A Dose of Competition & Side Effects of Prescription Limits

HARVARD UNIVERSITY
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DISSERTATION ACCEPTANCE CERTIFICATE

The undersigned, appointed by the

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A Dose of Competition & Side Effects of Prescription Limits

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A Dose of Competition & Side Effects of Prescription Limits

A DISSERTATION PRESENTED
BY
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Abstract

Drug spending in the US continues to rise year over year due to price and volume increases for existing drugs and the launch of new brand drugs. The US health system uses multiple strategies to manage spending, including generic substitution to reduce unit prices and utilization control to contain volume. Generic copies of the same drug from different manufacturers are undifferentiated products, resulting in generic drug prices that are lower than brand prices and decline with additional generic entrants. In addition to encouraging generic substitution when possible, insurers control utilization by requiring providers to seek approval to prescribe certain medications or by imposing limits on covered drugs. Utilization control tactics that successfully target low value utilization may reduce costs without compromising patient health. In this dissertation, I examine price competition between generic manufacturers and generic entry decisions in the context of pending patent litigation. I also evaluate the impact of monthly prescription limits, a utilization control strategy employed by some Medicaid programs.

Paper 1: In the past decade there has been considerable consolidation among generic manufacturers as well as reported price increases for some generic drugs. The effect of mergers on generic prices is ambiguous. Generic manufacturers compete on price, rather than quality, and efficiency gains from mergers could result in lower prices. Conversely, given the cost and time required to obtain FDA approval, entry may not be sufficient or timely enough to restore competition should prices rise post-merger. I find that acquisition costs paid by pharmacies increased post-merger for generic drugs both merging firms produced pre-merger. Mergers did not influence acquisition costs

in markets with divestitures. These findings imply that lower entry costs are not sufficient to ensure continued competition in generic markets and underscore the importance of regulatory oversight and structural remedies to maintain competition. I also find that pharmacy reimbursement does not increase in response to higher acquisition costs, indicating that pharmacies, rather than insurers or consumers, bear the cost of increased generic prices.

Paper 2: Controlling the growth of prescription drug spending in Medicaid remains a policy challenge. Some Medicaid programs limit the number of prescriptions covered per enrollee per calendar month as an attempt to control cost. Monthly prescription limits may reduce utilization of clinically beneficial medication and lead to increased medical spending due to poor medical management of chronic conditions. This paper evaluates how a reduction in Louisiana's prescription limit, from 8 to 5 drugs per enrollee per month, impacted utilization and spending. I implement a differences-in-differences analysis and find reductions in total monthly prescription drug utilization and utilization of medications that treat chronic disease. I also exploit an age cut off in the exemption from prescription limits at age 21 to study the effects of prescription limits on spending. I do not find effects on total monthly spending per beneficiary.

Paper 3: Generic drug manufacturers may enter the market before all patents on the referenced brand drug expire, if their generic product does not infringe on outstanding patents or outstanding patents are invalid or unenforceable. During this process, referred to as a paragraph IV challenge, the brand may sue the generic manufacturer for patent infringement. In some cases, a generic manufacturer receives FDA approval to market the drug before the litigation has concluded. Generic manufacturers in this position may elect to launch "at risk", but they will pay damages if they lose the lawsuit. The generic can mitigate its risk of damages by waiting to launch until after a favorable litigation outcome. However, waiting may result in lower profits if demand for the drug is decreasing or additional generic manufacturers obtain approval. We examine generic drugs that received FDA approval with "first-filer" status, granted to the first manufacturer to submit an application

with a paragraph IV challenge. Subsequent applicants cannot launch before the "first-filer." We find that when FDA approval is granted during active litigation, generic manufacturers rarely wait until the litigation process is complete to launch; they typically launch at risk either before or after the district court decision. Although some generic firms eventually pay damages to the brand, we find that at-risk launches have been profitable for generic firms on average.

Contents

Listing of figures

I would like to dedicate this dissertation to my parents. It is not lost on me that many Burudian-born women do not have access to the opportunities that I have been given. I greatly appreciate all my parents have done to make my educational achievements possible. Education was always emphasized in my household as a mechanism to better myself and to bring change to social issues. My parents noted my curiosity and encouraged me to continue asking questions and learning. This dissertation is for you, mommy and daddy.

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1

How do generic prices respond to mergers between generic manufacturers?

1.1 Introduction

Providing incentives for innovation in prescription drugs to improve population health comes at the expense of increased healthcare spending and patient out of pocket costs.[28,138,86] Drug spending

continues to rise year over year due to price and volume increases for existing drugs and the launch of new brand drugs.[78] Generic copies of off-patent brand drugs offset drug spending growth by providing an affordable alternative to expensive brand drugs. In 2018, retail prescription drug spending in the United States increased 2.5% to $335 billion, accounting for 9 percent of total healthcare spending. From 2017 to 2018, savings from increased utilization of generic prescription drugs helped to offset increased spending on newly launched oncology and autoimmune drugs.[66] The generic share of prescriptions dispensed has risen steadily, from 75% in 2009 to 90% in 2018. In total, the FDA reports that generic drugs generated $1.67 trillion in savings for the United States from 2007 to 2016.[78,49]

Generic drugs are less expensive than brand drugs because they are homogeneous products with lower entry costs, whereas brand drugs are differentiated products with restricted entry. After patents and exclusivity periods expire for a brand drug, approved manufacturers are permitted to begin marketing generic copies, with the same active ingredient and formulation. The cost of obtaining FDA approval to market generic drugs is considerably lower than that of brand drugs, facilitating extensive entry for high volume drugs.[25] Drugs with a lower sales have fewer entrants.[100,64] The FDA approves generic drugs on the basis of therapeutic equivalence to the reference brand drug and pharmacists are generally permitted to substitute among therapeutically equivalent suppliers of the same drug, subject to state regulations.[114] Payers typically reimburse pharmacies for generics at a fixed price per drug, regardless of the manufacturer. Pharmacists maximize profits by purchasing from the lowest priced therapeutically equivalent supplier, causing generic manufacturers to compete on price and availability, rather than quality.[25,13]

Conversely, brand drugs are differentiated products with high entry costs and entry restrictions. Newly approved brand drugs are rewarded for costly and risky innovation with patent protection and market exclusivity periods granted by the Food and Drug Administration (FDA), establishing a monopoly on a molecule and formulation.[50] Protected brand drugs without therapeutic substitutes

set monopoly prices and those with therapeutic substitutes engage in monopolistic competition.[13] After a drug loses exclusivity, brand drugs do not compete with their generic counterparts. The market for a given drug is segmented into a generic market of price sensitive consumers and a brand market of price insensitive consumers.[110,54] Market structure and competition are important in delivering benefits to consumers from availability of affordable generic drugs. Generic drugs with multiple manufacturers are priced, on average, 85% less than the corresponding brand drug.[128,49] Generic prices are lower in markets with more suppliers and the marginal effect of a an additional supplier diminishes with more suppliers.[111] While generic prices remain low for most drugs, there is also recent evidence of generic price increases. About 20% of generic drugs had a price increase of at least 100% between 2010 and 2015.[102] Another analysis found that the mean inflation-adjusted price increase in generic drugs was 38% from 2013 to 2014, while the median increase was 2%.[26] Price increases in the past decade have been linked to drug shortages and markets with fewer competitors.[70,113,31]

This paper examines the effect of mergers on generic prices, exploiting the increase in merger activity among generic manufacturers from 1996 to 2016.[55] While the overall market for generic drugs in the U.S. remained relatively unconcentrated,[24] mergers between generic manufacturers with overlapping drug portfolios resulted in consolidation at the drug level, in drug markets where both firms were present pre-merger. In some instances, the Federal Trade Commission(FTC) has required one of the merging firms to divest ownership in a drug, thereby preserving the pre-merger number of suppliers in the market.[98] Mergers also change multimarket contact between manufacturers and overall generic market share of merging firms, both of which can impact competition even in the case of divestiture.[140,34]

Retrospective merger analyses generally find that horizontal mergers increase prices for retail consumer products,[73,5,6] health insurance,[29] 31 and healthcare services.[30,43,81] Horizontal mergers, between actual or potential competitors, may raise prices due to unilateral action by the newly

merged entity or due to coordinated action, i.e. increased likelihood of tacit collusion.[135] In the market for generic drugs, merging manufacturers may raise prices by leveraging increased bargaining power in bilateral negotiations with buyers or coordinate with competitors to raise prices through tacit collusion.

Efficiency gains and potential entry may mitigate anticompetitive effects of mergers. Improved efficiency can reduce welfare loss from merger if cost reductions are passed through to consumers in the form of reduced prices.[22] In practice, evidence of post-merger efficiency gains is mixed.[6] In order to restore competition, market-level entry must be timely, likely, and sufficient. So, in theory, horizontal mergers may not lessen competition in markets inexpensive and prompt entry.[92,32]

The price effect of mergers in generic markets with undifferentiated products and entry costs is ambiguous. With fewer competitors present post-merger, prices may rise. In response to higher prices, a new firm may enter and restore competition to pre-merger levels. However, entry is likely only if expected profits justify entry costs and must be timely to restore competition. Therefore post-merger price increases may be more likely in drugs with higher entry costs and longer development times, such as injectables or other complex generics.[100]

Conversely, consolidation may result in lower or unchanged prices in overlapping markets. Mergers may reduce marginal costs, enabling the merging firm to charge lower prices post-merger to capture market share from competitors. Lower prices post-merger may also be evidence of entry deterrence. In small volume generic markets, incumbent manufacturers reduce prices to deter to anticipated competition.[128] Alternatively, consolidation may not change prices if the marginal effect of a reduced supplier on competition is negligible. For example, the marginal effect of an additional generic supplier on prices is negligible once there are more than 8 suppliers of a drug.[49,111] Thus, if a drug with 15 suppliers experiences consolidation, there may be no effect on prices.

There were 23 mergers valued over $100M between generic manufacturers announced between 2014 and 2017. The analytic approach addresses the endogeneity of mergers by constructing a con-

trol group of drugs that face similar demand and supply drivers, an approach that has been used in merger literature.[73,6] The primary outcome of interest is pharmacy acquisition cost, the price that pharmacies pay to purchase generic drugs. I obtain cost data from the National Average Drug Acquisition Costs report that surveys retail pharmacies across the country to estimate national average costs at the market level, by brand and generic status. I perform a secondary analysis on retail prices, based on national average pharmacy reimbursement.

This paper implements a cohort level event study model, that addresses challenges that arise from applying a standard two-way fixed effects model in a setting where treatment timing varies across units.[127,60] Drug markets where both firms were present pre-merger are considered treated and treatment time is defined as merger effective date. Following prior retrospective merger analyses, I use unaffected markets facing similar market conditions to approximate a counterfactual.[73,43,5] I group treated drugs into cohorts by merger date and construct a control group of never treated drugs, using coarsened exact matching to achieve cohort level balance on covariates. Control drugs are assigned the same event time as the treated drugs in their respective cohorts. The estimation is an event study specification with unit, time and cohort-event time fixed effects.

I find a statistically significant relative increase in acquisition costs post-merger in overlapping markets without divestiture, where mergers result in fewer firms present in the market. The effect size is larger and also statistically significant in markets with fewer than six drugs premerger. Markets where one of the merging firms was required to divest their drug to another competitor, thereby maintaining the same number of suppliers, were unaffected by mergers. These results suggest that mergers lead to increased acquisition costs due to consolidation at the drug level and highlight the importance of remedies that maintain competition through divestitures. I also find that retail prices paid to pharmacies do not increase in overlapping markets, implying that increased acquisition costs are not passed through to insurers or consumers.

This paper contributes to a large literature on generic competition and retrospective merger anal-

ysis by examining the effect of mergers on prices at different levels of the generic drug supply chain, focusing on mature drug markets and providing evidence from recent data. Previous studies have used a national sample of prices paid by pharmacies and providers.[15,19] This is one of few studies to use the National Average Drug Acquisition Cost data reported by Medicaid to analyze generic competition.[85] I also analyze retail prices paid by insurers and patients.

It is of growing importance to understand drug competition in mature generic drug markets. The share of generic drugs dispensed that have been on the market for over 25 years has increased from about 50% in 2004 to 75% in 2016.[25] Because prices in nascent generic markets are volatile and have not yet reached equilibrium, I drop markets that experience mergers less than four years after loss of exclusivity. Lastly, this paper adds to existing work on merger analysis by providing evidence on merger effects in generic markets. Previous work on generic mergers has examined trends in merger activity and financial performance of merging firms.[55,133]

The remainder of the paper is organized as follows. Section 1.2 provides details on the supply chain for prescription drugs. Section 1.3 details how I obtained data on mergers between generic manufacturers, generic drug prices, and drug characteristics. Section 1.4 lays out the empirical approach and section 1.4 presents the results. Section 1.6 concludes the paper.

1.2 Background: Supply Chain for Prescription Generic Drugs

The effect of mergers on generic prices is mediated by the nature of the supply chain for generic prescription drugs. Moreover, mergers may have a different impact on prices at different levels of the supply chain. I focus the discussion on the supply chain for generic drugs sold at retail pharmacies as I only observe prices paid by pharmacies. Generic manufacturers either sell drugs directly to pharmacies or sell drugs to wholesalers, who in turn sell them to pharmacies.[46] Wholesaler and pharmacy demand for generic drugs with multiple suppliers is elastic, driven by substitution.[7] When

consumers fill their prescriptions, pharmacies are typically permitted dispense any therapeutically equivalent generic drug with the prescribed active ingredient, dosage form, route, and strength.[136] As a result, generic drugs with multiple therapeutically equivalent suppliers can be purchased as commodities. The total reimbursement to pharmacies, referred to as the retail price, includes cash payments, co-payments, and insurer reimbursement.

Wholesalers negotiate confidential contracts with manufacturers and pharmacies that may include discounts and volume commitments. Even when generic manufacturers negotiate prices directly with pharmacies, wholesalers may act as intermediaries. In this case, if pharmacies reimburse wholesalers a negotiated price that is less than the price wholesalers paid to manufacturers, manufacturers provide a chargeback to the wholesaler for the difference.[80,99]

Traditionally, large chain pharmacies were more likely to bypass wholesalers and purchase generic drug directly from manufacturers. However, in the past decade, chain pharmacies and wholesalers have formed purchasing partnerships to increase their market power. As a result, the share of total unit sales sold through wholesalers – 40% as of 2012 – may have grown.[46,99] Increased downstream purchasing power generates downward pressure on generic prices that might prevent post-merger price increases.

Pharmacy Benefit Managers (PBMs), who administer prescription drug benefits on behalf of insurers, negotiate with pharmacies on network inclusion and reimbursement. Generic reimbursement is generally determined with maximum allowable cost (MAC) prices, reflecting the maximum reimbursement for each off-patent drug with generic substitutes. A schedule of MAC prices is included in confidential contracts between PBMs and pharmacies.[99]

Mergers may have a different impact on wholesale prices, pharmacy acquisition costs, and retail prices. The primary analysis in this paper will examine the impact of mergers on pharmacy acquisition cost. I do not observe prices paid by wholesalers to manufacturers. However, given the practice of chargebacks, changes in acquisition costs likely indicate changes in revenue received by generic

manufacturers.

I also examine the effect of mergers on retail prices to explore if changes in pharmacy acquisition costs are passed through to insurers and consumers. In theory, the pass-through rate, the extent to which upstream savings are passed onto downstream purchasers in the form of reduced prices, depends on price elasticity and competition in the downstream market.[44] Thus, even if pharmacies pay higher prices for generic drugs post-merger, retail prices paid by insurers may remain unchanged. This is more likely if insurers and consumers are price sensitive or if insurers have bargaining power in negotiations with pharmacies.

1.3 Data

1.3.1 Mergers

Generic mergers are identified using the Securities Data Company (SDC) Platinum and Capital IQ databases. The databases identify the universe of mergers and acquisitions, along with relevant merger information such as target name, acquiror name, announcement date, effective date, transaction value, merger status, and industry. I study mergers announced between 2014 and 2017, valued at over $100M where both of the merging firms are generic manufacturers marketing drugs in the United States. High-value mergers are more likely to include manufacturers with overlapping drug portfolios. Only completed mergers are ultimately included in the study.

I confirm that firms are generic manufacturers based their generic drug approvals in the Drugs @ FDA database of all approved brand and generic prescription drugs.[51] For each approved drug, Drugs @ FDA includes active ingredient, dosage form(s), route, strength(s), approval date and manufacturer name. Drugs are identified by FDA application number. I use Drugs @ FDA to categorize merging firms as generic if over fifty percent of approvals are ANDAs or if the company holds over 20 ANDAs at the time of merger.

