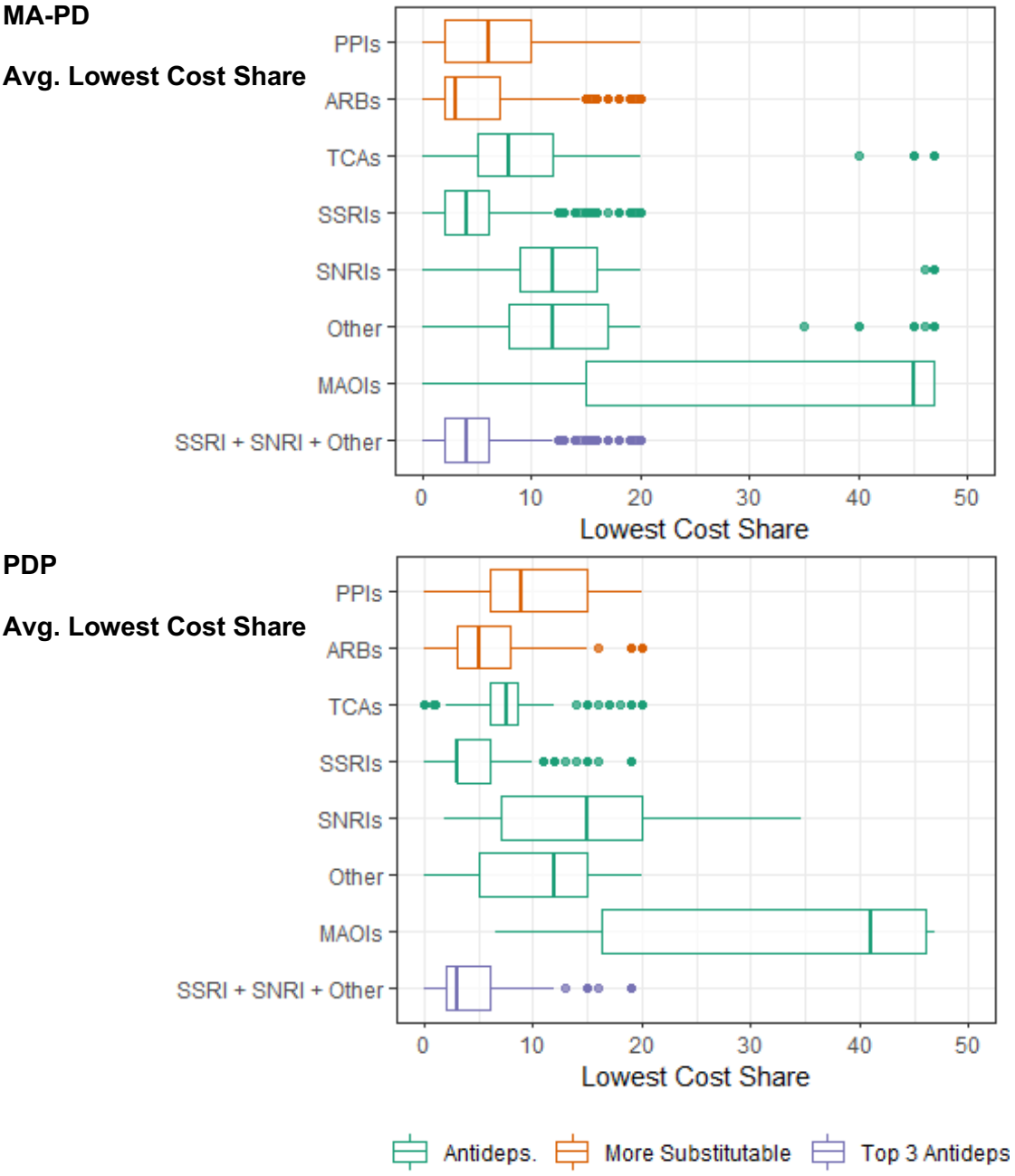


Figure 3.2 shows that the average Cost Share Index for antidiabetics is high, partly because all products are branded, and because these are classes where selective contracting can lead to formulary exclusion (relative to protected classes or classes with strong generic penetration). On this measure, MA-PD is more generous than PDP, consistent with offset incentives.

With few exceptions in the antidepressant classes, the MA-PD average Lowest Cost Share is less than in PDP, meaning that on average, the least expensive drug in a class in a MA-PD plan is cheaper than the least expensive drug in that class in a PDP plan. For classes like ARBs and PPIs where drugs are more substitutable, this is a relevant measure of generosity. For antidepressants it is less so, as what matters is not that "any drug" is cheap, but rather the "one drug" that works for a beneficiary. The lowest cost share is a relatively salient feature of a plan. It is possible that MA-PD plans compete on this measure.

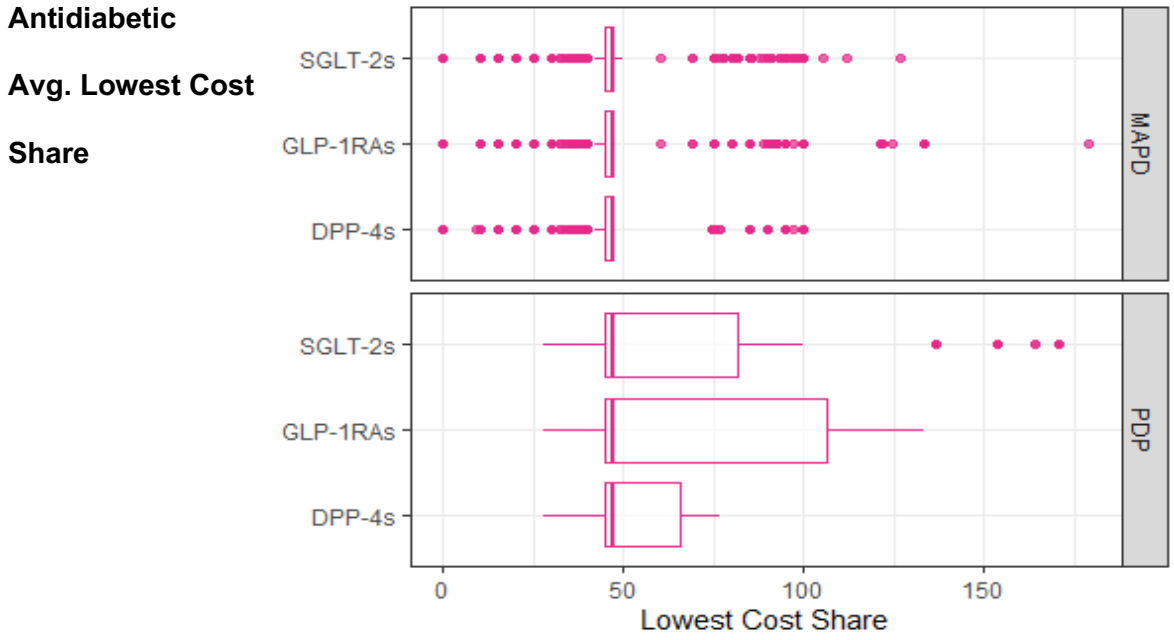
Figure 3.3 and Figure 3.4 illustrate the distribution of the Lowest Cost Share by class for MA-PD plans and PDP plans. The classes that have generics (i.e., all but the three antidiabetic classes) are depicted in Figure 3.3. In MA-PD, the lowest cost share for PPIs and ARBs is lower than in PDP. To illustrate, 75% of MA-PD beneficiaries have a PPI lowest cost share of $10 or less, whereas in PDP, 75% of beneficiaries have a PPI lowest cost share of $15 or less. In antidepressants, MAOIs, used by very few people, have a very wide range for lowest cost share, across both MA-PD and PDP. Plans do not have to cover MAOIs generously because there are such few people who use them. In addition, beneficiaries who use them have often been unsuccessful on other types of antidepressants, and as a result have more inelastic demand. SSRIs, which are mostly generic, have a narrow range of average lowest cost sharing. In both MA-PD and PDP, 75% of beneficiaries can get a 30-day supply of one SSRI for under $7. However, that is only helpful if the product that is priced at the lowest cost share is clinically effective for the enrollee—not a guarantee with antidepressants.

Figure 3.3: Distribution of Average Lowest Cost Share by Plan Type, for non-Antidiabetics



For classes with exclusively branded drugs (captured by the antidiabetic classes in Figure 3.4), there is little variation in lowest cost share generosity: in a majority of plans, at least one drug in each of the three classes is offered at a 30-day cost share of just under $50. PDP plans vary more widely in the lowest cost share for a drug in each of the classes, though the median lowest cost share is also just under $50, more plans will have lowest cost shares in antidiabetic classes that are higher.