Table 1.1: Mergers Between Generic Manufacturers Announced 2014 - 2017

Target	Acquirer	Announced	Effective	Status	$ M
Precision Dermatology, Inc.	Bausch Health Co. Inc.	14-Feb	14-Jul	closed	$500
Forest Laboratories Inc	Actavis Plc	14-Feb	14-Jul	closed	$25,440
Pack Pharmaceuticals Llc	Rising Pharmaceuticals Inc	14-Mar	14-Apr	closed	$100
Ranbaxy Laboratories Ltd	Sun Pharm Inds Ltd	14-Apr	15-Mar	closed	$3,226
Versapharm Inc	Akorn Inc	14-May	14-Aug	closed	$440
Bedford Laboratories	Hikma Pharmaceuticals Plc	14-May	14-Jul	closed	$300
Dava Pharmaceuticals Inc	Endo International Plc	14-Jun	14-Aug	closed	$600
Innopharma Inc	Pfizer Inc	14-Jul	14-Sep	closed	$360
Shasun Pharm Ltd	Strides Arcolab Ltd	14-Sep	15-Nov	closed	$182
Famy Care Ltd-Cert Female	Mylan Laboratories Ltd	15-Feb	15-Nov	closed	$800
Hospira Inc.	Pfizer Inc.	15-Feb	15-Sep	closed	$17,743
Perrigo Company Plc	Mylan N.V.	15-Apr		cancelled	$40,432
Mylan N.V.	Teva Pharm Inds Ltd	15-Apr		cancelled	$39,679
Par Pharm. Holdings	Endo International Plc	15-May	15-Sep	closed	$8,036
Gavis Pharms Llc,Novel Labs	Lupin Ltd	15-Jul	16-Mar	closed	$880
Allergan Plc-Generic Drug Bus	Teva Pharm Inds Ltd	15-Jul	16-Aug	closed	$38,750
Roxane Laboratories Inc	Hikma Pharmaceuticals Plc	15-Jul	16-Feb	closed	$2,066
Kremers Urban Pharm.	Lannett Co Inc	15-Sep	15-Nov	closed	$1,230
Invagen Pharm. Inc	Cipla (Eu) Ltd	15-Sep	16-Feb	closed	$500
Renaissance Acq Hldg-Top	Mylan Nv	16-May	16-Jun	closed	$1,000
Akorn, Inc.	Fresenius Kabi Usa, Llc	17-Apr		cancelled	$5,098
Impax Laboratories Inc	Amneal Pharm. Llc	17-Oct	18-May	closed	$1,372
Unichem Labs Ltd-Branded	Torrent Pharmaceuticals Ltd	17-Nov	17-Dec	closed	$558

There were 23 mergers announced between 2014 and 2017 between generic manufacturers valued at least $100 M, listed in table 1.1. The three largest mergers were between Mylan, Perrigo, Allergan Generic and Teva. In April 2015, Mylan attempted to acquire Perrigo and Teva attempted to acquire Mylan. Both hostile takeover attempts were unsuccessful and Teva announced a successful acquisition of Allergan's generic business a few months later. The market consensus during this period of "merger mania" in 2015 was that divestitures would be required given the level of overlap between Teva, Mylan, and Allergan Generic but the merging firms would ultimately benefit from tax savings and decreased operating expenses. [120,112,3] Endo pharmaceuticals made multiple acquisitions during the study period, exhibiting substantial growth in its share of the US generics market. [109]

1.3.2 Pharmacy Acquisition Costs

Quarterly Orange Book files were used to identify markets where both firms were present pre-merger.[52] The Orange Book is an FDA database of all approved drugs with therapeutic equivalence evaluations including manufacturer name, and therapeutic equivalence rating. Like Drugs @ FDA, the Orange Book identifies drugs by the FDA application number and includes active ingredient, dosage form, route, strength(s), and approval date for each drug. The Orange Book is updated monthly with new drugs, discontinued drugs, and changes to manufacturer name or therapeutic equivalence of existing drugs. For example, after Teva divested generic clarithromycin extended release tablets to Mayne, the applicant name was updated in the Orange Book from Teva Pharmaceuticals USA Inc to Mayne Pharma LLC. In this analysis, drugs with the same ingredient, dosage form, route, strength and therapeutic equivalence rating form a market.

Pharmacy acquisition costs are obtained from the National Average Drug Acquisition Cost (NADAC) dataset from November 2013 to September 2020.[18] The dataset captures average acquisition cost for outpatient drugs covered by Medicaid based on surveys of retail community pharmacies, including chain and independent pharmacies. Importantly, the NADAC data does not include drugs that are exclusively administered in in-patient settings and therefore not sold in retail pharmacies. The surveys are intended to provide a benchmark of the national average acquisition cost pharmacies pay per drug and does not reflect Medicaid specific prices or Medicaid rebates. NADAC has been shown to be a better estimate of actual acquisition costs than the list price, AWP.[85] Acquisition cost is reported weekly and I aggregate to the monthly level.

The NADAC data identifies drugs by ingredient, form, strength, and National Drug Code (NDC). The average acquisition cost is reported at the market level by brand and generic status, where market is defined by active ingredient(s), strength, dosage form, route, and therapeutic equivalence. Manufacturer-specific acquisition cost for each market is not included in the data. I do not

aggregate the NADAC data across strengths because quantities are not included so I cannot properly calculate the average acquisition cost at a higher level.

I use the FDA NDC Directory to create a cross walk between NADAC data and the Orange Book. The NDC is a unique identifier assigned to all drugs marketed for commercial distribution. The NDC Directory identifies the FDA application number linked to each NDC code. I use the NDC code and FDA application number to merge quarterly orange book files to the NADAC data, allowing me to designate the manufacturer who owned each drug in each quarter.

Additional drug market characteristics are computed using Drugs @ FDA. Market vintage, defined as time since loss of exclusivity, is calculated as time since the earliest generic approval date. Drugs are classified as oral solids, injectables, or other based on dosage form and route. Tablets and capsules are classified as oral solids, all other oral formulations, such as oral syrups, are classified as other. The number of manufacturers present in each month is calculated as the number of unique applicants in each market based on Orange Book Quarterly files. For merging firms, I consider the target and acquiror firm as a single unique firm after the merger effective date. Mandated divestitures are identified in an overview of FTC actions in the pharmaceutical industry.[98] Lastly, firm exit is defined as the last month of sales for a given manufacturer in the market followed by three or more months of no sales. Firm entry is defined as the first month of sales for a given manufacturers followed by three or more months of no sales.

The NADAC study sample is constructed with monthly observations at the drug market level, including the names of manufacturers present in the market. I define treated markets as those where both merging firms are present in the year before the merger was announced. The control group is constructed using coarsened exact matching, described in detail in section 3. Included drug markets must be sold for at least 15 months before and 15 months after the merger effective date, however individual manufacturers may enter or exit the market during the sample period. I also exclude generic markets where the merger occurs less than 4 years after loss of exclusivity. Prices are volatile

in new generic markets as it takes time for prices to reach equilibrium, which could muddle the estimation.

1.3.3 Retail Prices

I obtain retail prices from IQVIA sales data reported quarterly at the firm-drug level from Q4 2012 to Q1 2018. The data includes the retail price, including insurer reimbursement and out of pocket payments, and total quantity for the US market. Drugs are identified by firm name, drug name, active ingredient name, and therapeutic class. I calculate total quantity and average price at the drug market level, defined by active ingredient. Unlike the NADAC data, the IQVIA retail data does not identify drugs by dosage form, route, and strength. For example, Akorn Pharmaceuticals produces albuterol sulfate as an oral syrup and inhalation solution. However, the retail data only includes one drug from "Akorn Pharmaceuticals" called "albuterol sulfate" that represents an average across formulations. As a result, market definition is less granular in the retail data than the NADAC data.

A secondary study sample is constructed to include market level average prices and quantities for the same matched treated and control drugs as the NADAC study sample. I use active ingredient and drug name to link drugs between NADAC and IQVIA data. Similar to the NADAC data, included markets have to be in the data for 15 months, or 5 quarters, before and after the merger effective date. I observe NADAC data from November 2012 through September 2020 and retail sales data from Q4 2012 through Q1 2018. Therefore, mergers that occurred in 2017 or later are not included in the retail price analysis, as they do not have enough post-merger observations. Specifically, the mergers between Impax Laboratories and Amneal Pharmaceuticals and between Unichem Labs and Torrent Pharmaceuticals are included in the pharmacy acquisition cost analysis but not included in the retail data.

1.3.4 Study Sample

For mergers between firms with overlapping drug portfolios, table 1.2 details the level of market presence and overlap by ingredient and market. Present refers to markets where target or acquiror were present pre-merger and overlap refers to markets where both firms were present. Divested includes divestitures identified in the sample. The extent of overlap varied across mergers. Eight of the 20 completed mergers did not feature any overlapping markets, suggesting that market overlap is not a necessary motivation for merger. Most of the overlapping markets come from the acquisition of the Allergan generic drug business, formerly Actavis, by Teva Pharmaceutical Industries. The Allergan-Teva merger also featured the most divestitures, involving 52 drugs that were previously sold by both firms. There were also divestitures for 19 pipeline products that were not yet on the market and therefore not included in this analysis. The drug characteristics of the treated and control groups are outlined in table 3. The average price in the total sample is quite low, at about $1.50. This reflects the fact that NADAC captures acquisition costs per unit, meaning cost per ml for an injectable or cost per tablet or capsule. The price for the standard volume dispensed per script may be considerably higher.57 As discussed in section 4, coarsened exact matching helped to balance treated and control groups.

1.4 Research Design

1.4.1 Identification

Multiple identification strategies have been used to analyze the effect of mergers between firms that compete across many markets. For example, a rival analysis models mergers as an exogenous shock to competitor firms in the same market and has been used in merger analysis in hospital markets.17 Another approach is to exploit variation in the anticipated impact of mergers between multimarket

Table 1.2: Ingredient and Market Level Overlap by Merger

		Ingredient - Formulation			Market		
Target	Acquiror	Overlap	Present	Divested	Overlap	Present	Divested
Precision Dermatology, Inc.	Bausch Health Co. Inc.	2	29	0	5	57	0
Forest Laboratories Inc	Actavis Plc	2	239	0	6	508	0
Pack Pharmaceuticals Llc	Rising Pharmaceuticals Inc	2	239	0	6	508	0
Ranbaxy Laboratories Ltd	Sun Pharm Inds Ltd	5	221	2	13	418	5
Versapharm Inc	Akorn Inc	0	36	0	0	41	0
Bedford Laboratories	Hikma Pharmaceuticals Plc	2	77	0	2	143	0
Dava Pharmaceuticals Inc	Endo International Plc	2	115	0	7	250	0
Innopharma Inc	Pfizer Inc	0	65	0	0	140	0
Shasun Pharm Ltd	Strides Arcolab Ltd	0	17	0	0	32	0
Famy Care Ltd-Cert Female	Mylan Laboratories Ltd	0	305	0	0	758	0
Hospira Inc.	Pfizer Inc.	3	90	1	5	180	1
Par Pharm. Holdings	Endo International Plc	3	182	2	6	402	4
Gavis Pharms Llc,Novel Labs	Lupin Ltd	3	103	0	7	236	0
Allergan Plc-Gen. Drug Bus	Teva Pharm Inds Ltd	94	450	52	244	1003	141
Roxane Laboratories Inc	Hikma Pharmaceuticals Plc	6	156	3	17	288	12
Kremers Urban Pharm.	Lannett Co Inc	0	55	0	0	92	0
Invagen Pharm. Inc	Cipla (Eu) Ltd	3	43	0	8	109	0
Renaissance Acq Hldg-Top	Mylan Nv	0	317	0	0	782	0
Impax Laboratories Inc	Amneal Pharm. Llc	18	156	11	40	339	28
Unichem Labs Ltd-Branded	Torrent Pharmaceuticals Ltd	5	64	0	12	181	0
		150	2959	71	378	6467	191

entities on concentration across markets. I cannot implement these approaches because I do not have market share at the drug-manufacturer level. Instead, I use a differences-in-differences estimator and approximate a counterfactual by constructing a control group of markets with demand and supply drivers that mirror merging markets. The identification assumes that prices in markets where merging firms overlapped pre-merger would have evolved at the same rate as control markets had the merger not occurred. Previous merger analysis have implemented a similar approach.[73,6,119]

This paper estimates the effects of mergers. Consolidation is one of the consequences of mergers and these results provide some insight on its effect on generic markets. We can interpret the results as the causal effect of consolidation, if we assume that market overlap between merging firms is random and, as a result, the merger is exogenous to the market. Portfolio overlap between merging firms is likely not random, but mergers may also be motivated by factors other than market level consolidation. For example, acquisitions that diversify a manufacturer's drug portfolio with new

therapeutic classes and dosage forms expand a manufacturer's technical capabilities and may enable entry into complex generic markets.[133,132] Other reported drivers for merger include tax advantages, expansion into new markets internationally, and savings from increased scale.[112,35]

Divestitures provide an experiment to evaluate the impact of mergers without consolidation. The FTC has required divestitures as a remedy to prevent decreased competition for a given drug, arguing that there would not be sufficient, timely entry to mediate decreased competition as a result of merger.[24,45,98] In the complaints for the Impax & Amneal and Teva & Allergan Generics mergers, the FTC justifies it's decision to require divestiture based on the number of firms present in the market, market share of the merging entities, and likelihood of future entry on competition. In the data, I identify successful divestitures based on changing ownership of the drug in the Quarterly Orange Book Files. I assume divestitures reported by the FTC that I'm unable to confirm were not completed.

Markets with successful divestitures avoid consolidation, but are still susceptible decreased competition. Mergers change multi-market contact between generic manufacturers, which dampens competition by introducing the prospect of collusive pricing and has been shown to increase prices in pharmaceutical and hospital markets.[116,27] Secondly, mergers may change bargaining power of generic manufacturers in negotiations with wholesale distributers, which could influence prices in markets not facing consolidation.[137] I perform a subset analysis on divested vs. non-divested markets to compare the effect of merger in markets with and without consolidation.

1.4.2 Estimation

I Implement a variation of the differences in differences model with two way fixed effects (TWFE). Recent work on differences in differences have documented that when observed units are treated at different times, the standard two way fixed effects estimate, outlined in equation 1.1, produces coefficients that are difficult to interpret.[60] In equation 1, β represents the differences in differences

coefficient estimate, D_{it} represents the treatment dummy and α_i and α_t represent unit and time fixed effects. The unit of observation is a generic drug market and treated markets are those where both firms were present pre-merger.

$$Y_{it} = \alpha_i + \alpha_t + \beta * D_{it} + \varepsilon_{it} \tag{1.1}$$

Mergers occur at different points during the sample. As a result, if I implement the standard TWFE model, the control group would be made up of never treated drugs and treated drugs. The β coefficient in equation 1.1 would be weighted average of the treatment effects across all possible two group, two period pairs in the data, including both treated and never treated controls. In this paper, I want to measure the average effect of mergers. Consider each merger as its own experiment, with its own treatment effect. The objective is to estimate a coefficient that represents the average of merger specific treatment effects.

Following Sun and Abraham, I group drugs into cohorts by merger date and estimate an event study specification.[127] This approach generates a weighted average of cohort specific treatment effects, producing coefficients that can be causally interpreted. I group treated drugs into cohorts by merger date and construct a control group of never treated drugs. For each cohort, a parallel control group is constructed using markets unaffected by the mergers in that cohort and excluding markets that were ever treated during the study period. Markets are considered unaffected by a merger if neither merging firm was present pre-merger. I then assign the control drugs the same treatment date as treated drugs in their respective cohort.

The primary specification, outlined in equation 1.2, estimates a distinct coefficient for each time period pre- and post- merger. The event time, or lag variable, l, indicates time since treatment and D_{il} is the treatment dummy. In addition to unit and time fixed effects, I include cohort-event time fixed effects, α_{cl}, to account for cohort specific variation. The month prior to the merger effective

date, $l = -1$, is the base level for the event study the estimation. I also calculated a pooled differences in differences model, outlined in equation 1.3, that generates a single coefficient, β. Standard errors are clustered at the merger cohort level.

$$Y_{it} = \alpha_i + \alpha_t + \sum_{l=-24}^{24} [\beta_l * D_{it} + \alpha_{cl}] + \varepsilon_{it} \tag{1.2}$$

$$Y_{it} = \alpha_i + \alpha_t + \beta * D_{it} + \sum_{l=-24}^{24} [\alpha_{cl}] + \varepsilon_{it} \tag{1.3}$$

Coarsened exact matching (CEM) is performed before estimation to balance control and treated groups on covariates that mediate the effect of mergers. The data is coarsely grouped into bins based on values of selected covariates, then control and treated groups are matched. Bins that do not contain at least one treated and one control unit are dropped from the analysis. The CEM program also generates weights to be used in estimation to adjust for mismatches in the number of treated and control units within each bin. [14]

I perform this matching exercise separately for each cohort, matching based on formulation, market vintage, and number of firms present in the market. Oral solids generally have lower entry costs than injectables and other dosage forms and a greater threat of entry may impact competition. [100,128] Similarly, market vintage and the number of firms present in the market have been shown to effect competition. [25,13]

The results of coarsened exact matching are displayed in figure 1.1. Each dot in the plot represents a treated (+) or control (x) unit. The top graph plots the unmatched sample and the bottom graph plots the matched sample, and the marker size denotes the weight assigned to the unit. As the figures show, a considerable number of control units were dropped and the balance between treated and control is greatly improved through matching.

The summary statistics presented in table 1.3 highlight the importance of the matching proce-

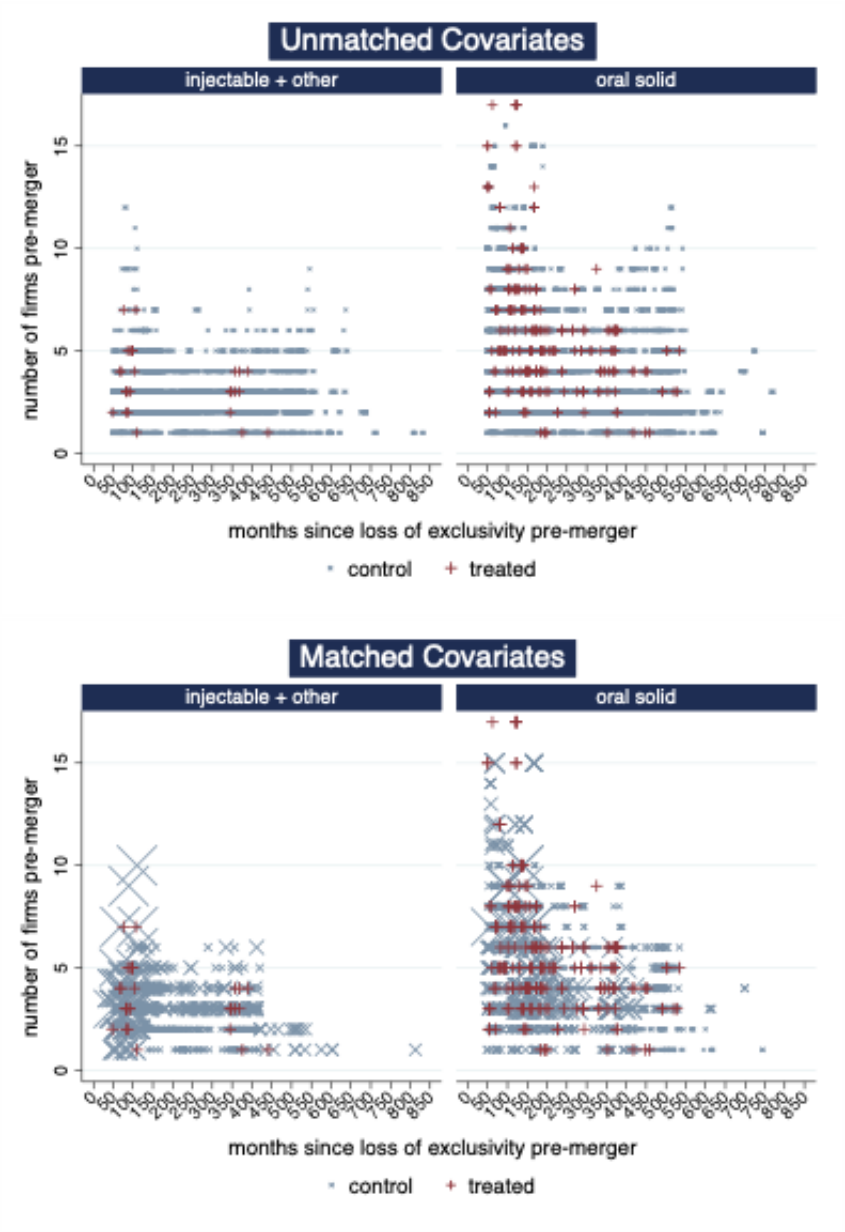


Figure 1.1: Results of Coarsened Exact Matching

dure. Without weighting, the treated drug markets had more suppliers, were slightly younger markets and had a higher share of oral solid drugs. Control drugs are more expensive than treated drugs, possibly driven by the fact that they were more likely to be non-oral formulations. Adding weights brings the number of manufacturers, share of oral solid formulations, and acquisition costs in the control group closer to that of the treated group.

In a secondary analysis, I investigate the effect of mergers on markets with only one of the merging firms present pre-merger. In this estimation the treated group include markets with only one merging firm present in the year before merger announcement and excludes markets where both merging firms were present during the sample period. The control group for this analysis include markets that never had a merging firm present within 2 years of a merger effective date. I perform the same coarsened exact matching procedure as described above, with the same parameters to construct a control group that is similar to the treated group.

1.5 Results

Merger have a statistically significant and persistent effect on acquisition costs. Figure 1.2 plots the coefficients from the event study specification (equation 1.2) by event time, with and without coarsened exact matching. Adding coarsened exact matching improves the fit between treated and control group in the pre period and decreases the standard errors. However, the general trend is unaffected by the matching procedure. The acquisition costs in treated markets increases between 10 and 20 cents relative to controls drugs post-merger. Confidence intervals are narrow and above zero in the post period.

The increase in treated drugs relative to control drugs may be a results of having fewer manufacturers in the market post-merger. First, I test if divestitures succeed in maintaining the same number of firms in the market. The number of firms may evolve similarly in markets with and without

Table 1.3: Summary Statistics

Unmatched Sample

	Control	Treated	Total
acquisition cost	2.281	1.025	2.246
	(7.162)	(2.692)	(7.079)
# manufacturers	3.666	5.689	3.722
	(2.268)	(3.240)	(2.324)
market vintage (months)	234.1	194.1	233.0
	(146.8)	(116.0)	(146.2)
oral	0.698	0.889	0.704
	(0.459)	(0.314)	(0.457)
injectable	0.0301	0.0185	0.0297
	(0.171)	(0.135)	(0.170)
other	0.272	0.0922	0.267
	(0.445)	(0.289)	(0.442)
N	9,744	272	10,016

Matched Sample

	Control	Treated	Total
acquisition cost	1.477	1.062	1.442
	(6.406)	(2.737)	(6.188)
# manufacturers	5.154	5.434	5.177
	(2.819)	(3.023)	(2.838)
market vintage (months)	181.2	196.8	182.5
	(112.9)	(117.0)	(113.3)
oral	0.885	0.885	0.885
	(0.319)	(0.319)	(0.319)
injectable	0.00951	0.0193	0.0103
	(0.0971)	(0.137)	(0.101)
other	0.106	0.0958	0.105
	(0.307)	(0.294)	(0.306)
N	2,925	262	3,187

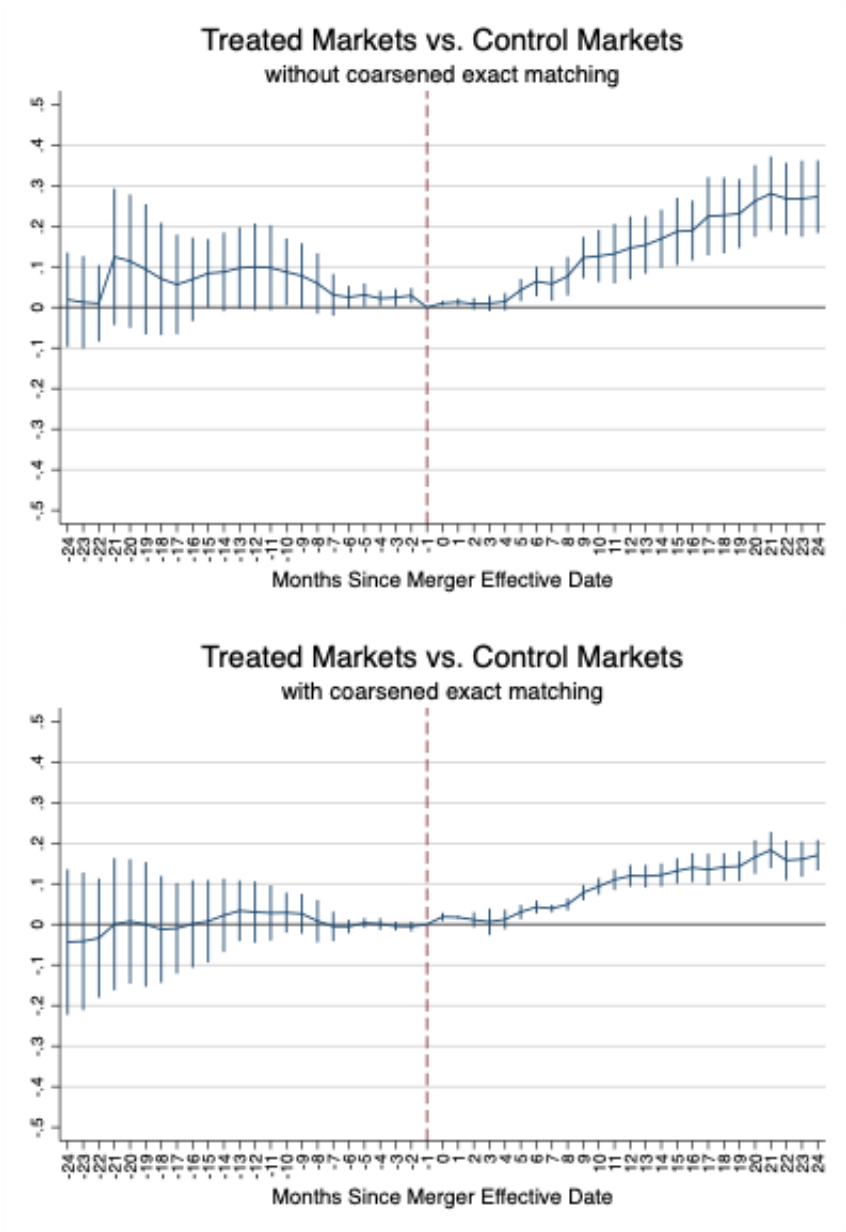


Figure 1.2: Effect of Mergers on Pharmacy Acquisition Cost

Figure 1.3: The Effect of Mergers on the Number of Firms Present in the Market

divestiture due to non-divestiture related entry or exit. Then, I test if the effect of mergers on acquisition costs differs in markets with and without a divestiture. For both tests, I repeat the event study specification on treated markets with and without divestitures, comparing treated groups to their cohort specific control markets.

The Figure 1.3 plots the coefficients from estimation on number of firms. Markets without divestiture see a decline in the number of firms per market. Conversely, the number of firms remains stable in markets with divestiture. These results imply that divestitures are important to maintaining number of generic manufacturers per market.

The effect of mergers on acquisition cost is greater in markets without divestiture. As shown in figure 1.4, the coefficients in the post period are positive with confidence intervals above zero for divested markets, however they never rise above the level of pre-period coefficients and therefore may not indicate a merger related price change. The treated markets without divestiture, on the other hand, exhibit a clear shift in prices relative to control markets in the post period. The effect

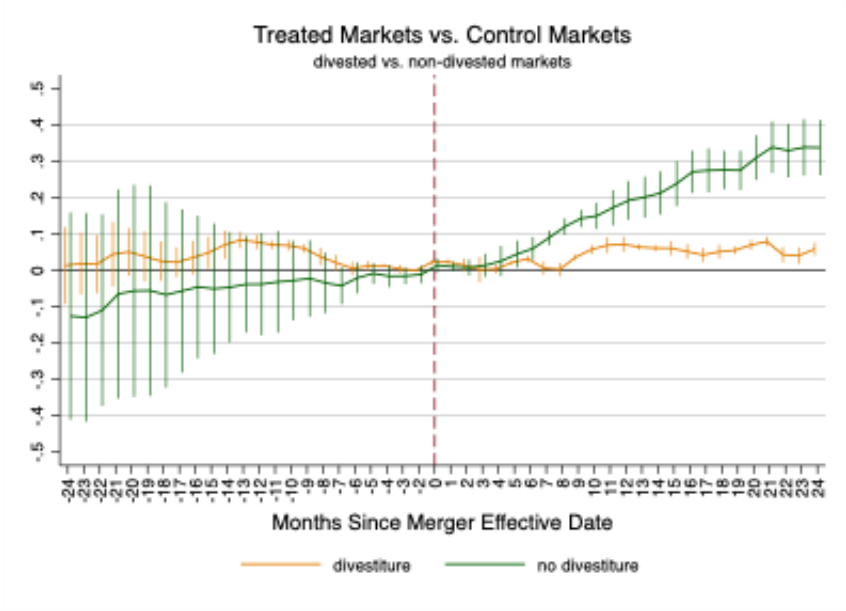


Figure 1.4: The Effect of Mergers on Pharmacy Acquisition Costs in Markets with and without Divested Drugs

size in markets without divestiture is greater than the effect size of the overall analysis in figure 2b. The positive slope in the post-period coefficients, in both figure 1.2 and 1.4, suggests that mergers change the evolution of acquisition costs over time rather than producing a one-time level shift.

The pooled differences in differences results, presented in table 1.4, mirror the results from the event study plots. I implement the difference in difference specification (equation 1.3) on the entire sample, then among subsets of the sample by number of manufacturers and divestiture status. Mergers increase acquisition costs by 10 cents relative to control drugs, a statistically significant result. This effect is higher and also statistically significant among markets without divestiture, with coefficients of 0.23 and 0.32 for all non-divested markets and non-divested markets with fewer than six manufacturers, respectively. In non-divested markets with six or more manufacturers in the market the effect size is 0.10 but effect is not statistically significant.

Mergers do not affect acquisition costs in divested markets, yielding a coefficient of 0.01 that is not statistically significant. The coefficient in divested markets with fewer than six manufacturers,

Table 1.4: The Effect of Mergers on Pharmacy Acquisition Costs in Markets with and without Divested Drugs

VARIABLES	(1) all markets acq. cost	(2) not divested acq. cost	(3) not divested <6 firms acq. cost	(4) not divested >=6 firms acq. cost	(5) divested acq. cost	(6) divested <6 firms acq. cost
treated x post	0.10**	0.23***	0.32**	0.10	0.01	0.08***
	(0.04)	(0.07)	(0.14)	(0.09)	(0.01)	(0.02)
Observations	152,880	145,241	109,749	35,492	147,799	115,125
R-squared	0.03	0.03	0.03	0.07	0.03	0.04
Number of id	3,187	3,030	2,290	740	3,082	2,400

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

0.08, is positive and statistically significant. But, given that pre-period coefficients in the event study specification among markets with divestiture are about 0.05, the result should be evaluated with caution. Still, the results suggest that mergers may affect prices in markets with fewer manufacturers premerger, even when the number of competitors in the market remains unchanged due to divestiture.

To further examine how mergers influence prices in markets that do not experience consolidation, I test the impact of mergers on acquisition costs in markets where only one of the merging firms were present pre-merger. The coefficients from this analysis are plotted in figure 1.5. In the pre-period, the coefficients are positive indicating that prices in effected markets decline relative to control markets in the month leading up to merger effective date. The difference in pre-period trends between the treated and control markets violate the standard assumption in differences in differences estimates, therefore the results should interpreted with caution. In the post-period, the coefficients are less slightly less than zero but the result isn't statistically significant, with standard errors above zero. In markets with only one merging firm, acquisition costs may decline around the time of merger, but they remain stable relative to control markets post-merger.

Figure 1.5: Effect of Mergers on Pharmacy Acquisition Costs in Markets with One of the Merging Firms Present Pre-Merger

I explore additional market outcomes including exit, entry, and total market quantity. Mergers may influence the likelihood of firm exit. When mergers reduce the number of firms, non-merging incumbent firms who were considering exiting may chose not to. Firm entry may mediate the impact of mergers on prices by restoring competition. I find that mergers do not impact entry or exit. In table 1.5, results on exit are in columns 1-3 and entry are in columns 4-6, including a subset analysis on markets with and without divestiture. The coefficients are near zero in all estimates, ranging from -0.01 to 0.02, indicating the likelihood of entry and exit are not impacted by mergers.