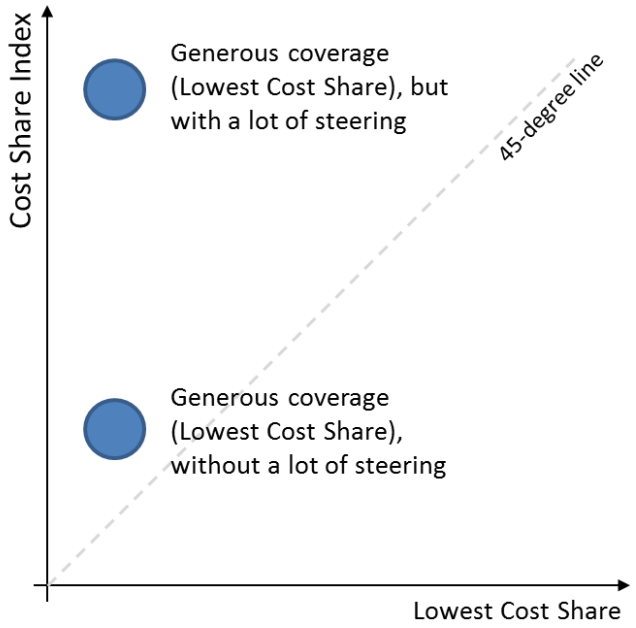
Figure 3.4: Distribution of Average Lowest Cost Share by Plan Type, for Antidiabetics



The cost share index and lowest cost share capture distinct but related aspects of coverage generosity. A beneficiary may be interested in understanding how coverage generosity varies for the same therapeutic class across plans. For instance, a patient who knows that she will likely be put on a new antidiabetic in the following year, but not know which one, may want to know each plan's antidiabetic Cost Share Index. Another beneficiary might want to know how much the cheapest drug in a class will be, regardless of which drug it is. This is captured by the Lowest Cost Share.

By construction, the Cost Share Index will be greater or equal than the Lowest Cost Share for a given plan-class. Looking at both measures together can be informative. For example, a high Cost Share Index (i.e., less generous), combined with a low Lowest Cost Share (i.e., more generous) would suggest that at least one drug in a class is affordable, but the plan steers within the class. A Cost Share Index that is roughly equal to the Lowest Cost Share means that all drugs in the class are covered at similar amounts. If we plot both measures on a graph, with the Cost Share Index on the Y axis and the Lowest Cost Share on the X axis, plans will appear as points above the 45-degree line. Figure 3.5 shows an interpretation of areas on said graph.

Figure 3.5: Interpretation of Cost Share Index and Lowest Cost Share Graphs



This pattern is apparent with the coverage of antidiabetics, as seen in Figure 3.6, where plans with high steering cluster towards the top. As these drugs are branded, cost share amounts vary widely, and even the Lowest Cost Share can range beyond $100.

Figure 3.6: Comparison of Antidepressant Coverage for Two Antidiabetic Classes

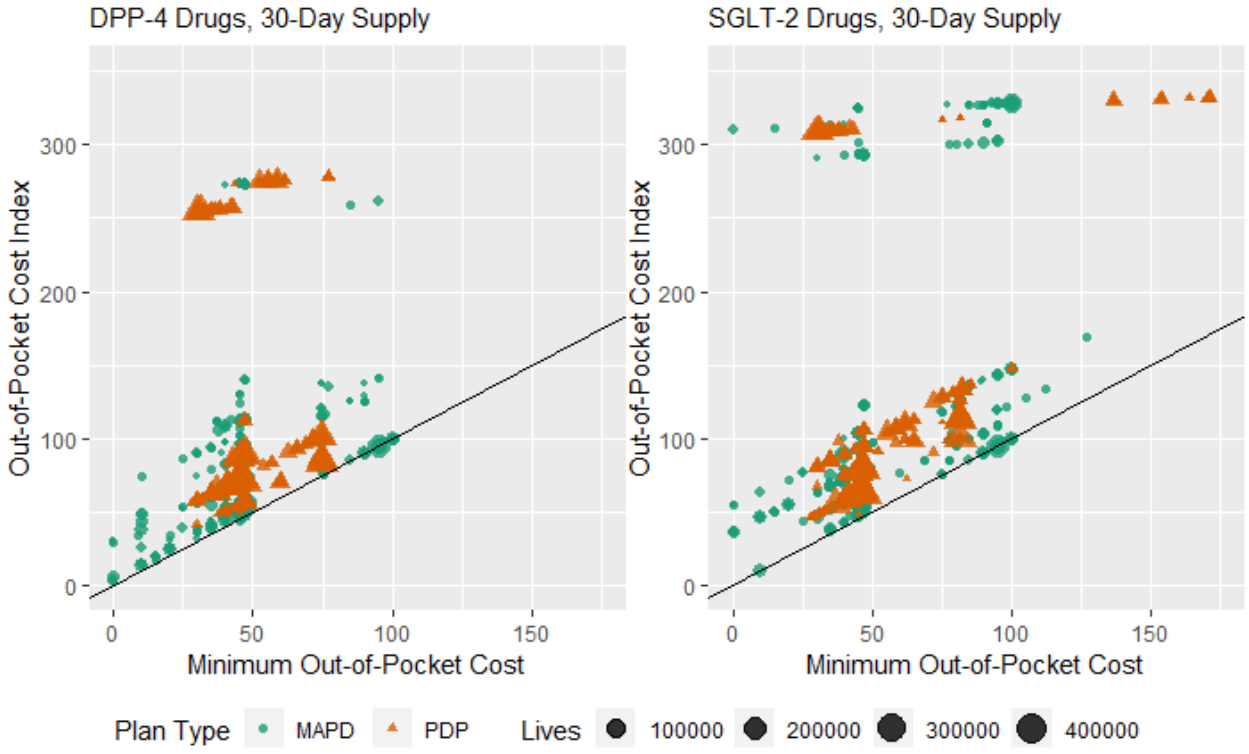
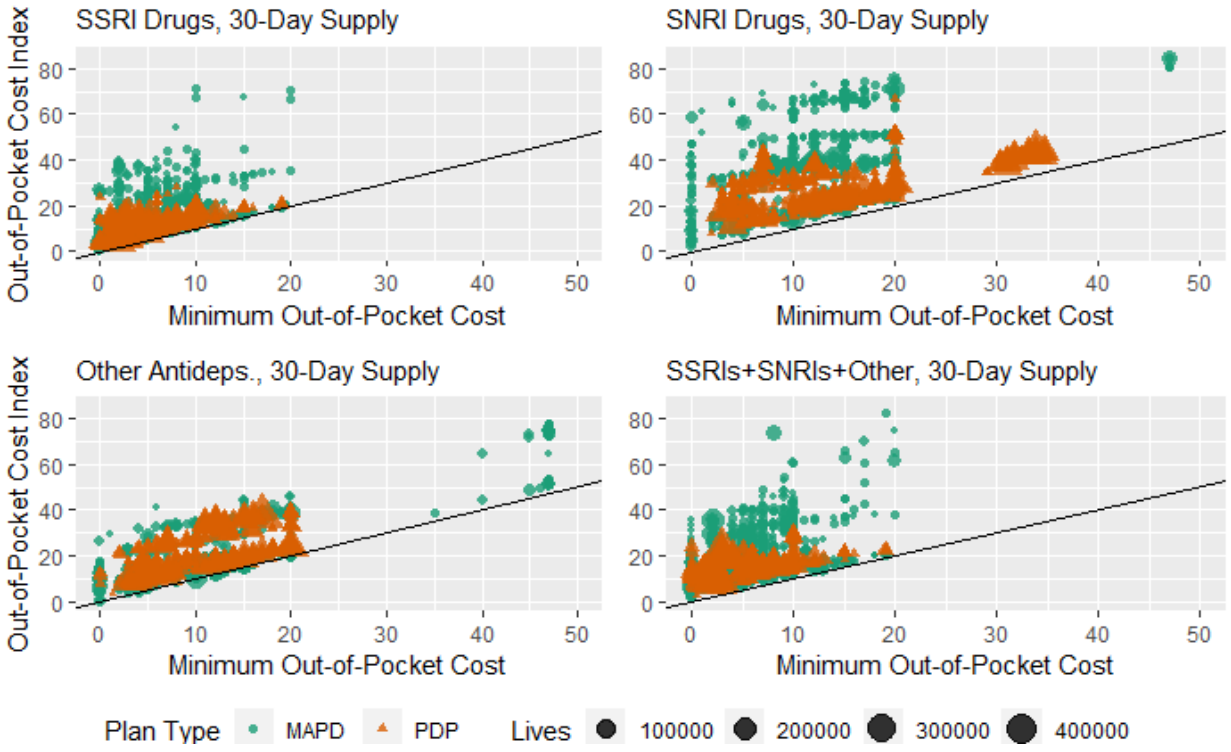


Figure 3.7 compares generosity measures for the three largest antidepressant classes, SSRIs, SNRIs, and Other, as well in aggregate across the three. Figure 3.7 shows how the definition of the drug "bundle" affects the measures. The Lowest Cost Share for the aggregate class reflects values from the SSRI class. Similarly, since SSRI product weights are so high relative to SNRI and Other Antidepressant product weights, the aggregate measure looks more generous. Appendix Table C.3 lists products and shares in the aggregate antidepressant class. From a generosity perspective, the SSRI+SNRI+Other coverage looks reasonable, but from the beneficiary's perspective the aggregate class does not capture the nuances of the different classes in a way that is clinically relevant.

Figure 3.7: Comparison of Antidepressant Coverage for Major Antidepressant Classes



3.4.3 Plans Steer Even When There is Clinical Uncertainty on Optimal Drug

Protected classes were included in Part D regulation with both access and selection in mind. As described above, since patients respond differently to antidepressants within and across classes, designating antidepressants as protected means that every drug is covered by every plan. This can be

seen in the data. As shown in Table 3.6, every plan covers the top four products in the three primary classes of antidepressants. Despite these classes being protected, there are no restrictions on cost sharing within the class, and cost sharing may affect access or be used by insurers for selection.