Quantity restrictions are one of the possible mechanisms for price increases post-merger. In commodity markets, where products compete on price and availability rather than quality, merging firms may decrease output to increase prices. Figure 1.6 plots with the results from the analysis of market quantity where treated markets are those with both firms present pre-merger. Mergers do not appear to lead to changes in market quantity.

Table 1.5: Effect of Mergers on Entry and Exit, Differences in Differences Results

	(1)	(2)	(3)	(4)	(5)	(6)
	all	not-divested	divested	all	not-divested	divested
Variables	exit	exit	exit	entry	entry	entry
treated x post	0.02**	0.00	0.02***	0.01	-0.01	0.02*
	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)
Observations	160,553	152,714	154,982	160,553	152,714	154,982
R-squared	0.05	0.06	0.06	0.04	0.04	0.04
Number of id	3,340	3,179	3,225	3,340	3,179	3,225

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

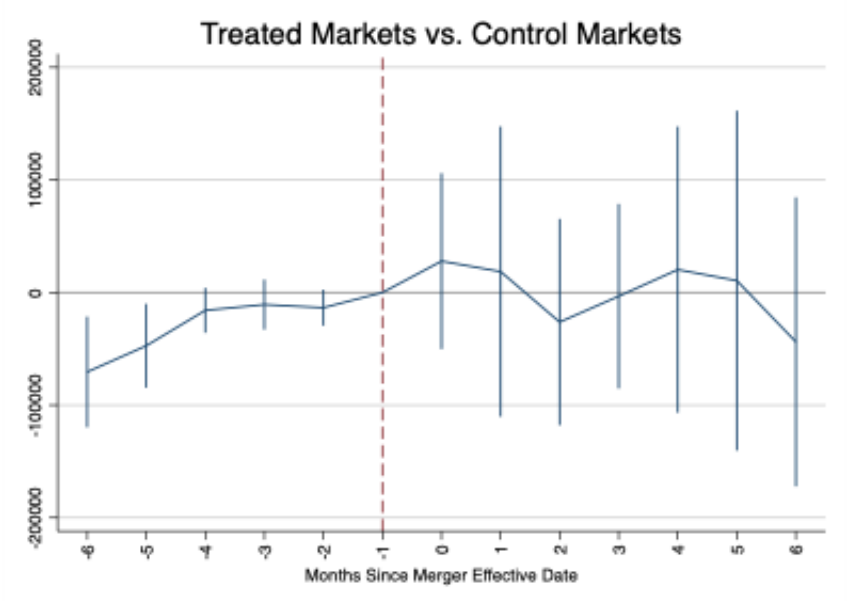


Figure 1.6: Effect of Mergers on Quantities in Markets with Both Merging Firms Present Pre-Merger

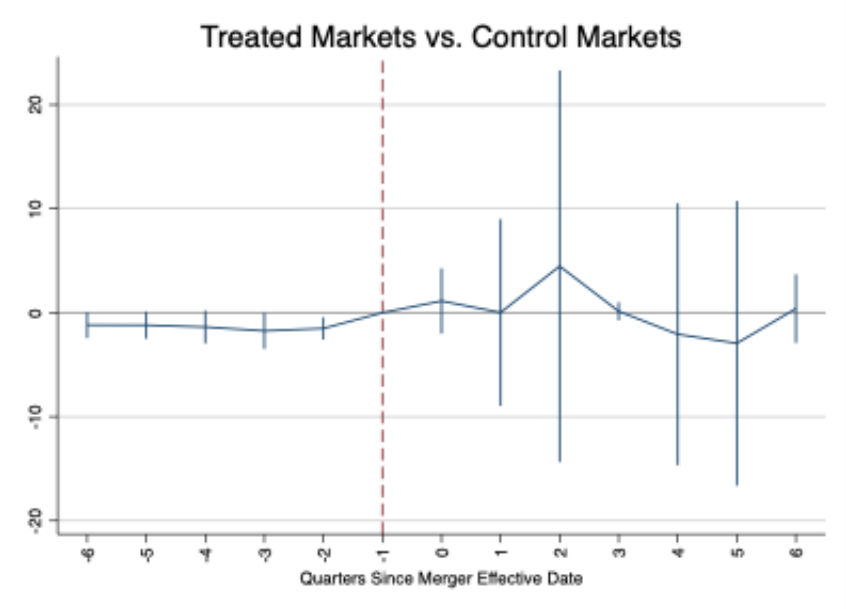


Figure 1.7: Effect of Mergers on Retail Prices in Markets with Both Merging Firms Present Pre-Merger

Lastly, I investigate if increased pharmacy acquisition costs are passed through to consumers in the form of higher retail prices. Results from these regressions are presented in figure 1.7. The pre-period coefficients are stable and slightly below zero. In the post-period the coefficients are both positive and negative, with confidence intervals that cross zero. The results imply that mergers do not effect retail prices in markets where both merging firms were present pre-merger.

1.6 Discussion

This study evaluated the effect of horizontal mergers between generic manufacturers on pharmacy acquisition costs of generic drug. Bioequivalent generic drugs are perfect substitutes and in theory pharmacies would purchase them as undifferentiated commodities. Additionally, wholesale distributers and pharmacies have created purchasing partnerships to increase their leverage on generic manufacturers.68 Yet, the effect of mergers on generic prices is ambiguous due to entry costs, po-

tential for increased multimarket contact and increased bargaining power of merging manufacturers due to larger product portfolios.

Pharmacy acquisition costs increase in treated markets relative to control markets post-merger. FTC actions may have helped sustain competition in markets with divestitures. I find statistically and contextually significant results in markets without mandated divestitures. Whereas acquisition costs of treated markets with divestitures do not vary relative to control markets in the post period. In other words, mergers impact acquisition costs in markets where the number of suppliers decreases but have no effect on markets where the number of suppliers remains unchanged, suggesting that consolidation is the driving force behind changes in costs. The FTC and Department of Justice (DOJ) should continue to closely monitor merger activity in generic markets and implement remedies, such as divestitures, to prevent eroding competition.

I infer that changes in pharmacy acquisition costs mirror changes in wholesale prices paid to manufacturers, given the practice of using chargebacks to adjust for differences between the amount wholesalers pay to manufactures and the amount they collect from pharmacies. However, as I cannot observe wholesaler prices, I cannot confirm this hypothesis. The post-merger increase in average prices may reflect price increases for both merging and non-merging manufacturers. Pharmacy acquisition data at the drug-manufacturer level would help answer this question.

A chief policy concern regarding generic price increases is the implications for patient out of pocket costs and overall drug spending by insurers, including public programs. I find that retail prices paid by insurers and customers do not increase in overlapping markets, implying pharmacies bear the cost of post-merger price increases. Pharmacies may not be able to negotiate increased reimbursement from payers (PBMs or insurers) for drugs with increased acquisition costs. Payers often reimburse generic drugs using maximum allowable cost (MAC) lists, which have been shown to be unresponsive to changes in acquisition costs. [104]

The inability to pass through changes in input prices may hurt pharmacies and shield payers from

any effects of reduced competition among generic suppliers. Closures of rural and independent pharmacies are a current policy issue in the US. [115,121,47] If eroding competition between generic manufacturers results in reduced margins for pharmacies, policy makers should take note because generic drugs generate the majority of pharmacy profits. [121] The results from this paper are based on national average prices and may mask policy relevant variation, such as differential effects on rural and urban or chain and independent pharmacies. Granular transaction data for a representative sample of pharmacies would enable a more thorough analysis.

The key limitation of this analysis is the inability to completely correct for the endogeneity of mergers. Characteristics of the market and merging firms that influence the likelihood of merger as well as market level prices may be driving the result. For example, many of the generic manufacturers that merged during my study period had large product portfolios prior to merger. My results could be driven by the presence of these large manufacturers rather than mergers. However, this would not explain the sharp difference in merger effect in markets with and without divested drugs or the difference in markets where both firms were present as compared to markets with only one of the merging firms present.

Another limitation is the inability to observe retail prices and market quantity at the dosage form or route level. The drugs in the retail sales data are denoted by drug name, so it is not possible to differentiate between prices for different dosage forms of the same generic drug. Retail sales data at the same level of granularity as the acquisition costs data would enable a more precise estimate of pass through.

Limitations aside, this paper provides compelling evidence in favor of continued merger scrutiny and insight into how changes in generic competition impact different levels of the supply chain. Had divestitures not been required, generic mergers could have led to price increases for more drugs. The results suggest that generic mergers do not increase prescription drug spending. However, generic mergers result in shift of surplus from pharmacies to generic manufacturers in consolidating

markets. The policy implications of shifting surplus away from pharmacies require further analysis. Additionally, a thorough consideration of welfare implications should also consider possible pro-competitive outcomes of merger. For example, mergers may enable more entry into complex generic or even biosimilar markets.

2

Side Effects of Prescription Limits

2.1 Introduction

In 2017, net prescription drug spending in Medicaid amounted to $29.1 billion, making up about 5 percent of overall Medicaid spending.[97] Controlling the growth of prescription drug spending in Medicaid remains a policy focus at the state and federal level.[96,95] Drug spending in Medicaid is controlled in part through rebate programs that reduce the net price paid and utilization control

that regulates the volume of drugs covered, generally focused on reducing low-value utilization. This paper focuses on the latter, exploiting a policy change Louisiana's Medicaid program to evaluate the impact of monthly prescription drug limits on utilization and spending.

Optimal health insurance design involves a trade-off between efficient utilization and financial risk protection.[94] Insurance decreases patient costs at the point of care, resulting in moral hazard, defined as utilization of care that is not valued at the social cost of production. Insurers employ demand-side (e.g. patient cost sharing) and supply-side (e.g. managed care) mechanisms to limit low-value use and reduce spending. In Medicaid, patient cost sharing is limited to shield its low-income beneficiaries from financial risk and maintain access to critical healthcare services.[a] As a result, Medicaid programs rely heavily on supply side measures, such as utilization review, prior-authorization, and other forms of managed care. There is some evidence that managed care can reduce low-value utilization without compromising patient health, suggesting some forms of utilization controls may help achieve more efficient utilization.[9,94,83] However, if poorly implemented, rationing policies bear the risk of reducing access to high-value services, resulting in potential harmful effects on patient health.

Some Medicaid programs limit the number of prescriptions covered per enrollee per calendar month, which is a mechanism that appears to be unique to Medicaid (i.e. 5 covered outpatient prescriptions per enrollee per month). As of July 2019, 13 states had prescription limits in place. Prescription limits are a blunt instrument for managing drug utilization in that they apply universally across all drugs, including drugs that are clinically effective and have low cost generic substitutes. If the goal of managed care is to reduce utilization of drugs whose marginal cost exceeds its marginal benefit, the ideal mechanism would target high cost drugs and drugs with low or variable clinical benefit across patients. Universal monthly prescription limits may reduce take up or adherence to

[a] Maximum cost sharing for prescription drugs in Medicaid is $4 for generic drugs and $8 for branded drugs. Total out of pocket costs are capped at 5% of family income.

medications with high clinical value, which could result in poorer health outcomes or increased medical spending due to poor pharmaceutical management of chronic conditions. Drug limits may be especially impactful for Medicaid beneficiaries with comorbid mental and physical illness, who may be prescribed multiple chronic disease medications each month to manage their conditions. Despite these concerns, states continue to employ monthly prescription limits, perhaps because they are straightforward mechanism to reduce spending.[56] Policy makers may also believe that permitting some exemptions or overrides of the prescription limit would avoid reducing access to necessary medications.[b]

This paper evaluates a change in the prescription drug limit per enrollee-month from 8 to 5 in Louisiana's Medicaid program implemented in May 2009. The limit was then changed from 5 to 4 in December 2010. The prescription limit in Louisiana can be negated by an override request from a prescriber. I implement a differences-in-differences analysis, with Alabama as the control state, and find that the policy change results in a decrease in total monthly prescription drug utilization and a decrease in utilization of medications that treat chronic disease.

I also evaluate the policy with event study estimates using Louisiana data only. The first event study evaluates the total number of drugs filled each day near the first of the month. Louisiana enrollees were also more likely to fill prescriptions on the first of the month after the policy change, suggesting patients who have reached the monthly limit may have delayed filling their prescriptions until the next calendar month. I also explore spending outcomes using data from Louisiana only to control for state-level factors, such as provider prices, that might nullify the parallel trends assumption of a difference-in-differences design. In this analysis, I exploit an age cut off in the exemption from prescription limits at age 21 to study the effects of prescription limits on spending. I do not find effects on total spending or total non-drug spending per beneficiary per month.

[b] In 9 of the 13 states, the prescription limit can be overridden. Some classes of drugs may be excluded from prescriptions limits, such as family planning products, cancer drugs, and HIV antiretrovirals.

This paper adds to a decades-old series of studies evaluating the impact of a 3 drug per beneficiary per month limit implemented in 1981 by the New Hampshire Medicaid program. For Medicaid recipients over 60 years old, drug limits were associated with increased rates of admission to nursing homes, but did not incur increased risk of hospitalization.[123] For Medicaid recipients with schizophrenia, drug caps were associated with decreased use of antipsychotic and antidepressant medication, increased ER usage and no change in hospital admissions.[122] These finding may not extend to a more contemporary setting. Elderly beneficiaries are likely to be dual-eligible and today would receive their drug benefits from Medicare Part D, where monthly prescription limits are not implemented.[c] Secondly, the set of prescription drugs available to beneficiaries has evolved, therefore the impact of reduced utilization may differ.

A more recent analysis of prescription drug limits, using state-level data from 2001-2010, found correlations between inclusion of monthly prescription drug limits and lower utilization with no effect on spending.[87] The broader literature on prescription drug rationing in Medicaid evaluates the impact of changes to copay and prior authorization on utilization and costs. Prior authorization has been shown to reduce rates of treatment initiation for some mental health conditions.[90] Copayments have been shown to reduce adherence, with differential effects by diagnosis and therapeutic class.[67]

This project also adds to literature on "offset effects" of prescription drug spending, when spending on prescription drugs results in savings (i.e. offsets) in a substitute service, such as inpatient utilization. For example, increased patient copays for prescription drugs have been shown to result in increased non-drug spending that offset any savings from reduced drug utilization.[19] Conversely, a pilot of Value Based Insurance Design (VBID), which assigns lower copays to high-value drugs, increased adherence without increasing total spending, due to offsets in medical spending.[21]

[c] Since 2006, dual eligible Medicare and Medicaid beneficiaries have received their prescription drug benefit from Medicare part D and are therefore not subject to Medicaid prescription limits. Aged beneficiaries and beneficiaries with mental illness are disproportionally dual eligible.[33]

2.2 Background

All state Medicaid programs elect to cover prescription drugs, though it is not federally mandated. The Medicaid program is administered and financed as a partnership between the federal government and states. The federal government determines minimum requirements for eligibility and benefits and states may expand eligibility or offer additional benefits. States are permitted to manage prescription utilization through copayments, prior authorization, preferred drug lists and quantity limits.[95] In 2012, 12 states had limits on the number of covered drugs per beneficiary per month, ranging from 3 to 6 drugs per month. In 2018, six states imposed drug limits, also ranging from 3 to 6 drugs per month.[131] Beneficiaries who are pregnant, under age 21, and nursing home residents are generally exempt from drug limits. Limits may not apply to some protected drug classes, such as HIV antiviral drugs.

A policy change in Louisiana presents a natural experiment to test the effect of more restrictive drug limits on spending and utilization. In May 2009, Louisiana Medicaid lowered its prescription drug limit from 8 to 5 drugs per enrollee per month. In December 2010, the drug cap was further reduced from 5 to 4. For most drugs, beneficiaries were allowed up to 30 days supply per fill.[d] In Louisiana, enrollees who are pregnant, under 21, or living in long term care facilities are exempt from the drug cap.

If a patient has already reached the number of allowed prescriptions in a calendar month and is prescribed an additional prescription, there are multiple possible outcomes. The prescribing physician can override the limit by writing "Medically Necessary Override" on the prescription and providing a diagnosis code. If the drug requires prior authorization, the prior authorization alone does not override the drug cap. Prescribers are not permitted to use stamped signatures or check boxes to

[d] For Louisiana Medicaid beneficiaries in the study sample, over 97% of prescriptions filled included 30 or fewer days supply.

obtain the override. Among non-elderly adult beneficiaries that are not dually enrolled in Medicare in 2008, 9% exceeded the prescription limit at least one month during the year.

If the prescribing physician does not override the cap, a beneficiary may circumvent the cap by waiting to fill the prescription until the first day of the next calendar month. If the beneficiary anticipates reaching the limit again next month when they refill existing prescriptions, they would then require an override for one or more of those medications in order to fill them all next month. The 'work around' of delaying a fill to the next month would not enable a patient to adhere to maintenance medications that exceeded the prescription limit, as they would exceed the limit each month.

In practice, prescription drug utilization for Louisiana Medicaid beneficiaries subject to the prescription limit depends on their prescribing provider. An illustrative model of prescription fills in this setting is presented in equation 2.1 below. The number of drugs prescribed to a beneficiary depends on medical necessity, λ_{it}, which varies by patient. If the beneficiary has reached the prescription limit in a given month, denoted by the indicator $I_{it} = 1$, the willingness of their physician to submit an override request for patient i, δ_{ij}, determines if the additional prescription can be covered by Medicaid. For simplicity, I assume that all requests made are granted and that Medicaid beneficiaries cannot afford to fill uncovered prescriptions. The beneficiaries propensity to adhere to prescribed, covered medications, α_i, ranging from 0 to 1, determines what share of prescribed and approved prescriptions will be filled. Note that if a patient does not reach the prescription limit, the willingness of the prescriber to override the limit does not effect the number of prescriptions filled in that month.

$$Y_{ijt} = \alpha_i[\lambda_i + I_{it} * \delta_{ij}] \tag{2.1}$$

If the prescription limit is reduced, as was the case in Louisiana, the likelihood that a beneficiary will be at the limit increases. If physicians do not increase their propensity to submit an override

request for a given enrollee, ∂_{ij}, the number of prescriptions filled per month would decrease. Alternatively, if physicians increase their use of the overrides to account for the increased number of beneficiaries who would have exceeded the new limit, utilization may be unchanged. Thus, differences in prescription utilization between beneficiaries with similar health status may be partially explained by differences in physician propensity to override the limit.

This paper will explore multiple hypotheses. First, I anticipate that monthly prescription utilization will decline and beneficiaries will be more likely to delay filling their prescriptions to first of the next month following the policy change. Secondly, decreased prescription drug utilization may lead to increased non-drug spending, thus the impact on total spending is ambiguous. I expect total spending to be unaffected or increase after the policy change. Lastly, differences in prescription utilization among beneficiaries is mediated by differences in physician prescribing and willingness to submit an override request.

2.3 Study Design

2.3.1 Outcomes

In the first stage analysis, I evaluate the impact of a more restrictive limit on monthly prescription drug utilization. Patients may reduce initiation of new treatments in response to the more restrictive drug limit. As a result, changes in adherence, as measured by medication possession ratio, may be difficult to interpret. For example, if the patients with the highest propensity to adhere to medications are also the least affected by the policy, a comparison of adherence may find that the policy leads to greater adherence. Instead, I measure utilization as the number of scripts filled per calendar month per beneficiary and a binary indicator for a patient-month being over the new prescription limit.

Utilization for chronic disease medications is measured as the number of prescriptions filled in a

given month for a particular indication. To test the hypothesis that beneficiaries may not fill their medications in the same month that they are prescribed, I focus on months when a beneficiary received an inpatient or outpatient diagnosis for a condition based on the presumption that they would have been prescribed a medication during that visit. The outcome is the number of drugs filled that are indicated to treat the condition they were diagnosed with in that month.

To test the hypothesis that beneficiaries delay fills to circumvent prescription limits, I evaluate the day of the month a prescription is filled. I focus on prescriptions filled between last 10 days of the month and the first 11 days of the following month. If patients delay fills to circumvent the prescription limit we should see a jump in prescriptions filled on the first days of the month, relative to the adjacent days.

The chronic conditions evaluated in this paper were chosen based on their prevalence in the Medicaid population. In 2009, 28% of non-elderly adult Medicaid beneficiaries were diagnosed with cardiovascular disease (including hypertension and other heart diseases), 9% were diagnosed with diabetes, and 23% were diagnosed with chronic respiratory diseases. In the same year, 35% of beneficiaries were diagnosed with mental illness.[130] The chronic diseases considered in this paper include heart disease, hypertension, chronic pulmonary disorders, diabetes, and mental illness. Heart disease includes congestive heart failure, ischemic heart disease, arrhythmia's and valvular disease. Mental illnesses include bipolar disorder, schizophrenia, and depression.

I use the Elixhauser comorbidity statistical package and World Health Organization guidelines to identify chronic diseases based on beneficiary diagnoses.[139,124] Drugs used to treat chronic conditions are identified based on their therapeutic class designation. Table 2.1 outlines the diagnoses and associated therapeutic classes. The policy change may not have the same impact on medication used to treat chronic and acute conditions. Therefore, I also examine the impact on utilization of anti-infective medications to test for the effect on medications for acute conditions.

For each utilization outcome, I perform the same analysis for the entire study sample as well as

Table 2.1: Chronic Conditions and Associated Therapeutic Classes

Chronic Condition(s)	Drug Classes: Anatomical Therapeutic Chemical (ATC1-4)
diabetes	insulin and non-insulin diabetic drugs (A10)
heart disease	anti-arrhythmic (C01B), vasodilators (C01D), diuretic (C03), beta-blockers (C07), CCB (C08), ACEI, ARB (C09), statins (C10A, C10B)
hypertension	hypertensive drugs (C02), diuretic (C03), beta-blockers (C07), CCB (C08), ACEI, ARB (C09)
chronic pulmonary disorders (including COPD and asthma)	drugs for obstructive airway diseases (R03)
mental illness (depression, bipolar disorder, schizophrenia)	anti-depressants (N06A), antipsychotics (N05A), anxiolytics (N05B)

the subset of beneficiaries with comorbid mental and physical illness. Medicaid beneficiaries with mental illness are more likely than those without a mental illness diagnosis to have at least one non-mental health chronic disease. More than 50% of Medicaid beneficiaries in 2009 diagnosed with cardiovascular disease and respiratory disease also had a comorbid mental health diagnosis.[130] Chronic disease patients with comorbid mental illness may have poorer adherence to medications than patients without a comorbid mental illness.[59] Therefore, a more restrictive prescription drug policy may have a greater impact on patients with comorbid mental and physical chronic conditions. Comorbid beneficiaries are identified as those diagnosed with schizophrenia, major depression, or bipolar disorder and at least one other chronic condition identified in table 2.1.[79,4,72,125]

2.3.2 Spending and Offsets

In addition to utilization, I evaluate the impact of the policy change on total health care spending to identify possible offsets. If drug utilization declines, beneficiary health might decline and medical care utilization may increase as a result, including emergency department and inpatient utilization.[19] As a result a policy intended to reduce prescription drug spending may not result in total cost savings. The spending outcomes I evaluate include total monthly spending per beneficiary, measured by total Medicaid payments made per beneficiary per month. I also measure total non-

drug spending per beneficiary.

2.4 Estimation

2.4.1 Difference in Differences

I use difference-in-differences estimation to evaluate monthly utilization outcomes. The key assumption in the difference-in-differences research design is that the rate of change in the outcome would be the same in the treatment and control groups absent the treatment. This assumption is strengthened by parallel trends in the outcome in treated and control groups. The trend in monthly prescription drug utilization is likely impacted by the presence of a prescription drug limit. Therefore, I select a control state with a prescription limit similar to the pre-period prescription limit in Louisiana, the treated state, based on the presumption that it would be more likely to exhibit parallel trends in the pre-period. Louisiana reduced its prescription limit from 8 to 5 on May 2009. The control state is Alabama, which had a prescription limit of 10 during the entire study period. I also measure and plot the difference in differences coefficient by time, with a baseline of the month prior to the policy change.

The estimation equations are outlined in equations 2.2 and 2.3. Beneficiary fixed effects, α_i, are included in the estimation, meaning the coefficients of interest represent differences in within beneficiary utilization trends between treatment and control groups. In equation 2.2, I estimate a pooled difference-in-differences result, with a single coefficient of interest β. In equation 2.3, I estimate β_t, for reach time period. D_{it} is a dummy variable equal to 1 after the policy change in the treated state, and α_t represents calendar time fixed effects.

$$Y_{it} = \alpha_i + \alpha_t + \beta * D_{it} + \varepsilon_{it} \tag{2.2}$$

$$Y_{it} = \alpha_i + \alpha_t + \sum_t [\beta_t * D_{it}] + \varepsilon_{it} \tag{2.3}$$

Matching is also conducted to adjust for differences in observables between Medicaid beneficiaries in Louisiana and Alabama. I match beneficiaries based on age, race, eligibility status, and comorbidities. The Elixhauser comorbidity algorithm is used to identify comorbidities based on inpatient and outpatient diagnoses. [124]

2.4.2 Event Study: Age 21

Quasi-experimental research designs that use a different state as a control for identification are not ideal for studying changes in Medicaid spending, especially during the period of the great recession. During the great recession, which lasted from December 2007 to June 2009, Medicaid enrollment increased as state tax revenue declined. Over 30 states made changes to provider payments in 2009 and 2010 to alleviate budget demands. [129] Differential changes in spending between treatment and control states driven by changes in provider rates would nullify the parallel trends assumption need to rationalize a difference in differences design. A research design that focuses on within state variation provides a more reliable estimate

Children and adults aged 18 to 21 are exempt from the prescription drug limit in Louisiana. I exploit the age cut off at age 21 in exemption from the limit along with the policy change to estimate a difference in discontinuity design. The event study design compares beneficiaries just below and just above the age 21 cut off. The identifying assumption is that beneficiaries on either side of the age cut off are similar in covariates other than exemption from the prescription limit and can therefore be compared to approximate a randomized experiment. The estimation is outlined in equation 2.4 below. Event time, l, is defined as the number of months since turning 21. Beneficiary fixed effects, α_i, are included to estimate within-beneficiary changes in utilization around the age 21 cut off. I also

exploit the policy change during the study period, comparing beneficiaries at the age cut off facing different prescription limits. The dummy variable D_{it} is equal to 1 after the policy change and α_t represents calendar time fixed effects.

$$Y_{it} = \alpha_i + \alpha_t + \sum_{t=-6}^{6} [\beta_t * D_{it}] + \varepsilon_{it} \tag{2.4}$$

2.4.3 Event Study: Prescriptions Filled Near the Start of the Month

An event study design is also used to evaluate the likelihood that beneficiaries are waiting until the first of the month to fill prescriptions. The outcome is the count of prescriptions filled per calendar day. The event time, l, is measured as days since the first day of the month. I include the last 10 days of the month and the first 11 days of the month, translating to 10 days prior to and following the event time. I test if the likelihood that Louisiana beneficiaries delay filling their prescription increases when the prescription limit changes from 8 to 5. I compare months before and after the policy change and drop the month of the policy change. The dummy variable D_{it} is equal to 1 in the post period. The study sample used for this analysis is continuously enrolled throughout the study period, therefore there is no need to control for differences in sample composition in the pre and post period. Calendar month fixed effects, α_t, are also included to account for any unrelated time-dependent changes in prescription demand that affect all beneficiaries.

$$Y_t = \alpha_i + \sum_{t=-10}^{10} [\beta_l * D_l] + \varepsilon_t \tag{2.5}$$

2.4.4 Physician Effects

Physicians can influence how the prescription limit impacts utilization among their patients by submitting override requests for prescriptions that exceed the limit. There may be variation across

physicians as well as within physician in the likelihood that they submit an override request. For example, physicians may be more likely to submit override requests for sicker patients or patients with certain conditions. I focus on the role of primary care physicians because they may be more likely to be aware of Medicaid prescribing rules and aware of the patients prescription needs. To test if being treated by different primary care physicians explain differences in prescription utilization among beneficiaries with similar health status and demographics, I regress measures of prescription utilization on a vector of patient characteristics and physician fixed effects.

The estimation for prescription utilization, presented in equation 2.6, follows the model of prescription utilization presented in equation 2.1. Enrollees are index by i and physicians by j. A vector of covariates, K_i, represents patient factors, including elixhauser comorbidities diagnosed in the previous year, disability status, age, and race. Zip code fixed effects, λ_{zip}, are included to account for regional differences in practice patterns and health care access. Physician fixed effects, δ_j, account for differences across physicians in prescribing patterns and likelihood of submitting an override request. Lastly, I include number of total primary care visits, visits, as a measure of the physician patient relationship. Primary care visits are defined as evaluation and management visits with the patients assigned PCP. The outcome Y_{ij} include an annual measures of prescription utilization, including the mean number of prescriptions per enrollee per month in a given year and number of months over the prescription limit per enrollee per year.

$$Y_{ij} = K_i + \lambda_{zip} + visits_i + \delta_j + \varepsilon_{ij} \tag{2.6}$$

For this analysis, I assign each beneficiary a primary care physician (PCP) following attribution methods used for attributing Medicare beneficiaries to ACOs.[93] I first assign PCPs as the provider with whom an enrollee had the plurality of their outpatient evaluation and management visits. For patients without an outpatient evaluation or management visit, I assign PCPs as the provider with a

primary care specialty that they had the most visits with.[e] Because of data limitations, I only include post period data from 2010 and 2011.[f]

2.5 Data

I construct my analytic files from Medicaid MAX claims data for 2007 through 2011 for Louisiana, the treated state, and Alabama, the control state. The data include inpatient, outpatient, long term care and prescription drug claims at the enrollee level. I also observe beneficiary information such as zip code, age, gender, race and monthly eligibility. Active ingredient and therapeutic class for each drug are obtained using RxNorm. [101] I identify beneficiary diagnoses using ICD-9 codes from inpatient and outpatient claims. Chronic physical health conditions are classified using the Elixhauser comorbidity score module. [124] Diagnoses for schizophrenia, bipolar disorder, major depression, and depression using ICD-9 diagnosis codes.

For the primary analysis, nursing home residents, pregnant women, children under the age of 21, and dual eligible beneficiaries also enrolled in Medicare are dropped from the analysis, as they are not subject to drug limits in Louisiana. Because selection would arise if the implementation of a new drug limit had an effect on enrollment and disenrollment decisions, I perform the analysis on the cohort of continuously enrolled Medicaid beneficiaries entering on or before January 2007 and remaining enrolled through December 2011. Excluding new enrollees also avoids identifying changes in utilization driven by changing beneficiary composition due the "Great Recession" rather than changes driven by prescription drug limits. The population that is continuously enrolled in Medicaid is more likely to qualify for Medicaid on the basis of disability and disabled enrollees are sicker and exhibits higher utilization relative to non-disabled beneficiaries. [82] In 2013, non-dual

[e] I follow the Louisiana state Medicaid guidelines for PCP network inclusion to determine PCP specialty types.

[f] The Medicaid MAX data for Louisiana does not include physician identifiers (NPI) for 2007 and 2008.

disabled beneficiaries accounted for 15% of Medicaid enrollment and 35% of Medicaid spending.[131]

For the differences in discontinuity analysis at age 21, I include Louisiana Medicaid beneficiaries aged 20 to 22. I include beneficiaries who were enrolled at least 6 months prior to and 6 months after their 21st birthday to avoid results that are driven by selective disenrollment near the beneficiary's 21st birthday. I only include disabled beneficiaries in this analysis to focus on a population where a prescription limit would be more likely to be binding.

2.5.1 Summary Statistics

The study sample for the differences in differences analysis includes 26,326 beneficiaries from Alabama and 25,613 beneficiaries from Louisiana. Matching is used to select control beneficiaries that are similar to treated beneficiaries on observables, including diagnosis code, race, age and disability status. The majority of beneficiaries, 90% of the study sample, are eligible for Medicaid on the basis of disability. Chronic physical and mental illness are prevalent in the sample. Over half of the sample has been diagnosed with hypertension, 27% have chronic pulmonary disease, 21% are diabetic and 23% have heart disease. Among mental illnesses, 5% of the beneficiaries were diagnosed with depression, 6% were diagnosed with schizophrenia, and 3% with bipolar disorder. Black beneficiaries make up 61% of the sample, which is consistent with the representation of Black people in the overall Louisiana Medicaid population. In 2012, 52% of Louisiana Medicaid beneficiaries were Black. The share of the sample that is female is consistent the female share of the Louisiana Medicaid population, about 60%.