Table 3.6: Top Drug Tier Placements for Major Antidepressant Classes

		MA-PD (1,676 plans)		
Class	**Drug**	**Plans Covering**	**Avg. Tier**	**Avg. Cost Share**
SNRI	Desvenlafaxine (Pristiq)	1659*	3.8	$86
SNRI	Duloxetine (Cymbalta)	1676	2.6	$35
SNRI	Venlafaxine (Effexor)	1676	2.2	$22
SNRI	Venlafaxine XR (Effexor XR)	1676	2.2	$21
Other Antidep.	Bupropion (Wellbutrin)	1676	2.3	$23
Other Antidep.	Bupropion SR (Wellbutrin SR)	1676	2.3	$23
Other Antidep.	Bupropion XL (Wellbutrin XL)	1676	2.3	$23
Other Antidep.	Mirtazapine (Remeron)	1676	1.9	$15
SSRI	Citalopram (Celexa)	1676	1.2	$8
SSRI	Escitalopram (Lexapro)	1676	1.8	$13
SSRI	Sertraline (Zoloft)	1676	1.3	$10
SSRI	Trazodone (Desyrel)	1676	1.2	$6
		PDP (791 plans)		
Class	**Drug**	**Plans Covering**	**Avg. Tier**	**Avg. Cost Share**
SNRI	Desvenlafaxine (Pristiq)	788*	3.6	$85
SNRI	Duloxetine (Cymbalta)	791	2.9	$25
SNRI	Venlafaxine (Effexor)	791	2.4	$26
SNRI	Venlafaxine XR (Effexor XR)	791	2.3	$22
Other Antidep.	Bupropion (Wellbutrin)	791	2.6	$24
Other Antidep.	Bupropion SR (Wellbutrin SR)	791	2.6	$22
Other Antidep.	Bupropion XL (Wellbutrin XL)	791	2.6	$24
Other Antidep.	Mirtazapine (Remeron)	791	1.9	$12
SSRI	Citalopram (Celexa)	791	1.1	$6
SSRI	Escitalopram (Lexapro)	791	2.4	$20
SSRI	Sertraline (Zoloft)	791	1.4	$6
SSRI	Trazodone (Desyrel)	791	1.5	$10

Note: Averages weighted by enrollment. Pristiq's generic entered in June 2015 and is not in the 2016 data consistently. Plans that do not cover Pristiq cover Khedelza, a drug with the same active ingredient.

Table 3.6 explores variation in cost sharing and formulary placement for the top four products by volume in the SSRI, SNRI and Other antidepressant classes. These products, their utilization, and generic share can be found in Table 3.3. Since every plan covers every drug, I can compare placement by summarizing each drug's tier as well as each drug's cost sharing. Many Part D formularies have five tiers, where Tier 1 is for preferred generics, Tier 2 is for non-preferred generics, Tier 3 is for preferred brands, Tier 4 is for non-preferred brands, and Tier 5 is for specialty drugs. Higher tiers are associated with higher cost sharing, and it is possible for generics to be placed on "branded" tiers. The averages in Table 3.6 are weighted by plan enrollment.

SSRIs are consistently on lower tiers than Other Antidepressants and SNRIs, across both MA-PD and PDP. In MA-PD, Zoloft, the top drug by sales, has an average cost share of $10 per 30-day supply. In PDP, Zoloft has an average cost share of $6 per 30-day supply. Lexapro, an enantiomer of Celexa, is markedly more expensive in PDP, which appears to be doing more steering within SSRIs than MA-PDs. SNRIs and Other Antidepressants are not covered as generously as SSRIs. Though a generic was widely available for each drug except SNRI Pristiq (which many plans cover in brand form), these products are on average placed on Tier 2 or above. Within Other Antidepressants, Remeron is cheaper than the Wellbutrin products across both MA-PD and PDP. For generics across these three classes, the maximum average cost share is $35 for SNRI Cymbalta in MA-PD and $26 for SNRI Effexor in PDP. The minimum is $6 for SSRI Desyrel in MA-PD and $6 for SSRIs Zoloft and Celexa in PDP. Given the tiering and cost shares across these classes, plans appear to consider all three classes as one larger class, and seem to be steering beneficiaries to generic SSRIs over SNRIs and Other Antidepressants.

There is also PBM-level variation in the coverage of each of these three antidepressant classes. Figure 3.8 depicts the Fixed Distribution Cost Index and Minimum Cost Share for the Top

4 drugs in SSRIs, SNRIs and Other, by PBM for CVS Caremark, Express Scripts, Humana, and OptumRx. The closer a point is to the 45-degree line, the less steering there is in a plan.

Figure 3.8: Coverage Measures for Three Major Antidepressant Classes, by PBM

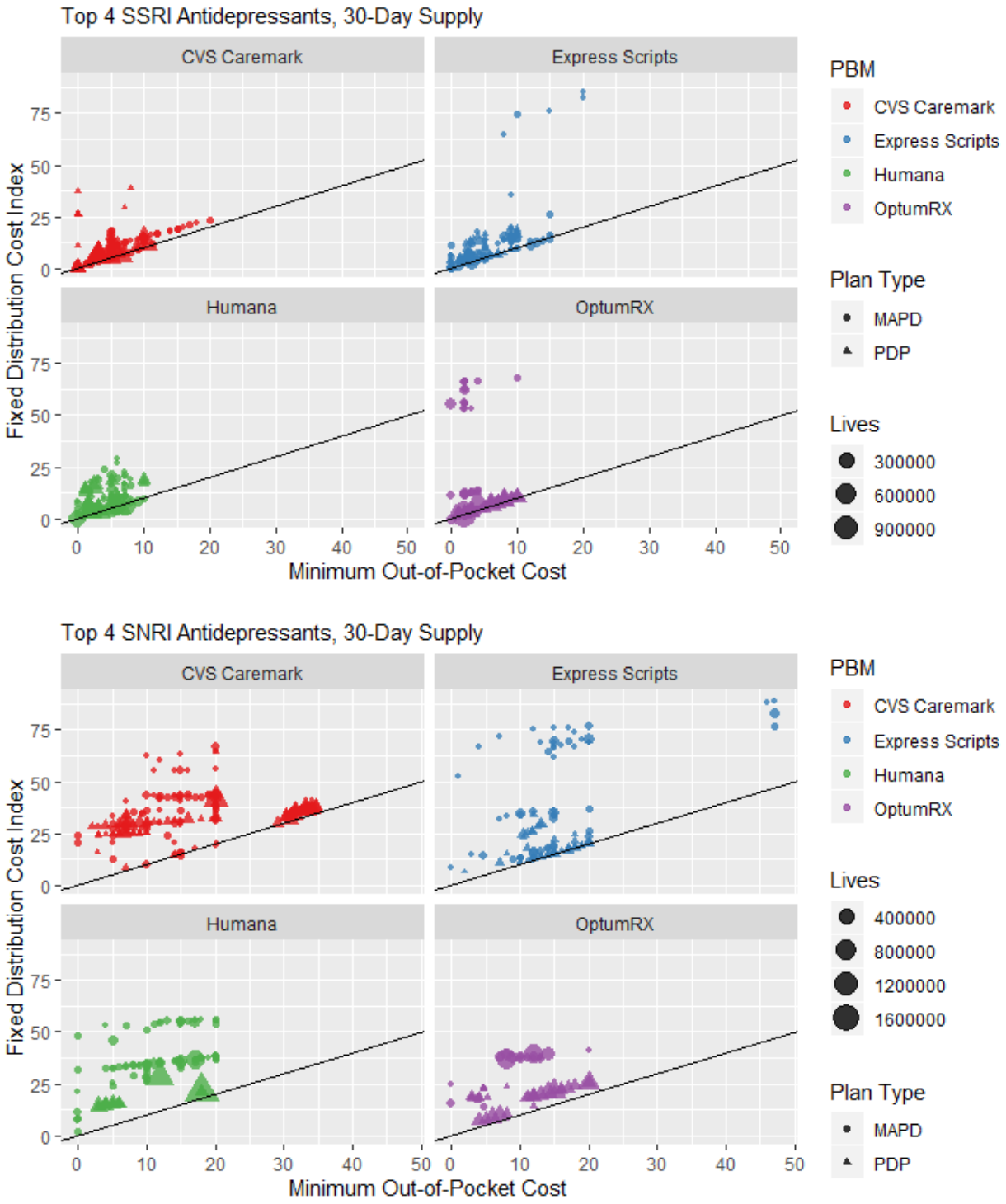
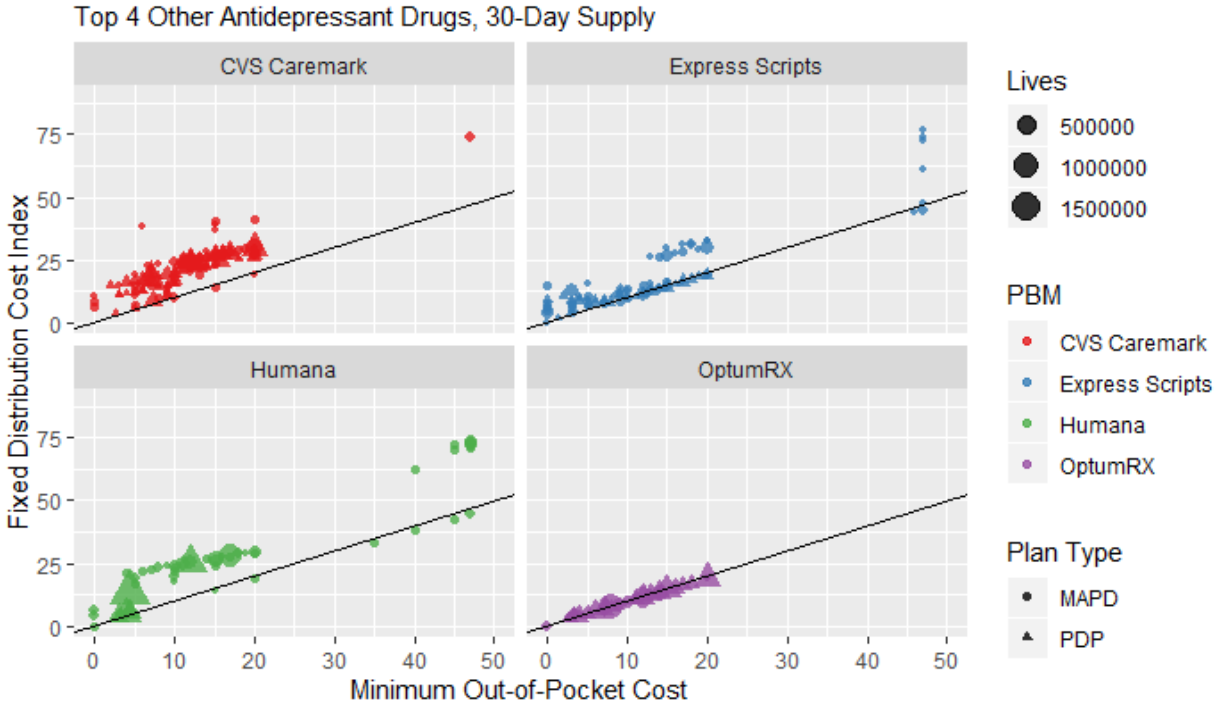