The sample used for the age cut off analysis includes 2,495 Louisiana Medicaid beneficiaries aged 20 to 21 during the study period. Consistent with age-related differences in morbidity, the rate of physical chronic disease was lower in this sample compared to the sample used for the differences-in-differences analysis, with 2% of beneficiaries diagnosed with diabetes and 6% with hypertension. However, the prevalence of mental illness is about the same. The prevalence of schizophrenia, bipo-

Table 2.2: Summary Statistics for Continuously Enrolled Beneficiaries in Louisiana and Alabama

	AL	LA	Total
black	0.61	0.61	0.61
	(0.49)	(0.49)	(0.49)
isfemale	0.59	0.59	0.59
	(0.49)	(0.49)	(0.49)
schizophrenia	0.06	0.06	0.06
	(0.23)	(0.23)	(0.23)
depression	0.05	0.05	0.05
	(0.21)	(0.21)	(0.21)
bipolar disorder	0.03	0.03	0.03
	(0.16)	(0.16)	(0.16)
heart disease	0.23	0.23	0.23
	(0.42)	(0.42)	(0.42)
hypertension	0.52	0.52	0.52
	(0.50)	(0.50)	(0.50)
diabetes	0.21	0.21	0.21
	(0.41)	(0.41)	(0.41)
chronic pulmonary disease	0.27	0.27	0.27
	(0.45)	(0.45)	(0.45)
sum of Elixhauser comorbidities	2.53	2.48	2.50
	(2.23)	(2.18)	(2.20)
N	26,326	25,613	51,936

Table 2.3: Summary Statistics for Beneficiaries near age 21 in Louisiana

	Pre-period	Post-period	Total
black	0.65	0.54	0.59
	(0.48)	(0.50)	(0.49)
hispanic	0.01	0.01	0.01
	(0.10)	(0.09)	(0.10)
white	0.29	0.23	0.26
	(0.46)	(0.42)	(0.44)
female	0.25	0.25	0.25
	(0.43)	(0.43)	(0.43)
schizophrenia	0.05	0.06	0.06
	(0.21)	(0.24)	(0.23)
depression	0.02	0.03	0.03
	(0.15)	(0.18)	(0.17)
bipolar disorder	0.04	0.07	0.06
	(0.20)	(0.26)	(0.24)
hypertension	0.05	0.07	0.06
	(0.23)	(0.26)	(0.25)
diabetes	0.03	0.02	0.02
	(0.16)	(0.14)	(0.15)
Elixhauser sum	0.86	1.05	0.96
	(1.31)	(1.40)	(1.37)
N	1,350	1,145	2,495

lar disorder, and depression were 6%, 3% and 6% respectively.

2.6 Results

2.6.1 Utilization

After Louisiana reduced the number of prescription drugs Medicaid covers for each beneficiary each month, prescription drug utilization decreased for Louisiana beneficiaries relative to Alabama beneficiaries. The event study plot in figure 2.1 plots the number of prescriptions filled per beneficiary per month in control and treatment states. The baseline level for these graphs is the month prior to

the policy change. The solid vertical red line represents when the limit changed from 8 to 5 covered drugs per month and the dashed red line represents the change from 5 to 4. The treated and control trends are overlapping in the pre-period and diverge when the policy changes, which strengthens the validity of the difference-in-differences estimation approach.

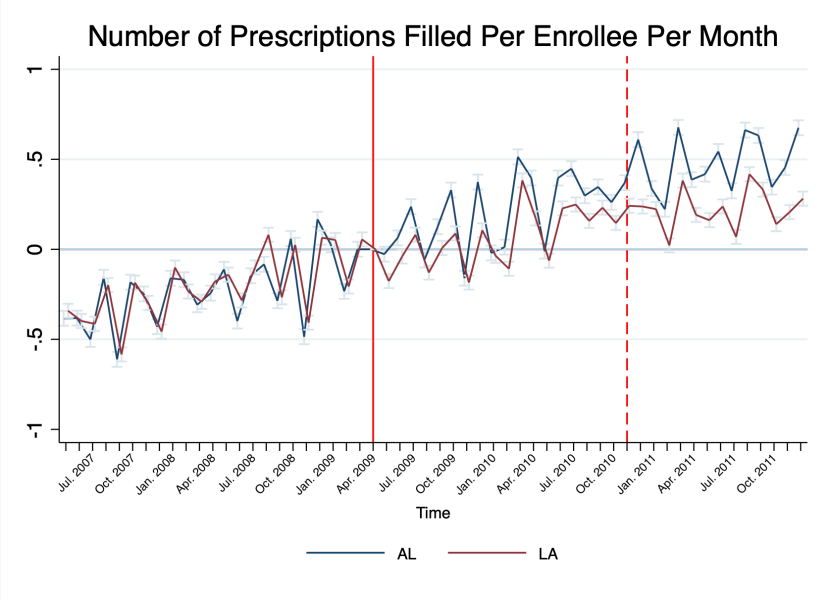
The difference in differences plot in figure 2.1, contains the coefficients from the difference-in-differences estimation in equation 2.3. When the drug cap is reduced from 8 to 5, the number of monthly fills per enrollee decreased for Louisiana enrollees relative to the control state enrollees. The difference between treated and control states expands when the prescription limit in Louisiana is further reduced from 5 to 4.

The results from the pooled difference-in-differences estimation in equation 2.2 in table 2.4. I perform the same analysis for all beneficiaries, then separately for beneficiaries with and without comorbid mental and physical health conditions. The number of prescriptions filled per month decreases by -0.169 in Louisiana, after the policy change, which is about a 5% reduction from the pre-period mean of 3.10. The coefficients from the analysis of enrollees with and without comorbid mental and physical illnesses, -0.174 and -0.167 respectively, are similar. However the baseline utilization is higher for comorbid enrollees, therefore the percent reduction in utilization is lower for comorbid enrollees.

I also perform a differences-in-differences estimate on the likelihood of filling over 5 prescriptions per month per enrollee. I find that the likelihood decreases by about 3% (-0.03) in the total sample. Interestingly, the change in the likelihood of filling over 5 prescriptions per month is the same among comorbid and non-comorbid enrollees, even though the baseline levels are quite different. Following a similar pattern as the results on number of monthly fills, the baseline likelihood of filling over 5 prescriptions per month is almost double among comorbid enrollees at 46.1%, as compared to 20.1% among non-comorbid enrollees.

Next I explore the impact on utilization of chronic disease medications. I test if enrollees filled a

Event Study



Difference in Differences

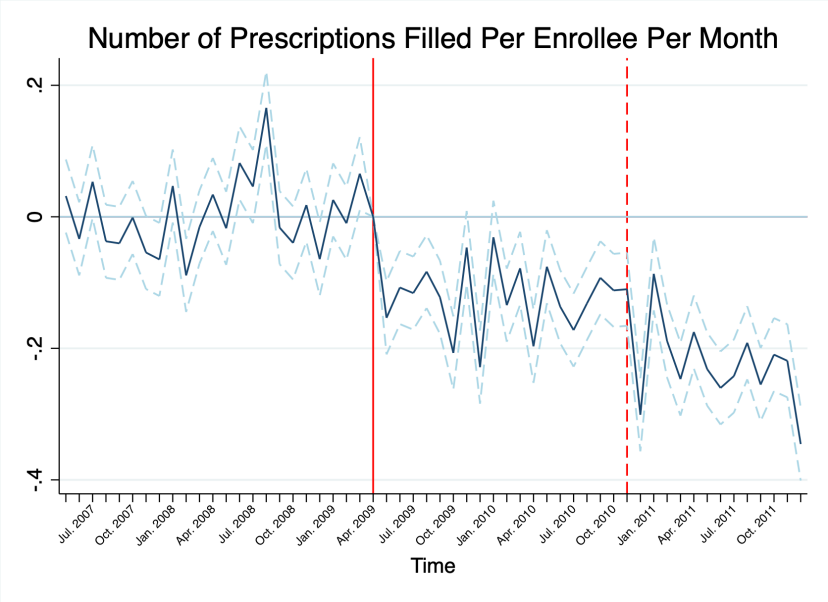


Figure 2.1: Number of Prescriptions Filled per Enrollee per Month

Table 2.4: Difference-in-Differences Results on Monthly Prescription Outcomes

Outcome	Number of prescriptions filled per month			Over 5 prescriptions filled per month		
	all	comorbid	not comorbid	all	comorbid	not comorbid
treated x post	-0.169***	-0.174***	-0.167***	-0.030***	-0.031***	-0.030***
	(0.005)	(0.024)	(0.006)	(0.001)	(0.003)	(0.001)
constant	3.103***	5.817***	2.881***	0.221***	0.461***	0.201***
	(0.002)	(0.009)	(0.002)	(0.000)	(0.001)	(0.000)
observations	2,908,584	263,816	2,655,016	2,908,584	263,816	2,655,016
r-squared	0.71	0.64	0.70	0.56	0.50	0.55

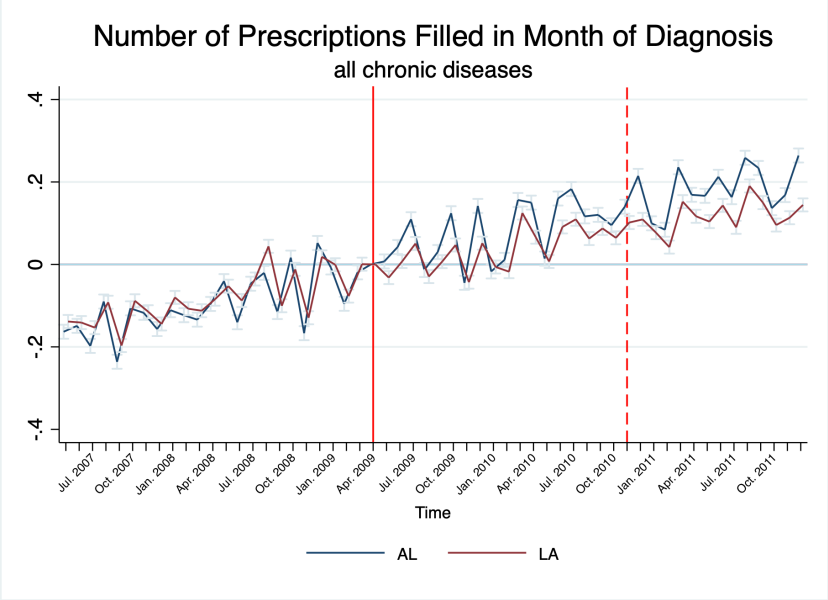
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

chronic disease medication in the same month when they received a diagnosis for that chronic disease. Again, I present an event study plot of the treatment and control groups separately as well as the coefficients from the difference-in-differences estimation in figure 2.2. Again treated and control trends overlap considerably in the pre-period and diverge following the policy change. The divergence is persistent and expanding in the post period. This result suggests that beneficiaries are either reducing utilization or delaying their prescription fills to the next month.

I also performed a pooled differences-in-differences estimation on the total sample and stratified by chronic disease or population. I plot the coefficient of interest, β, for each subsample in figure 2.3. The coefficient for all chronic diseases is -0.129, which implies a 5% reduction from a pre-period mean of 2.36. The result labeled chronic pulmonary disease represents the change in the likelihood of filling a prescription in a drug class treating chronic pulmonary disease in the same month an enrollee received a diagnosis for chronic pulmonary disease. The result labeled 'Black (all chronic)' represents the change in likelihood of filling a prescription for a chronic condition in the same month that a Black enrollee received a diagnosis for that chronic condition.

The effect size varied across different chronic diseases, with the largest effect being for heart disease, measured at -0.111 (though confidence intervals are wide) and hypertension, measured at -

Event Study



Difference in Differences

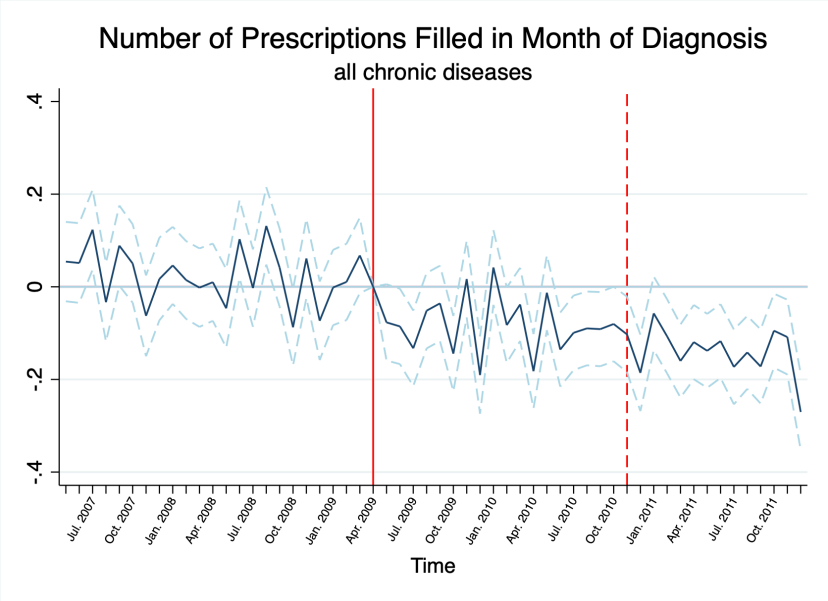


Figure 2.2: Number of Fills within Month of Diagnosis for a Chronic Disease Medication

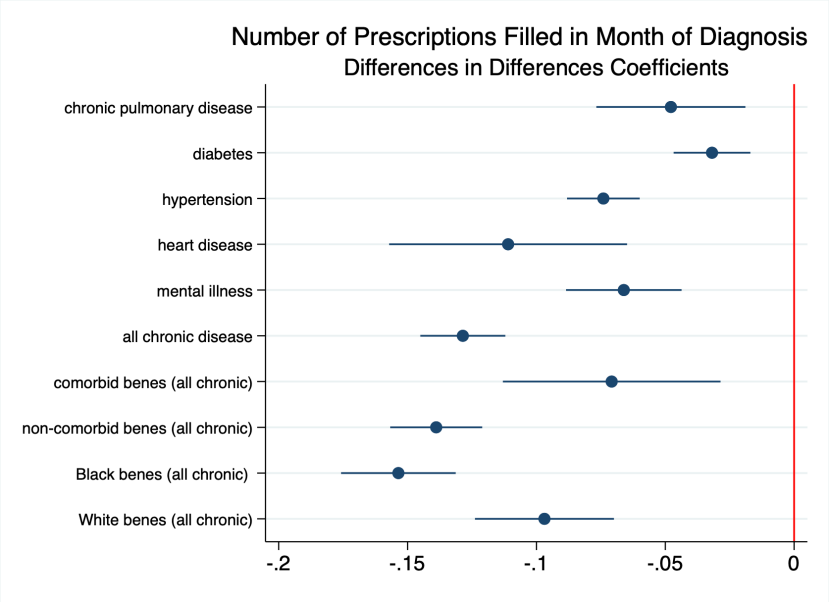


Figure 2.3: The figure plots coefficients from differences in differences estimates. All chronic diseases includes chronic pulmonary disease, diabetes, heart disease, and hypertension.

0.074. Interestingly, the chronic conditions with the smallest effect size, diabetes (-0.0319) and chronic pulmonary disease (-0.0478) exhibit acute symptoms when untreated. Hypertension, on the other hand, often does not present with obvious symptoms. Among beneficiaries, beneficiaries without comorbid mental and physical health conditions exhibited a greater reduction in the likelihood of filling a chronic disease prescription in the same of diagnosis. Black beneficiaries were less likely than White beneficiaries to fill chronic disease medications in the same month they were diagnosed. Differential impact for patients of different races may be driven by differences in patient needs, physicians' propensity to override prescriptions limits, or a combination of both.