Figure 3.8: Coverage Measures for Three Major Antidepressant Classes, by PBM (Continued)



Apart from some Express Scripts and OptumRX plans, SSRIs appear to have little steering. Most plans are in the low-steering, high-generosity space. Other Antidepressants also do not have much steering, and OptumRX specifically has no steering at all – all Other Antidepressants are covered and at the same cost sharing amount, which is of $20 or less. SNRIs, on the other hand, have much more steering across plans, as evidenced by the dispersion of points on the SNRI graphs.

3.4.4 PBMs have Different Formulary Strategies

In this section I examine variation across formularies by PBM, focusing on branded products and the Top 4 PBMs by covered Part D lives. Since rebates and selective contracting occur for products that do not face generic competition, I consider the three antidiabetic classes and look for PBM-level variation on which products are on or off formulary.

Table 3.7 lists the number of unique formularies (defined as mappings of drug products onto tiers) associated with each PBM in the Part D data. The Top 4 PBMs by lives covered are CVS

Caremark, Express Scripts, Humana and OptumRx (see Table 3.1). Table 3.7 shows that CVS Caremark and Express Scripts have more formularies (20 and 28, respectively) than Humana and OptumRx (9 and 6, respectively). Both Humana and OptumRx are "in-house" PBMs that manage pharmacy benefits for their parent insurers, Humana and UnitedHealth. MedPAC discussed this strategy, making reference to offset effects of drug benefit design: "a potential advantage of this approach is that analyzing combined data on medical and drug use and spending could help plans evaluate the effectiveness of treatments and integrate patients' care" (MedPAC, 2017). On the other hand, CVS Caremark and Express Scripts contract with many insurers, including in 2016 Anthem, Aetna, and Cigna, as well as smaller plans. The sorting of insurers to PBMs and beneficiaries to plans are likely drivers of formulary placement, but I am unable to quantify that amount.

Table 3.7: Unique Formulary Counts by PBM

	Unique Formularies		
PBM	**MA-PD**	**PDP**	**Total**
Express Scripts	20	12	28
Prime Therapeutics	14	12	21
CVS Caremark	12	11	20
Catamaran	7	3	9
Humana	6	3	9
OptumRX	2	4	6
Medimpact	2	3	5
Blue Shield of California	-	2	2
Envision RX Options	-	2	2
MagellanRX	-	1	1
National Pharmaceutical Services	1	-	1
SelectHealth Prescriptions	1	-	1
Missing	133	5	138
Total	198	58	243

Table 3.8 documents the percent of each of the top 4 PBMs' formularies that included each drug in the three antidiabetic classes that I study. Though I do not have rebate data and am unable to draw conclusions on the leverage different PBMs have, it appears from the distribution of "on formulary" drugs that negotiation is at the manufacturer and class level, not at the product level nor at the manufacturer level, across classes. For example, Express Scripts appeared to favor AstraZeneca's two drugs in GLP-1RA, but not in SGLT-2. In addition, though MA-PD and PDP formularies for the same PBMs look similar, MA-PD plans tend to have more "on formulary" drugs.

There are two coverage patterns for antidiabetics. CVS Caremark and Express Scripts include every antidiabetic product on at least one formulary. Except for Express Script's coverage of SGLT-2s, every formulary includes the drugs of at least one manufacturer in each class. (for CVS, Merck and BI in DPP-4, Novo Nordisk in GLP-1RA, and Janssen in SGLT-2. For Express Scripts, Merck (and BI in PDP) for DPP-4, AstraZeneca in GLP-1RA). The other pattern involves Humana and OptumRx. These formularies have more "absolute" decisions on formulary inclusions and exclusions. Some drugs are excluded from all formularies. There is also no variation in the sets of drugs included on these PBMs' MA-PD formularies, and both include all DPP4-s in MA-PD. DPP-4s have higher utilization, and broad inclusion could be a marketing point for MA-PD plans.

3.5 Discussion

This paper documents immense variation in benefit design across Medicare Part D plans. This suggests that selective contracting is happening, and that plans are competing for beneficiaries with their offerings and coverage. However, it is difficult to compare plan coverage, and good measures are important for beneficiaries to understand which plans are best for their needs, and for policymakers to evaluate benefit design. This paper defines three measures to study different aspects

Table 3.8

Class	Firm	Drug Product	CVS Caremark		Express Scripts		Humana		OptumRX	
			MA-PD	PDP	MA-PD	PDP	MA-PD	PDP	MA-PD	PDP
DPP-4	Merck	Sitagliptin (Januvia)	100%	100%	100%	100%	100%	100%	100%	75%
DPP-4	Merck	Sitagliptin+Met (Janumet XR)	100%	100%	100%	100%	100%	100%	100%	75%
DPP-4	Merck	Sitagliptin+Met (Janumet)	100%	100%	100%	100%	100%	100%	100%	75%
DPP-4	Boehringer Ingelheim	Linagliptin (Tradjenta)	100%	100%	75%	100%	100%	100%	100%	75%
DPP-4	Boehringer Ingelheim	Linagliptin+Met (Jentadueto)	100%	100%	75%	100%	100%	100%	100%	50%
DPP-4	AstraZeneca	Saxagliptin (Onglyza)	33%	9%	70%	42%	100%	100%	100%	100%
DPP-4	AstraZeneca	Saxagliptin+Met (Kombiglyze)	33%	9%	70%	42%	100%	100%	100%	75%
DPP-4	Takeda	Alogliptin (Nesina)	8%	9%	35%	25%	100%	33%	100%	**0%**
DPP-4	Takeda	Alogliptin+Met (Kazano)	8%	9%	30%	17%	100%	33%	100%	**0%**
DPP-4	Takeda	Alogliptin+Pioglitazone (Oseni)	8%	9%	20%	17%	100%	33%	100%	**0%**
GLP-1RA	Novo Nordisk	Liraglutide (Victoza)	100%	100%	80%	67%	100%	100%	100%	75%
GLP-1RA	Eli Lilly	Dulaglutide (Trulicity)	58%	45%	35%	50%	100%	100%	100%	75%
GLP-1RA	AstraZeneca	Exenatide (Bydureon)	67%	73%	100%	100%	**0%**	**0%**	100%	100%
GLP-1RA	AstraZeneca	Exenatide (Byetta)	58%	73%	95%	92%	**0%**	**0%**	100%	100%
GLP-1RA	GlaxoSmithKline	Albiglutide (Tanzeum)	8%	18%	25%	50%	**0%**	**0%**	**0%**	**0%**
SGLT-2	Janssen	Canagliflozin (Invokana)	100%	100%	85%	75%	100%	100%	100%	75%
SGLT-2	Eli Lilly	Empagliflozin (Jardiance)	8%	9%	40%	33%	100%	100%	100%	75%
SGLT-2	Janssen	Canagliflozin+Met (Invokamet)	100%	100%	85%	58%	100%	100%	100%	75%
SGLT-2	AstraZeneca	Dapagliflozin (Farxiga)	58%	73%	75%	42%	**0%**	**0%**	**0%**	25%
SGLT-2	AstraZeneca	Dapagliflozin+Met (Xigduo XR)	25%	9%	75%	42%	**0%**	**0%**	**0%**	**0%**

Note: "Met" in this table is short for Metformin, a first line antidiabetic. Eli Lilly's SGLT-2 Empagliflozin/Met (Synjardy) is excluded from this table. It was launched in October 2015 and as a result it was not included on any of the 2016 Part D formularies studied in this paper.

of plan coverage, but it is important to recognize that all measures have limitations. With the Cost Share Index, for example, it is difficult to introduce new products to make comparisons over time, and though the Cost Share Index is based on the "representative" beneficiary's utilization, a particular beneficiary's consumption may deviate from the national average utilization. Similarly, while intuitive, the Lowest Cost Share is helpful as a measure of generosity in classes where products are close to perfect substitutes. Finally, the measures in this paper do not account for utilization management, which is another way for plans to steer utilization.