The reduction in prescriptions filled within the month may reflect delays in filling prescriptions. To explore this hypothesis I examine the number of prescriptions filled near the first of the month, comparing the pre- and post-period using an event study. Figure 2.4 plots the coefficients from the event study estimation, with a baseline set at 10 days prior to the first of the month. The spike in the

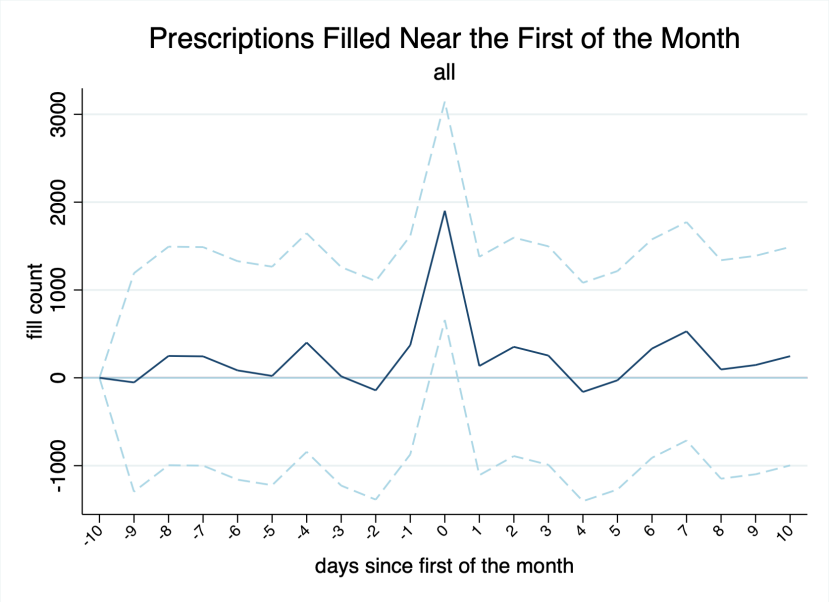


Figure 2.4: Total Prescriptions Filled Per Day Near the First of the Month

number of prescriptions filled on the first of the month in the post period relative to the pre-period suggests that beneficiaries may be delaying filling their prescriptions.

In Figure 2.5, I plot the coefficient on the first of the month from stratified analysis conducted by drug class and across all drugs by beneficiary group. Similar to the results on prescriptions filled within the month of diagnosis, the effect size is larger for heart disease and hypertension and lower for diabetes and chronic pulmonary disease. The effect size is also lower for anti-infective medications that are commonly used to treat acute conditions. Mirroring results from the previous outcome, effect sizes are higher for Black relative to White enrollees and lower for beneficiaries with comorbid mental and physical health conditions relative to those without comorbid conditions.

2.6.2 Spending and Offsets

I exploit the age 21 cut-off in exemption from prescription drug limits to study possible forgone offsets of prescription drug spending. The results from the event study analysis are presented in

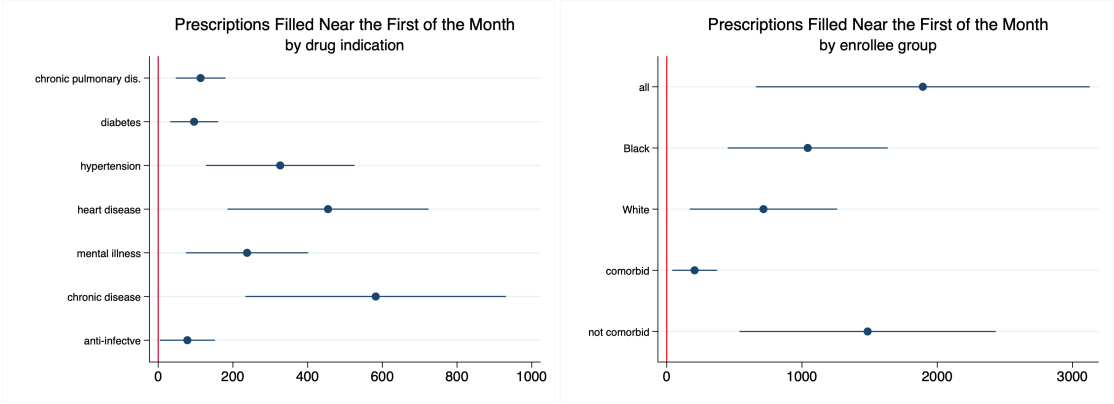


Figure 2.5: Total Prescriptions Filled Per Day Near the First of the Month - Stratified Analysis

figures 2.6 and 2.7. The likelihood of filling over 5 prescriptions after age 21 decreases in the post period, though there is a slight dip in the pre-period trend and the confidence intervals are above zero in the post period. The number of prescriptions filled per month also declines. While the pre-period trend is better for this outcome, the confidence intervals in the post period are above zero. For enrollees near age 21, total monthly spending and total monthly non-drug spending remain unchanged, suggesting the decline in utilization observed did not result in higher total spending or higher non-drug spending.

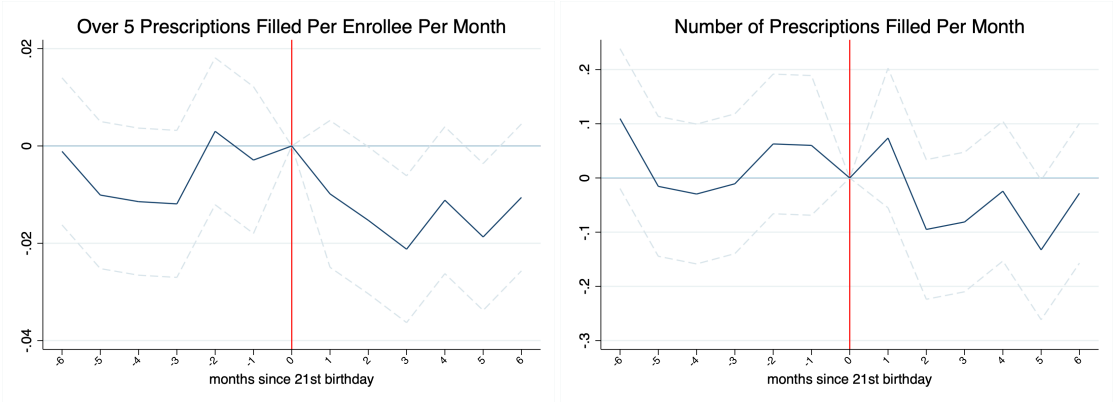


Figure 2.6: Prescriptions Utilization Per Month Near the 21st Birthday

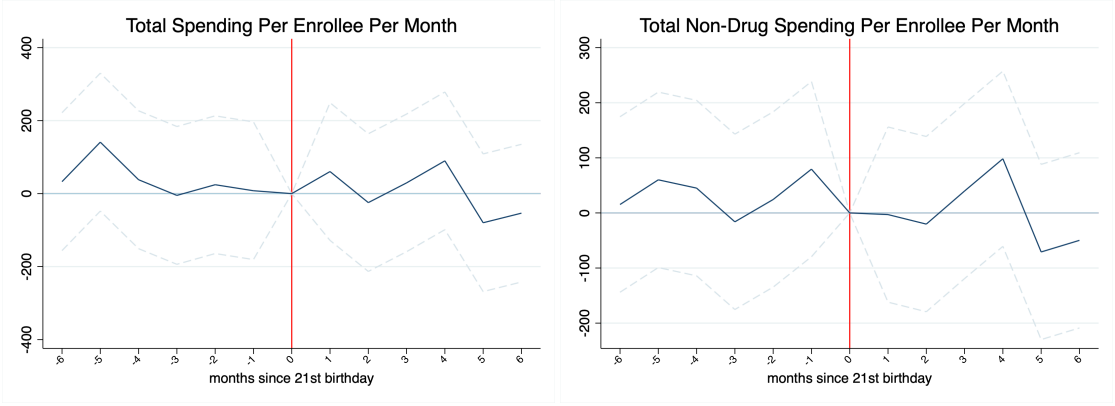


Figure 2.7: Spending Per Month Near the 21st Birthday

2.7 Physician Effects

The results from the estimation of prescription utilization with physician fixed effects is presented in table 2.5. I regress measures of utilization on a vector of enrollee covariates, zip code fixed effects, number of primary care visits in a year and physician fixed effects. The data used for this analysis is at the enrollee-year level and includes only post-period data from 2010 and 2011. Each enrollee is assigned to one PCP and physician fixed effects are applied using the provider identifier (NPI) for their PCP.

The first outcome is number of months per year over the limit. The F-test on the fixed effects show that the physician fixed effects explain a statistically significant level of variation in the regression. After controlling for variation across enrollees in health status, race, gender, age, disability status, zip code, and number of PCP visits, physician fixed effects explain about 32% of the remaining variation, as characterized by ρ in the regression table. In other words, about one-third of the residual difference in how often enrollees exceed the limit that is not accounted for by enrollee covariates in the model, can be explained by differences between physicians.

The second two outcomes are mean and median number of prescriptions filled per month. The

physician fixed effects are statistically significant and explain about 32% and 31% of residual variation in enrollee utilization, respectively. Enrollees with more PCP visits per year exceeded the prescription limit more often and fill more prescriptions per month. More PCP visits might indicate that a enrollee is sicker, has a stronger relationship with their PCP, or a combination of the two.

Table 2.5: Variation in Prescription Drug Utilization Explained by Physician Level Effects

	months over limit	mean fills per month	median fills per month
pcp visits	0.15***	0.14***	0.14***
	0.00	0.00	0.00
constant	0.63	0.95**	0.62
	-0.46	-0.37	-0.39
observations	48,308	48,308	48,308
number of pcp_id	3,177	3,177	3,177
F-stat	2.05	2.42	2.27
p >F	0.00	0.00	0.00
	0.32	0.32	0.31
r-squared within pcp	0.36	0.38	0.37
r-squared overall	0.40	0.42	0.41
r-squared between pcp	0.46	0.49	0.49

standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

2.8 Discussion

Stricter prescription limits in the Louisiana Medicaid program led to a decline in overall monthly prescription utilization. In the first analysis, I compare a cohort of continuously enrolled beneficiaries in the treated state, Louisiana, to a similar cohort of beneficiaries a control state, Alabama. I find considerable overlap in pre-trends of utilization measures indicating that data from Alabama can be used to create a counterfactual trend in utilization for Louisiana beneficiaries. I find that monthly prescriptions declined by about 5% in the post-period. I also find that beneficiaries who are diagnosed with a chronic disease within a given month filled 5% fewer prescriptions indicated to treat

chronic disease. Beneficiaries may be delaying filling their prescriptions to the following month. The number of total prescriptions filled on the first of the month after the policy change increased relative to the pre-period.

There is notable and consistent variation in the effects of the policy change across drug classes. For example, beneficiaries appear more likely to not fill or delay fills for drugs treating hypertension and heart disease, as compared to diabetes drugs, drugs for chronic pulmonary disease and anti-infective drugs. This may be explained by the variation in how acutely patients can experience symptoms after delaying or stopping a particular medication. Still, lack of adherence to drugs that do not treat acute symptoms can have deleterious impacts on patient health. For example, decreased adherence to hypertensive medications can increase stroke risk.

The goal of prescription drug limits appears to be reigning in spending. However, I did not find differential changes in total spending or non-drug spending after beneficiaries turned 21 and were exposed to the prescription limit. This analysis on a young population and cannot be extrapolated to older and therefore potentially sicker populations. Secondly, there may have been changes to Louisiana provider rates that influenced this outcome. I attempted to analyze utilization measures exploiting the age 21 cut-off and the difference and differences estimation with Alabama as the control state. I attempted to analyse the effect on outcomes such as the number of emergency department visits and number of inpatient stays, however these results were noisy and could not be interpreted. Additional analysis is need to understand the effects of prescription limits on spending in older adult populations.

I conduct an analysis of monthly prescription utilization on Louisiana enrollees in the post-period with physician fixed effects to test if residual differences in utilization among similar enrollees is explained by variation between primary care physicians. Enrollees are assigned PCPs following the attribution method used for assigning Medicare beneficiaries to ACOs. I regress utilization measures at the enrollee-year level on physician fixed effects and enrollee covariates including past year

diagnosis, age, gender, race, zip code, and number of PCP visits. I find that physician fixed effects explain about one third of the residual variation in enrollee utilization not explained by enrollee covariates. This result inspires future work exploring how the impact of supply side utilization measures varies across physician.

The results from this paper shed light on the shortcomings of blunt instruments for managing prescription drug costs. Firstly, the policy was intended to save money, but I did not measure an impact on per month per enrollee spending. However, the policy did reduce utilization of high value chronic disease medications, such as drugs treating hypertension, heart disease, and mental health, despite the fact that prescribers may override the limit. Giving prescribers the ability to override the prescription limit does not appear to fully shield beneficiaries from negative risks of a more restrictive prescription drug limit.

The economic recession that occurred due to the covid-19 pandemic increased Medicaid enrollment and strained tax revenue in the United States. The impact to Medicaid programs may be reminiscent of the great recession in 2007 to 2009, which may have inspired the Louisiana policy change. States may consider introducing or tightening prescription limits as a mechanism to control costs. Results from this analysis may provide meaningful insight to lawmakers as they weigh policy options.

3

To Enter or Not to Enter [Yet]?

co-authored with Keith Drake, Robert He and Thomas McGuire

3.1 Introduction

The central issue in regulation of pharmaceutical drug markets is managing the tradeoff between encouraging innovator firms to invest in development of new products and making drugs available

to buyers at competitive prices.[11,58] In the pharmaceutical industry, a combination of patent protection and market exclusivities governed by the Food and Drug Administration (FDA) balance these objectives by intellectual property protection. Patent policy involves statutory exclusivities, requirements to obtain a patent, rules for challenging and defending a patent, and other elements, some of which are unique to the drug industry.[84] Market exclusivities are periods during which the FDA will not accept applications from follow-on competitors for an innovator drug (e.g. generic manufacturers). The Hatch Waxman Act of 1984 changed the incentives for both innovator and generic pharmaceutical firms. For innovator firms, the policy increased incentives to invest in innovation by introducing new exclusivity periods and extending existing exclusivities. For follow-on competitors, the policy created an opportunity for accelerated entry in the case of invalid or uninfringed patents through a special pathway for generic firms to challenge patents. One Hatch Waxman-created mechanism (described below) allows a generic firm to technically "infringe" on a brand firm's patent(s) without actually selling, thereby initiating a patent lawsuit without the generic challenger running the risk of paying damages to the patent holder.

The technical-infringement mechanism created by Hatch Waxman has led to more patent challenges,[53,69] which frequently end with an agreed-upon entry date for the generic in a settlement.[65] If brand and generic litigants don't settle, the generic firm makes a decision about whether to infringe in the conventional way by selling product prior to resolution of the patent litigation. After approval from the FDA, based on criteria unrelated to patent validity, the generic firm can, in the parlance of the drug industry, enter and sell "at risk;" "at risk" because generic sales reduce profits of the patent holder, presenting the generic seller with a risk of paying compensation to the brand if the patent is found valid and infringed.

While the joint decision about settlement has received a great deal of attention in the academic literature, a generic firm's unilateral decision to enter at risk has received much less, in spite of the

potentially massive consequences for social welfare of a generic firm's at-risk entry.[a] The price at which the brand sells a drug typically vastly exceeds the price at which the generic sells a bioequivalent product. [13] For example, at-risk entry accelerating competitive pricing of a single "blockbuster" drug with annual sales of $2 billion by one-year effects a transfer of $1.4 billion or more from brand firms to buyers, with welfare consequences in the short and long term.

This paper sets up a simple model of the generic's decision to enter at risk and compares the model's predictions with data on the frequency of at-risk opportunities and launches from 2005-2020. Our data include information about whether the at-risk launch was found to infringe, and if so, what information we could glean about how much the generic paid in damages to the brand.

Our conceptual model predicts that if a generic has won a district court decision and received final FDA approval, it will launch at risk unless the cost of waiting is very low. Our empirical results support this prediction. Generics always launched at-risk unless they had received final FDA approval close in time to the appeals court decision (indicating the cost of waiting was low) or they had forfeited the exclusivity period (also reducing the cost of waiting). We also find that generics often launch prior to a district court decision if they have received final FDA approval, but this is a more complicated decision that depends on the generic's chance of winning a district court decision and the timing of the FDA approval relative to the district court decision.

Section 3.2 provides background on the relevant regulations of the pharmaceutical industry. In Section 3.3, we present a model of the at-risk generic entry decision. Section 3.4 and describes our data and empirical methods and 3.5 presents our results. Section 3.6 discusses the implications of our findings for policy and social welfare. We argue that a policy combining sufficient compensation for a brand if the generic is found to infringe and an easing of rules for at-risk entry would be in the interest of consumers in not just the short run by lowering prices, but the long run as well as by

[a] The concern is that an agreement about the terms and timing of competition between potential rivals may maximize their joint profits at the expense of consumers. [11,7,40,38,39,37]

directing incentives for research to innovative products.