The variation in Part D coverage showcased in this paper suggests that there are likely better plan choices for many Part D enrollees. Given the literature on sub-optimal plan choice, inertia, and low take-up of decision aids for coverage decisions, it might be beneficial to instate smart auto-re-enrollment for beneficiaries. For example, in PDP, every five years a beneficiary could make an active choice to keep her plan or be assigned to one that is most optimal based on utilization over the past five years. Though that choice would be based on past utilization, it could be used in conjunction with the Cost Share Index, which captures a broader measure of generosity should the beneficiary require a drug in a different class. This paper also showed how utilization in most therapeutic classes is highly concentrated. There is likely not only inertia in plan choice but also in drug choice. In classes like ARBs and PPIs, everyone should be taking the lowest cost drug, and benefit design ought to steer beneficiaries to low-cost options even within already low-cost generics.

PBMs and plans market themselves as caring about beneficiary health. P&T committee members include doctors and surely have clinical appropriateness of drugs in mind when they make formulary recommendations. However, this paper shows that different antidepressant subclasses are not covered by plans equally. Plans favor SSRIs and appear to steer beneficiaries to SSRIs, especially from SNRIs. Given the clinical literature on antidepressants, patients respond differently to different drugs both within and across classes. From an access perspective, they would require equal coverage

across the primary antidepressant classes. Another explanation for this finding is that plans have determined that patients who take SNRIs are not profitable. Plans may also view antidepressants as one class, and conclude that if they generously cover most SSRIs, then that should suffice. From the beneficiary perspective, those taking antidepressants cannot rely on "protected class" status to ensure that their drug will be covered generously, and would likely have to pick a plan based on the cost associated with their drug. To streamline this process and increase the generosity of coverage for antidepressants, plans could make more use of step therapy, prior authorization and other utilization levers. Though utilization management is helpful to balance cost and access, both patients and doctors find utilization management burdensome and inconvenient.

Finally, this paper highlights how the top PBMs differ in their formulary coverage of antidepressant products. Humana and OptumRx, which at the time were the two "in house" PBMs of the four, looked different from CVS Caremark and Express Scripts, which contracted with many plans. Since 2016, both CVS Caremark and Express Scripts have merged with insurers Aetna and Cigna, so now all four of these PBMs have "in house" capabilities. Vertical integration does have the benefit of aligning incentives (for example, in terms of offsets), and as insurers gather more data on their beneficiaries, benefit design has the potential to improve health outcomes and keep costs down. These vertically integrated PBMs will design formularies both for the insurers they are integrated with and for other competing insurers, and this will be a space for regulators to watch.

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Appendix A: Chapter 1

Examples of Line Extensions and their Original Formulations

Abilify and Abilify Maintena

Manufacturer: Otsuka

OF 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

OF Active ingredient: memantine

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

OF Active ingredient: sitagliptin

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

OF 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

Detail on Monte Carlo Simulation Set-Up

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. I first evaluate the baseline cumulative hazard function at each elapsed year from approval 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 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.

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

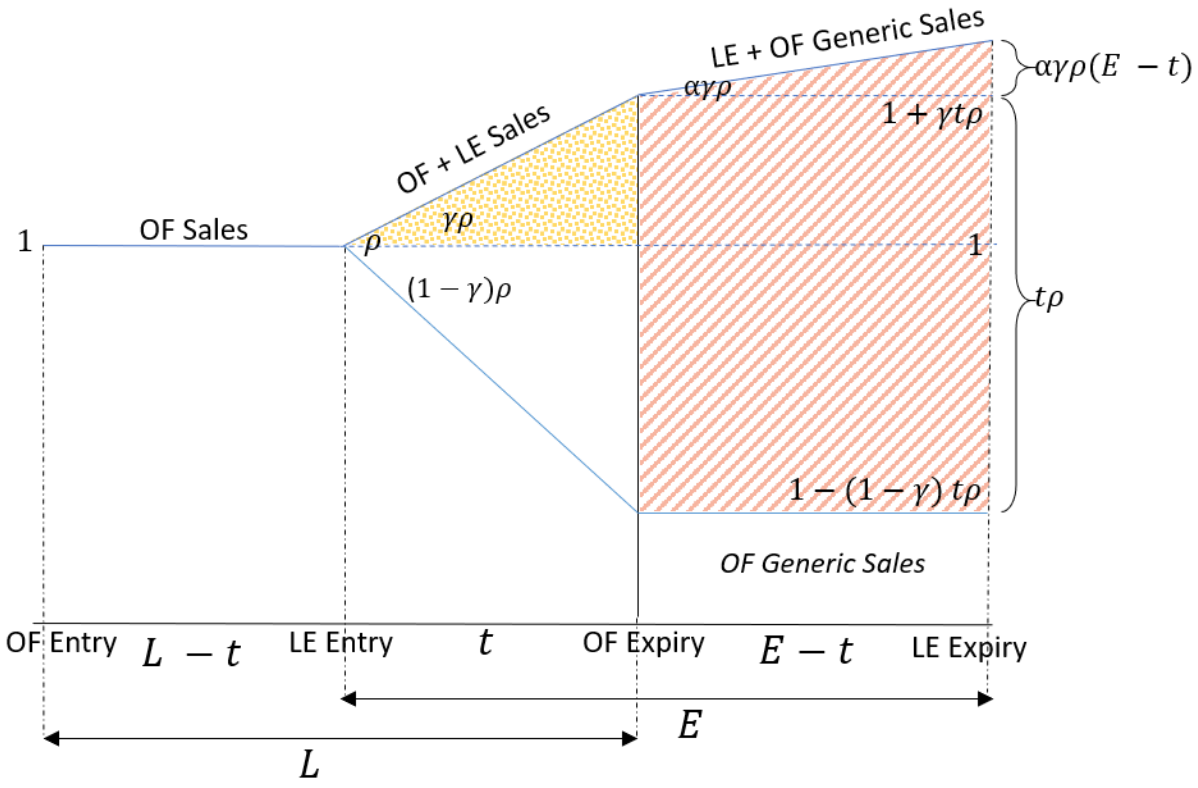
NDAs	Sample and Restrictions
2,628	Rx NDAs approved from 1985-2016
2,565	Excluding NDAs for medical gases
2,562	Excluding NDAs listed as OTC in NDC data
767	Approved as Type 1 – New Molecular Entity or Type1/4 where a New Molecular Entity is combined with long-time generic
710	Excluding diagnostic and 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	Total OF NDAs in analysis sample

OF-LE Pairs	
341	LEs without own drug substance patents
184	LEs with own drug substance patents
525	Total OF-LE Pairs

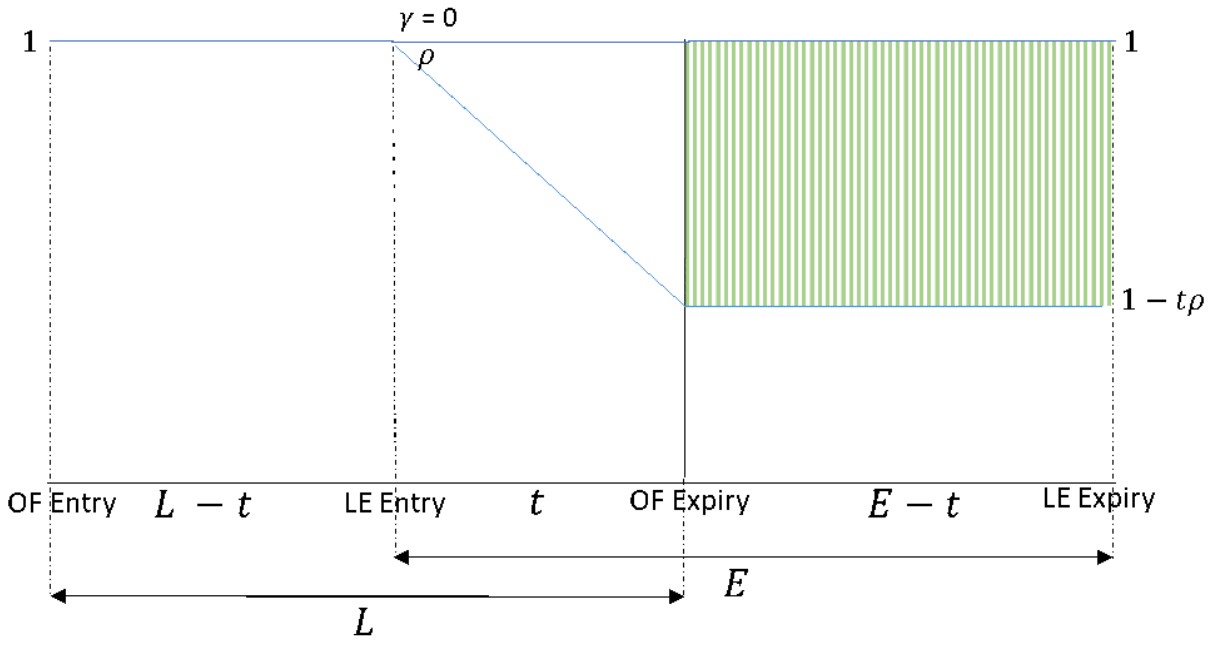
Note: OF stands for Original Formulation. LE stands for Line Extension. NDA stands for New Drug Application, which firms must submit to the Food and Drug Administration for regulatory approval. OTC stands for over-the-counter, which are excluded because they are not affected by generic entry in the same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

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



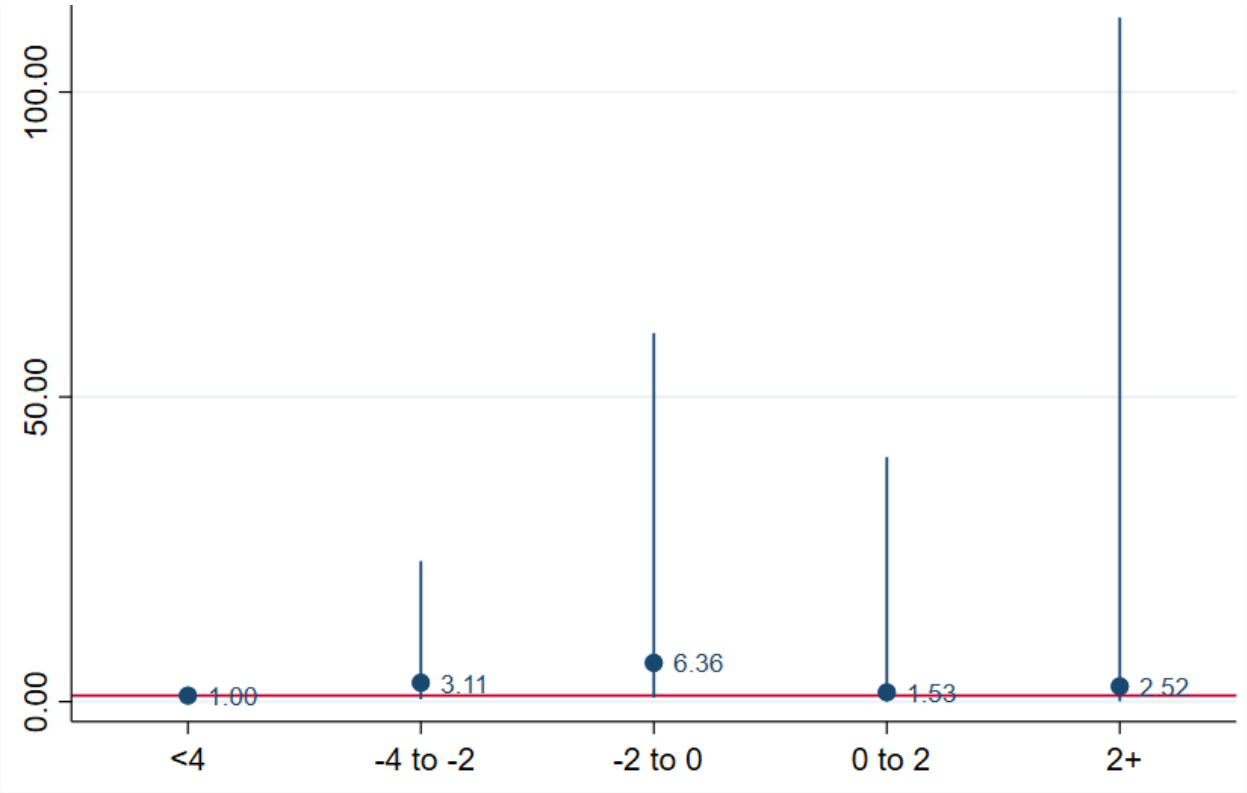
Note: OF stands for Original Formulation. LE stands for Line Extension. L is the OF's market life from approval to OF Expiry. E is the LE's market life from approval to LE Expiry (often three years). ρ is the LE adoption parameter. γ is the market expanding parameter or the share of LE sales that is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

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



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

Appendix B: Chapter 2

Figure B.1: Case Where Second-Best With Insurance is Worse than Without Insurance.

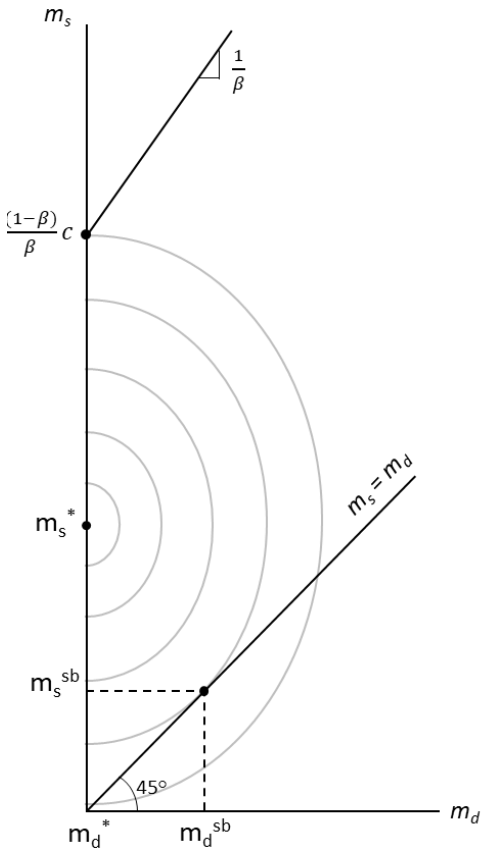
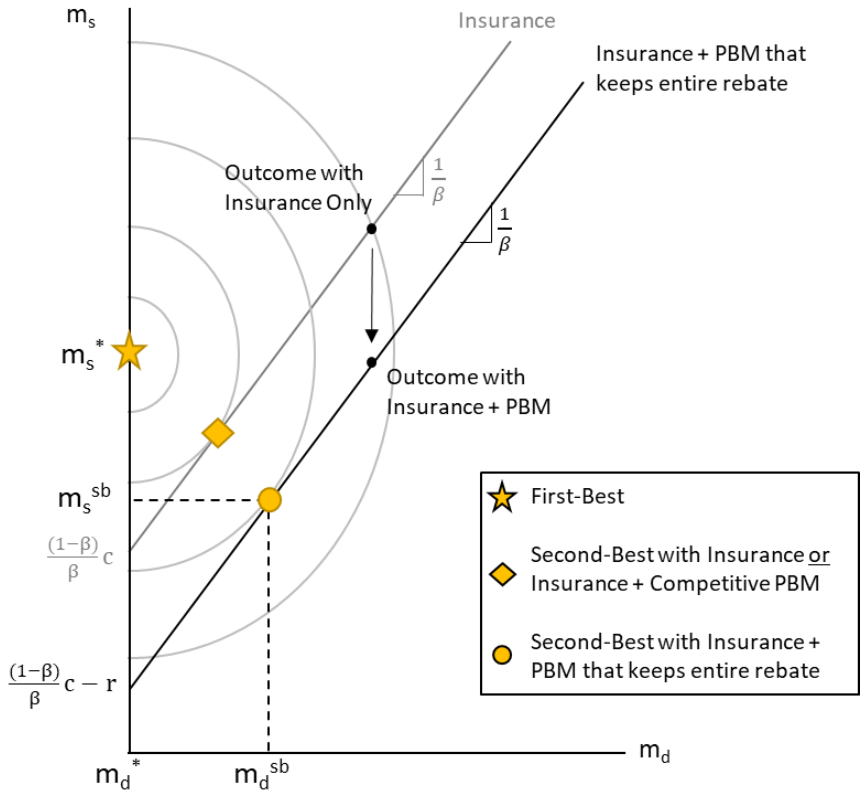


Figure B.2: Case where a PBM with Market Power Improves Welfare Relative to the Case with Insurance Only or Insurance and a Competitive PBM



Appendix C: Chapter 3

Table C.1: Summary of All Products, By Class

Class	Generic Name (Brand Name)	Product Type	N Plans Covering	Out-of-Pocket Cost (est.)	Product 30-Day Fills (est.)	Share of Fills
PPI	Omeprazole (Prilosec)	Generic	2,433	$8.34	53,678,670	60.0%
PPI	Pantoprazole (Protonix)	Generic	2,363	$8.89	20,579,402	23.0%
PPI	Esomeprazole (Nexium)	Brand	1,214	$257.29	7,821,652	8.7%
PPI	Lansoprazole (Prevacid)	Generic	1,698	$35.09	2,970,099	3.3%
PPI	Dexlansoprazole (Dexilant)	Brand	1,774	$215.20	2,212,552	2.5%
PPI	Esomeprazole (Nexium)	Generic	1,461	$195.64	1,366,931	1.5%
PPI	Rabeprazole (Aciphex)	Generic	678	$51.49	429,515	0.5%
PPI	Lansoprazole (Prevacid)	Brand	173	$362.45	146,939	0.2%
PPI	Pantoprazole (Protonix)	Brand	188	$267.84	100,716	0.1%
PPI	Omeprazole/NaHCO3 (Zegerid)	Generic	406	$427.11	64,744	0.1%
PPI	Rabeprazole (Aciphex)	Brand	95	$527.35	58,433	0.1%
PPI	Esomeprazole/Naproxen (Vimovo)	Brand	197	$1,328.60	31,060	0.0%
PPI	Omeprazole/NaHCO3 (Zegerid)	Brand	180	$1,222.56	13,684	0.0%
PPI	Omeprazole (Prilosec)	Brand	0	$327.55	11,982	0.0%
PPI	Lansoprazole/Amox/Clar (PrevPac)	Generic	758	$514.13	10,261	0.0%
PPI	Omeprazole (Prilosec Sus)	Brand	167	$332.58	4,439	0.0%
PPI	Omeprazole/Amox/Clar (Omeclamox)	Brand	135	$572.03	475	0.0%
PPI	Lansoprazole/Amox/Clar (PrevPac)	Brand	90	$713.59	472	0.0%
PPI	Rabeprazole (Aciphex Sprinkle)	Brand	139	$578.31	99	0.0%
ARB	Losartan (Cozaar)	Generic	2,467	$5.82	37,685,540	62.5%
ARB	Losartan/HCT (Hyzaar)	Generic	2,467	$6.85	11,898,109	19.7%
ARB	Ibesartan (Avapro)	Generic	2,353	$13.36	3,034,352	5.0%
ARB	Olmesartan (Benicar)	Brand	2,054	$161.20	2,692,998	4.5%
ARB	Olmesartan/HCT (Benicar HCT)	Brand	2,054	$171.70	1,561,138	2.6%
ARB	Irbesartan/HCT (Avalide)	Generic	2,305	$19.61	667,661	1.1%
ARB	Telmisartan (Micardis)	Generic	2,035	$53.83	665,026	1.1%
ARB	Amlodipine/Olmesartan (Azor)	Brand	1,552	$197.93	529,778	0.9%
ARB	Telmisartan/HCT (Micardis HCT)	Generic	1,613	$92.18	332,011	0.6%
ARB	Candesartan (Atacand)	Generic	2,060	$74.55	331,667	0.6%
ARB	Amlodi/Olmesar/HCT (Tribenzor)	Brand	1,539	$206.75	304,014	0.5%
ARB	Candesartan/HCT (Atacand HCT)	Generic	1,959	$71.62	90,072	0.1%
ARB	Azilsartan (Edarbi)	Brand	972	$148.47	79,826	0.1%
ARB	Azilsartan/Chlortha (Edarbyclor)	Brand	995	$145.55	79,462	0.1%
ARB	Losartan (Cozaar)	Brand	205	$109.10	61,850	0.1%
ARB	Telmisartan/HCT (Micardis HCT)	Brand	262	$137.08	50,412	0.1%

Table C.1: Summary of All Products, By Class (Continued)

Class	Generic Name (Brand Name)	Product Type	N Plans Covering	Out-of-Pocket Cost (est.)	Product 30-Day Fills (est.)	Share of Fills
ARB	Telmisartan (Micardis)	Brand	262	$162.95	41,422	0.1%
ARB	Losartan/HCT (Hyzaar)	Brand	205	$115.15	37,978	0.1%
ARB	Ibesartan (Avapro)	Brand	205	$156.33	35,939	0.1%
ARB	Candesartan (Atacand)	Brand	364	$117.41	27,999	0.0%
ARB	Amlodipine/Telmisartan (Twynsta)	Generic	1,511	$114.76	14,112	0.0%
ARB	Irbesartan/HCT (Avalide)	Brand	171	$183.70	11,659	0.0%
ARB	Candesartan/HCT (Atacand HCT)	Brand	398	$131.48	10,095	0.0%
ARB	Eprosartan (Teveten)	Generic	1,446	$77.83	4,076	0.0%
ARB	Amlodipine/Telmisartan (Twynsta)	Brand	155	$171.39	1,401	0.0%
ARB	Eprosartan/HCT (Teveten HCT)	Brand	288	$128.67	397	0.0%
ARB	Eprosartan (Teveten)	Brand	171	$135.34	371	0.0%
DPP-4	Sitagliptin (Januvia)	Brand	2,336	$316.64	6,731,808	57.6%
DPP-4	Sitagliptin/Met (Janumet)	Brand	2,332	$309.06	1,627,476	13.9%
DPP-4	Linagliptin (Tradjenta)	Brand	2,257	$312.99	1,621,894	13.9%
DPP-4	Saxagliptin Tab (Onglyza)	Brand	1,319	$314.50	838,494	7.2%
DPP-4	Sitagliptin/Met (Janumet XR)	Brand	2,293	$298.45	424,768	3.6%
DPP-4	Saxagliptin/Met (Kombiglyze)	Brand	1,246	$306.41	245,099	2.1%
DPP-4	Linagliptin/Met (Jentadueto)	Brand	2,216	$307.69	151,195	1.3%
DPP-4	Alogliptin/Pioglitazone (Oseni)	Brand	923	$319.46	23,944	0.2%
DPP-4	Alogliptin (Nesina)	Brand	948	$316.24	21,430	0.2%
DPP-4	Alogliptin/Met (Kazano)	Brand	919	$298.52	9,290	0.1%
GLP-1RA	Liraglutide (Victoza)	Brand	2,210	$533.59	1,420,583	66.2%
GLP-1RA	Exenatide (Bydureon)	Brand	1,571	$497.40	359,681	16.8%
GLP-1RA	Exenatide (Byetta)	Brand	1,437	$483.97	255,023	11.9%
GLP-1RA	Dulaglutide (Trulicity)	Brand	1,710	$533.36	66,928	3.1%
GLP-1RA	Albiglutide (Tanzenum)	Brand	526	$369.73	43,789	2.0%
SGLT-2	Canagliflozin (Invokana)	Brand	2,228	$342.28	1,192,337	79.9%
SGLT-2	Dapagliflozin (Farxiga)	Brand	648	$339.44	155,712	10.4%
SGLT-2	Empagliflozin (Jardiance)	Brand	1,391	$341.56	79,071	5.3%
SGLT-2	Canagliflozin/Met (Invokamet)	Brand	2,101	$325.75	58,346	3.9%
SGLT-2	Dapagliflozin/Met (Xigduo XR)	Brand	322	$311.06	6,851	0.5%
SGLT-2	Empagliflozin/Met (Synjardy)	Brand	0	$313.54	176	0.0%
SSRI	Sertraline (Zoloft)	Generic	2,467	$6.09	17,930,507	22.9%
SSRI	Citalopram (Celexa)	Generic	2,467	$4.59	15,729,735	20.1%

Table C.1: Summary of All Products, By Class (Continued)

Class	Generic Name (Brand Name)	Product Type	N Plans Covering	Out-of-Pocket Cost (est.)	Product 30-Day Fills (est.)	Share of Fills
SSRI	Trazodone (Desyrel)	Generic	2,467	$5.68	15,164,934	19.4%
SSRI	Escitalopram (Lexapro)	Generic	2,467	$10.28	11,062,541	14.2%
SSRI	Fluoxetine (Prozac)	Generic	2,467	$10.00	9,997,675	12.8%
SSRI	Paroxetine (Paxil)	Generic	2,467	$11.26	4,423,747	5.7%
SSRI	Paroxetine CR (Paxil CR)	Generic	1,628	$11.26	2,949,165	3.8%
SSRI	Vilazodone (Viibryd)	Brand	2,467	$187.32	350,852	0.4%
SSRI	Vortioxetine (Trintillix)	Brand	2,467	$267.99	214,423	0.3%
SSRI	Escitalopram (Lexapro)	Brand	93	$234.92	94,419	0.1%
SSRI	Nefazodone (Serzone)	Generic	2,467	$75.65	80,371	0.1%
SSRI	Sertraline (Zoloft)	Brand	96	$261.93	38,665	0.0%
SSRI	Fluoxetine (Prozac)	Brand	1,387	$545.53	32,829	0.0%
SSRI	Fluoxetine/Olanzapine (Symbyax)	Generic	1,080	$335.71	24,938	0.0%
SSRI	Paroxetine (Paxil)	Brand	2,467	$213.45	21,467	0.0%
SSRI	Paroxetine CR (Paxil CR)	Brand	96	$193.57	14,259	0.0%
SSRI	Citalopram (Celexa)	Brand	96	$214.59	14,162	0.0%
SSRI	Fluoxetine (Prozac Weekly)	Generic	1,885	$133.25	12,074	0.0%
SSRI	Paroxetine Mesylate (Pexeva)	Brand	325	$322.33	5,261	0.0%
SSRI	Trazodone ER (Oleptro)	Brand	0	$116.51	2,595	0.0%
SSRI	Fluoxetine (Prozac Weekly)	Brand	85	$193.77	1,889	0.0%
SSRI	Fluoxetine/Olanzapine (Symbyax)	Brand	162	$462.32	1,758	0.0%
SSRI	Fluoxetine (Sarafem)	Brand	147	$448.67	313	0.0%
SNRI	Duloxetine (Cymbalta)	Generic	2,467	$72.11	10,349,783	53.8%
SNRI	Venlafaxine XR (Effexor XR)	Generic	2,467	$18.75	6,497,859	33.8%
SNRI	Venlafaxine (Effexor)	Generic	2,467	$26.16	1,364,623	7.1%
SNRI	Desvenlafaxine (Pristiq)	Brand	2,435	$246.04	695,265	3.6%
SNRI	Duloxetine (Cymbalta)	Brand	795	$279.56	148,705	0.8%
SNRI	Levomilnacipran (Fetzima)	Brand	2,467	$258.73	92,570	0.5%
SNRI	Venlafaxine XR (Effexor XR)	Brand	96	$377.71	67,865	0.4%
SNRI	Desvenlafaxine (Pristiq)	Generic	868	$157.91	11,748	0.1%
SNRI	Desvenlafaxine (Khedezla)	Brand	693	$310.03	393	0.0%
Other Antidep.	Mirtazapine (Remeron)	Generic	2,467	$13.30	7,346,081	44.9%
Other Antidep.	Bupropion XL (Wellbutrin XL)	Generic	2,467	$29.36	4,738,680	29.0%
Other Antidep.	Bupropion SR (Wellbutrin SR)	Generic	2,467	$17.59	3,298,800	20.2%
Other Antidep.	Bupropion (Wellbutrin)	Generic	2,467	$28.98	883,262	5.4%
Other Antidep.	Bupropion XL (Wellbutrin XL)	Brand	119	$1,308.13	42,167	0.3%

Table C.1: Summary of All Products, By Class (Continued)

Class	Generic Name (Brand Name)	Product Type	N Plans Covering	Out-of-Pocket Cost (est.)	Product 30-Day Fills (est.)	Share of Fills
Other Antidep.	Bupropion SR (Wellbutrin SR)	Brand	133	$320.44	15,092	0.1%
Other Antidep.	Mirtazapine (Remeron)	Brand	96	$157.76	7,334	0.0%
Other Antidep.	Bupropion XL (Forfivo)	Brand	508	$279.07	5,822	0.0%
Other Antidep.	Bupropion HBR (Aplenzin)	Brand	346	$1,853.85	3,496	0.0%
Other Antidep.	Bupropion (Wellbutrin)	Brand	133	$188.97	2,984	0.0%
Tricyclic	Amitriptyline HCL (Elavil)	Generic	2,467	$15.21	5,666,878	55.4%
Tricyclic	Nortiptyline HCL (Pamelor)	Generic	2,467	$8.16	2,338,256	22.9%
Tricyclic	Doxepin HCL (Generic)	Generic	2,467	$24.39	1,228,692	12.0%
Tricyclic	Imipramine HCL (Tofranil)	Generic	2,467	$17.34	481,787	4.7%
Tricyclic	Clomipramine HCL (Anafranil)	Generic	2,467	$496.61	148,679	1.5%
Tricyclic	Desipramine HCL (Norpramin)	Generic	2,467	$73.69	147,958	1.4%
Tricyclic	Perphenazine/Amitriptyline	Generic	1,472	$62.26	75,985	0.7%
Tricyclic	Doxepin HCL (Silenor)	Brand	1,500	$297.07	63,560	0.6%
Tricyclic	Amoxapine (Asendin)	Generic	2,467	$45.34	18,041	0.2%
Tricyclic	Protriptyline HCL (Vivactil)	Generic	2,467	$128.18	15,069	0.1%
Tricyclic	Imipramine (Tofranil PM)	Generic	1,628	$280.59	13,205	0.1%
Tricyclic	Maprotiline (Ludiomil)	Generic	2,467	$65.20	9,973	0.1%
Tricyclic	Doxepin HCL (Prudoxin)	Brand	1,154	$270.50	3,618	0.0%
Tricyclic	Doxepin HCL (Zonalon)	Brand	707	$497.83	2,598	0.0%
Tricyclic	Trimipramine (Surmontil)	Brand	2,467	$335.92	2,444	0.0%
Tricyclic	Nortiptyline HCL (Pamelor)	Brand	83	$1,474.17	1,515	0.0%
Tricyclic	Desipramine HCL (Norpramin)	Brand	96	$228.91	1,140	0.0%
Tricyclic	Clomipramine HCL (Anafranil)	Brand	83	$2,087.61	810	0.0%
Tricyclic	Imipramine HCL (Tofranil)	Brand	111	$864.80	634	0.0%
Tricyclic	Imipramine (Tofranil PM)	Brand	83	$1,072.23	472	0.0%
Tricyclic	Trimipramine (Surmontil)	Generic	0	$182.42	33	0.0%
MAOI	Phenelzine (Nardil)	Generic	2,449	$65.18	21,438	42.4%
MAOI	Tranylcypromine (Parnate)	Generic	2,467	$248.34	17,031	33.7%
MAOI	Selegiline Transdermal (Emsam)	Brand	2,467	$1,312.69	7,991	15.8%
MAOI	Phenelzine (Nardil)	Brand	114	$161.29	1,733	3.4%
MAOI	Isocarboxazid (Marplan)	Brand	2,467	$489.15	1,187	2.3%
MAOI	Tranylcypromine (Parnate)	Brand	96	$1,005.86	1,153	2.3%

Table C.2: Products that had 2015 utilization and were not covered by any plan in 2016

Class	Drug	Note	Source
PPI	Omprazole (Prilosec), Branded	Discontinued as Rx in capsule form. Prilosec Suspension available as Rx in 2016 and studied separately	https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019810
SGLT-2	Empagliflozin and Metformin (Synjardi), Branded	Launched October 14, 2015	https://investor.lilly.com/news-releases/news-release-details/new-type-2-diabetes-treatment-synjardyr-empagliflozinmetformin?ReleaseID=936554
SSRI	Trazodone ER (Oleptro), Branded	Discontinued prior to February 15, 2014	https://www.moodtreatmentcenter.com/trazodone.pdf
TCA	Trimipramine (Surmontil), Generic	Approved 1979 and not widely used	https://www.ncbi.nlm.nih.gov/books/NBK547855/

Table C.3: Products, Shares and Utilization in the Aggregate Antidepressant Class

Sub-Class	Generic Name (Brand Name)	Product Type	N Plans Covering	Out-of-Pocket Cost (est.)	Product 30-Day Fills (est.)	Share of Fills
SSRI	Sertraline (Zoloft)	Generic	2,467	$6.09	17,930,507	15.76%
SSRI	Citalopram (Celexa)	Generic	2,467	$4.59	15,729,735	13.83%
SSRI	Trazodone (Desyrel)	Generic	2,467	$5.68	15,164,934	13.33%
SSRI	Escitalopram (Lexapro)	Generic	2,467	$10.28	11,062,541	9.73%
SNRI	Duloxetine (Cymbalta)	Generic	2,467	$72.11	10,349,783	9.10%
SSRI	Fluoxetine (Prozac)	Generic	2,467	$10.00	9,997,675	8.79%
Other	Mirtazapine (Remeron)	Generic	2,467	$13.30	7,346,081	6.46%
SNRI	Venlafaxine XR (Effexor XR)	Generic	2,467	$18.75	6,497,859	5.71%
Other	Bupropion XL (Wellbutrin XL)	Generic	2,467	$29.36	4,738,680	4.17%
SSRI	Paroxetine (Paxil)	Generic	2,467	$11.26	4,423,747	3.89%
Other	Bupropion SR (Wellbutrin SR)	Generic	2,467	$17.59	3,298,800	2.90%
SSRI	Paroxetine CR (Paxil CR)	Generic	1,628	$11.26	2,949,165	2.59%
SNRI	Venlafaxine (Effexor)	Generic	2,467	$26.16	1,364,623	1.20%
Other	Bupropion (Wellbutrin)	Generic	2,467	$28.98	883,262	0.78%
SNRI	Desvenlafaxine (Pristiq)	Brand	2,435	$246.04	695,265	0.61%
SSRI	Vilazodone (Viibryd)	Brand	2,467	$187.32	350,852	0.31%

Table C.3: Products, Shares and Utilization in the Aggregate Antidepressant Class (Continued)

Sub-Class	Generic Name (Brand Name)	Product Type	N Plans Covering	Out-of-Pocket Cost (est.)	Product 30-Day Fills (est.)	Share of Fills
SSRI	Vortioxetine (Trintillix)	Brand	2,467	$267.99	214,423	0.19%
SNRI	Duloxetine (Cymbalta)	Brand	795	$279.56	148,705	0.13%
SSRI	Escitalopram (Lexapro)	Brand	93	$234.92	94,419	0.08%
SNRI	Levomilnacipran (Fetzima)	Brand	2,467	$258.73	92,570	0.08%
SSRI	Nefazodone (Serzone)	Generic	2,467	$75.65	80,371	0.07%
SNRI	Venlafaxine XR (Effexor XR)	Brand	96	$377.71	67,865	0.06%
Other	Bupropion XL (Wellbutrin XL)	Brand	119	$1,308.13	42,167	0.04%
SSRI	Sertraline (Zoloft)	Brand	96	$261.93	38,665	0.03%
SSRI	Fluoxetine (Prozac)	Brand	1,387	$545.53	32,829	0.03%
SSRI	Fluoxetine/Olanzapine (Symbyax)	Generic	1,080	$335.71	24,938	0.02%
SSRI	Paroxetine (Paxil)	Brand	2,467	$213.45	21,467	0.02%
Other	Bupropion SR (Wellbutrin SR)	Brand	133	$320.44	15,092	0.01%
SSRI	Paroxetine CR (Paxil CR)	Brand	96	$193.57	14,259	0.01%
SSRI	Citalopram (Celexa)	Brand	96	$214.59	14,162	0.01%

Table C.3: Products, Shares and Utilization in the Aggregate Antidepressant Class (Continued)

Sub-Class	Generic Name (Brand Name)	Product Type	N Plans Covering	Out-of-Pocket Cost (est.)	Product 30-Day Fills (est.)	Share of Fills
SSRI	Fluoxetine (Prozac Weekly)	Generic	1,885	$133.25	12,074	0.01%
SNRI	Desvenlafaxine (Pristiq)	Generic	868	$157.91	11,748	0.01%
Other	Mirtazapine (Remeron)	Brand	96	$157.76	7,334	0.01%
Other	Bupropion XL (Forfivo)	Brand	508	$279.07	5,822	0.01%
SSRI	Paroxetine Mesylate (Pexeva)	Brand	325	$322.33	5,261	0.00%
Other	Bupropion HBR (Aplenzin)	Brand	346	$1,853.85	3,496	0.00%
Other	Bupropion (Wellbutrin)	Brand	133	$188.97	2,984	0.00%
SSRI	Trazodone ER (Oleptro)	Brand	0	$116.51	2,595	0.00%
SSRI	Fluoxetine (Prozac Weekly)	Brand	85	$193.77	1,889	0.00%
SSRI	Fluoxetine/Olanzapine (Symbyax)	Brand	162	$462.32	1,758	0.00%
SNRI	Desvenlafaxine (Khedezla)	Brand	693	$310.03	393	0.00%
SSRI	Fluoxetine (Sarafem)	Brand	147	$448.67	313	0.00%