3.2 Background

3.2.1 Circumstances of At-Risk Entry in the Drug Industry

The Hatch-Waxman Act was intended to balance the competing concerns of exclusivity periods for brand drugs and competition for generic drugs, resulting in lower drug prices, while maintaining pharmaceutical companies' incentives to develop new and better drugs. Hatch-Waxman increased the economic rewards for innovation by giving innovator, or brand name, drug manufacturers longer periods of market exclusivity for newly approved products.[68,62] To expediate entry, Hatch-Waxman also introduced the Abbreviated New Drug Application (ANDA) process, which enabled generic manufacturers to apply for approval based on proof of bioequivalence to an approved brand drug, relying on clinical results from the associated brand drug. The Act also created incentives for generic manufacturers to challenge weak, invalid, or improperly listed patents in order to prevent such patents from blocking competition from lower-priced generics.

A generic drug manufacturer submitting an ANDA to the Food and Drug Administration (FDA) with a "Paragraph IV" certification is asserting that patents purportedly covering the brand drug are invalid, unenforceable, or uninfringed by its product. The generic has 30 days to notify the brand manufacturer of its ANDA filing. The brand then has 45-days from receipt of the notice to sue the generic for patent infringement, initiating a 30-month stay during which the FDA will not approve the generic's drug unless the generic wins the litigation. During the 30-month stay, the generic can receive "tentative approval," which essentially means that, aside from the stay, the generic product has met the FDA's requirements for approval. After the 30-month stay expires, the FDA can approve the generic's product regardless of whether patent litigation is ongoing, which gives the generic the option to launch at risk. However, the brand can petition the court for an in-

junction that prevents the generic from launching during the litigation. [1,88]

Any launch before the conclusion of the patent infringement litigation is "at risk" because it exposes the generic to the risk of paying damages to the brand. The generic could end up paying more in damages than it earned in profits during the at-risk launch because the brand's profits are lost at a high price while the generic's profits are gained at a lower price. Furthermore, a court may require the generic to pay triple damages if the generic is found to have exhibited willful or wanton infringement.[b] The generic can mitigate its risk of paying damages by waiting to launch until after a favorable district court decision, or it can eliminate the risk entirely by waiting until the appeals process is complete or by settling with the brand at any time. [1,88]

However, waiting to launch may result in reduced profits, due to discounting of future revenues and potential unfavorable market developments. For example, the brand market may be getting smaller over time.[c] This is especially likely if the brand attempts to retain sales at a high price by claiming new patents for modifications of the original product, referred to as "line extensions," and works to move patients from the original formulation to the line extension prior to loss of patent protection on the original product. This strategy, also referred to as "product hopping," greatly reduces sales of the generic version of the original formulation. [20,74,76] Waiting to launch also provides other later-filing generics more time to receive FDA approval, which could result in a more competitive generic market after 180-day exclusivities – if applicable - expire.

A generic submitting the first substantially complete ANDA with Paragraph IV certification is referred to as a "first filer." First filers are granted a 180-day exclusivity period during which the FDA will not approve other ANDAs. [2,89] The exclusivity period begins on the first day that the first filer markets the product, meaning that subsequent filers cannot launch until the first filer has

[b] Triple damages, also referred to as "treble damage" award, are imposed at the discretion of the court. For further discussion of triple damages. [107]

[c] Brand drug sales are sometimes described as having a natural "life cycle" described by an inverted U-shaped sales curve. [48]

launched. The exclusivity in this period enables the first filer to charge prices above the competitive equilibrium price that would have resulted if there were multiple entrants. This "prize" encourages applications that challenge weak patents unnecessarily restricting generic entry. Multiple generics can share first-to-file status and the associated right to the exclusivity period if they file on the same day, and any first filer can launch at risk after receiving FDA approval. Additionally, the brand can launch its own "authorized generic" at any time and so can compete with first filers after an at-risk launch, including during the 180-day exclusivity period.[42] Later filing generics cannot launch at risk unless the exclusivity period has expired or been forfeited.[36] For example, the 180-day exclusivity period may be forfeited if the generic manufacturer does not obtain timely approval.

A first filer must receive tentative FDA approval within 30-months of filing its ANDA to retain its right to the 180-day exclusivity period.[2] If the first filer launches at risk, the exclusivity period begins upon launch; however, the 180-day period continues to run if the brand wins an injunction blocking the generic's sales. If the first filer chooses not to launch at risk, it can use its right to the exclusivity period (thus blocking later filers from entering) by either winning the litigation or settling for a licensed entry date, and it forfeits the exclusivity period if it loses the patent infringement litigation.

The brand and generics firms may elect to settle at any point during the litigation process if they reach an agreement that is mutually favorable. The settlement may include a payment from the brand firm to the generic firm and an agreed upon future generic entry date. A settlement may occur at any point during litigation.

3.2.2 Research on At-Risk Entry

At-risk entry is the norm in many industries.[84] Most entrants invent and begin selling products without notifying patent owners of potential infringement. Most new products are not accused of patent infringement, but when litigation does occur, it begins after the products have been sold and

patents have purportedly been infringed. In the pharmaceutical industry, the FDA does not permit entry of generic drugs during exclusivity periods awarded to newly approved brand drugs and strictly regulates entry after they expire. The Paragraph IV certification enables generic manufacturers to begin the required approval process for entry before applicable patents expire. However, unlike other industries, generic entrants in the drug industry must notify the patent owners before they start selling – at the time of application – triggering possible litigation.

Some authors have argued that, in the drug industry, generic companies file patent challenges indiscriminately hoping to obtain favorable settlement terms from the patent owner.[61,62,71] These authors argue that so-called "patent prospecting" undermines incentives to brand firms' to conduct R&D by diluting effective length of protection for intellectual property. Grabowski and colleagues found that Paragraph IV challenges have reduced the effective exclusivity period for brand drug, measured as time from brand drug launch to generic launch.[62,63] Over time, a greater share of brand drugs face a Paragraph IV challenge and the challenges are occurring earlier, meaning the time between a brand drug launching and facing its first challenge has declined.[63]

Other authors argue that patent challenges are targeted and the practice of creating a "patent thicket" offsets reduced exclusivity periods from generic challenges. Hemphill and Sampat found that, although the percentage of drugs facing a challenge has increased over time, the number of patents per drug has also increased, a counter strategy also referred to as "evergreening." Based on their empirical analysis, Hemphill and Sampat conclude that patent challenges usefully target weak and late-expiring patents, not just drugs with large sales.[69] Any prospecting versus evergreening contest appears not to have had much effect on the de facto exclusivity period enjoyed by patent holders.[d]

[d] Grabowski and Kyle (2007) found that effective patent length remained constant or slightly reduced for drugs experiencing generic entry from 1995-2002, despite the fact that they found an increase in the likelihood of a paragraph challenge during that time. During the same period, Hemphill and Sampat (2011) found an increase in the number of patents per drug and the share of drugs with non-active ingredient patents.[69,62]

There are some reports on the frequency of at-risk launches in the drug industry but none, so far as we know, containing recent data. After winning a district court decision on summary judgment, Geneva Pharmaceuticals was the first to launch at-risk in 2002 with its generic version of Augmentin.[91] By 2007, some larger generic companies were launching products even before a district court decision.[103] A 2010 financial analyst report examined the frequency of at-risk launches, finding 28 between 2003 and 2009.[65] A January 2014 legal publication reported that at-risk launches have occurred "at least 26 times" since the Augmentin launch.[91]

In cases where the generic has launched at risk and then lost the patent infringement case, the brand is entitled to damages based on its lost profits.[91] However, determining the magnitude of those lost profits can be complicated from both an economic and legal standpoint. For example, the brand often launches its own "authorized generic" in response to the infringing generic, and the question arises of whether the generic should be held responsible for lost brand sales and price erosion caused by the brand's own authorized generic. The small number of legal trials determining damages, usually taking place after the generic has lost a separate patent infringement trial, have all ended in settlement, so the law on damages "remains vague."[e]

3.3 Conceptual Model

A generic firm can launch at risk only after receiving final approval from the FDA, which could occur at any point during the patent infringement litigation. The phases of litigation can be divided into three periods: (1) before the initial district court decision, (2) after a district court decision, pending an appeals process, and (3) after an appeals court decision. A district court decision can end an injunction or end a 30-month stay, so the generic often (but not always) receives FDA approval soon after a district court decision. If the generic receives FDA approval after a final appeals

[e] As described below, the case that did not end in settlement involved the drug Plavix. But in that case, the brand and generic had previously agreed on how damages would be calculated in a settlement

court decision, a less common outcome, any subsequent generic launch in this case is not at risk because the litigation has ended. If the generic received FDA approval in period (1) or period (2) they have the opportunity to launch at risk, pending a final litigation outcome. Here we characterize the generic's decision to enter at risk for generics that receive final FDA approval during period (1) or period (2). We do not model the entry decision in period (3), as the generic no longer takes on risk by entering and therefore faces a different, simpler entry decision.

A generic manufacturer in patent litigation with a brand and has obtained final FDA approval faces decision of whether to and when to launch at risk as information emerges in discovery and in court decisions, and against the background of ongoing settlement negotiations. To characterize the generic's decision, we begin by considering the strategy of waiting to launch after a favorable appeals court decision and proceeding backwards in time from there.

By waiting to launch after litigation is concluded, the generic no longer takes on risk by entering. A first-filer generic will be entitled to 180 days without competition from other ANDA-based generics and is in a position to make profits roughly in proportion to the size of the brand market at the time of the appeals court decision. The generic's expected profits from launching after an appeals court decision are π_0. However, the generic can only launch if the appeals court rules in favor of the generic. Thus the expected payoff from waiting to enter after appeals is $p\pi_0$, where p represents the probability of a favorable litigation outcome. With this payoff in place, we can go one step back to consider whether a generic would maximize expected profits by waiting until the appeals decision to receive $p\pi_0$.

Next, we consider the payoff from entering at risk, before a final appeals court decision. Let π_g be the profits the generic gains by launching at risk prior to an appeals court decision (after reciving final FDA approval), and π_b be the profits lost by the brand during the generic's at-risk entry. If the patent is found valid and infringed, the generic can expect to pay some share, s, of the brand profits in damages, where s could be less than one or greater than one. The expected damages are $(1-p)s\pi_b$,

where $(1 - p)$ is the likelihood that the generic does not win patent litigation. Note that generic keeps any profits it makes during the at-risk entry even if it must pay some damages to the brand. With this set of considerations, the generic's profit from at-risk entry, recognizing the possibility of paying damages to the brand are:

$$E[\pi_{atrisk}] = \pi_g - (1 - p)s\pi_b \tag{3.1}$$

The generics decision rule will be to launch at risk if expected profits from launching at risk exceed expected profits from waiting to launch after the appeals court decision: $E[\pi_{atrisk}] > E[\pi_{afterappeals}]$.

$$\pi_g - (1 - p)s\pi_b > p\pi_0 \tag{3.2}$$

We expect $\pi_g > \pi_0$ due to discounting of revenue in future periods relative to the current period and potential declines in profitability due to decreased demand for the drug and presence of additional generic entrants over time. We can solve for the threshold probability required to make at-risk entry more profitable than waiting for an appeals court decision.

$$p^* > \frac{(\pi_g(t) - s\pi_b(t))}{(\pi_0(t) - s\pi_b(t))} \tag{3.3}$$

We can use the inequality in equation 3.3 to illustrate how the share of brand profits paid in damages influence the threshold probability for at-risk entry. Let $\pi_g = 1$, $\pi_0 = 0.8$, and $\pi_b = 1.5$. If s, the share of brand profits the generic manufacturer must pay in damages is equal to 133%, the total damages, $s\pi_b$, would amount to about 2. In this case the threshold probability for at-risk entry is 83%, meaning that if the generic firm believes its chance of winning the appeals court decision are 83% or greater, it will enter before the appeals court decision. If s is reduced to 100%, the total damages, $s\pi_b$, would amount to 1.5 and the threshold probability would be 71%. As s increases, the

threshold probability for at-risk entry also increases.

The entry decision is also influenced by the differences in profits gained through at-risk entry, π_g, as compared to entry after appeals, π_0. Again, let $\pi_g = 1$, and $\pi_b = 1.5$, and $s = 100\%$. But, assume the profits from entering after appeals is increased to $\pi_0 = 0.9$. The threshold probability would be 83%, which is greater than the 71% threshold probability when $\pi_0 = 0.8$. As expected, if the difference between profits gained through at-risk entry and entry after the appeals decision is smaller, the threshold probability to justify at-risk entry increases.

The entry model implies that the entry decision may change for a particular drug over time as the parameters in the model evolve. As litigation continues, the generic manufacturer's beliefs about the likelihood of winning the final appeals decision, p, may change. For example, winning at the district court level may be perceived as positive signal, increasing p. If p is higher, the expected profits from entering at risk may be lower as the expected damages are higher. However, there may also be contemporaneous changes in expected generic profitability due to changes in demand for the drug - thus the net effects on expected profits is not obvious. As the generic receives additional information about litigation or expected profits, they would recalibrate the decision model presented in equation 3.2, updating all the parameters of the model, as needed. Then, the same logic applies: if the expected profits from launching at-risk is greater than the expected profits from waiting until after the appeals decision, the generic should enter immediately after final approval.

3.4 Data

We started with a list of drugs with at least one first-to-file ANDA that was approved after January 1, 2005 and were listed in the "180-Day Exclusivity Tracker" on Hyman, Phelps, and McNamara PC's FDA Law Blog website.[77] We compared our list to the FDA's list of Paragraph IV Patent Certifications, updated November 17, 2020, and added additional ANDAs. Finally, we found additional

drugs with approved ANDAs by conducting internet searches for all the drugs in the data sources that were listed as not having an approved ANDA. Thus our list included drugs with at least one first-to-file ANDA approved in 2005 or later.

We consulted the FDA's ANDA approval letters to see if the generic was sued by the brand manufacturer and to find the case identifiers for the litigation (the case number) that would enable us to look up additional case information on legal databases.[51] We also examined Lex Machina data and conducted internet searches to check if litigation had been initiated. For drugs with associated patent infringement litigation, we used Lex Machina data and the Public Access to Court Electronic Records (PACER) to find district and appeals court rulings. We classified a decision as a generic win if every relevant patent were found to be invalid, unenforceable, or uninfringed. If the court found that a valid patent blocked the generic's immediate entry, we classified it as a brand win—thus we classify some split decisions, where the brand wins on some patents but not others, as brand wins. We also checked to see if an injunction had prevented the generic from entering.

We used the generic's press release or another publicly available source to determine when the generic launched its product. We compared the legal decisions to the generic's entry date to determine whether the drug had been launched at risk during the litigation. For cases where the generic launched at risk and then lost the patent infringement litigation, we conducted internet searches to gather information on damages paid from the brand to the generic.

Because we were interested in the generic's decision to launch at risk, we excluded drugs for which the brand had opted not to sue the generic and drugs where the litigation had settled before the generic received FDA approval. We also excluded drugs where the generic lost a district court decision before receiving FDA approval; where the generic did not launch at risk and settled before any legal decisions; the generic received FDA approval after the final appeal; and where an injunction prevented the generic from launching until after the final appeal.

We also gathered data on potential predictors of at-risk launches. Brand manufacturers must sub-

mit all patents that protect their approved drug to the FDA including the patent number, patent expiration date and an indication if the patent is a drug substance, drug product, or method of use patent.[f] As an indicator of patent strength, patent numbers in PACER were used determine whether a substance or product patent was involved in the litigation. We classify substance and product patents based on how they are classified in the Orange Book. We also gathered data on the brand market sales prior to generic entry using internet searches. The FDA approval letters, the FDA's website, and the 180-Day Exclusivity Tracker were used to determine whether the first filer had retained its 180-day exclusivity period. We obtained information on generic firm size and formulation from the FDA Orange Book and Drugs@FDA databases. Drugs are classified as oral solids, injectables, and topicals (including patches and inhalers). To classify manufacturers by firm size, we adopt the classification used in the Generic Drug User Fee program based on the number of approved ANDAs per firm in the year the drug was approved.

3.5 Results

3.5.1 At Risk Entry

Figure 3.1 illustrates our data on at-risk launch opportunities and decisions. Of the 43 drugs that had received FDA approval before a district court decision and were not prevented from entering by an injunction, 26 were launched at risk before a district court decision and 17 were not. Of the 17 drugs that were not launched at risk before a district court decision, two were launched at risk

[f] As defined by the FDA, "drug product is a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. Drug substance is an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient." Brand manufacturers must submit patent number, patent expiration date and indicate if the patent is a drug substance, drug product, or method of use patent. Active ingredient patents have been shown to be more likely than method of use patents to be upheld in court. We use the drug substance and drug product designations as proxies for patent strength. [1,2,69]

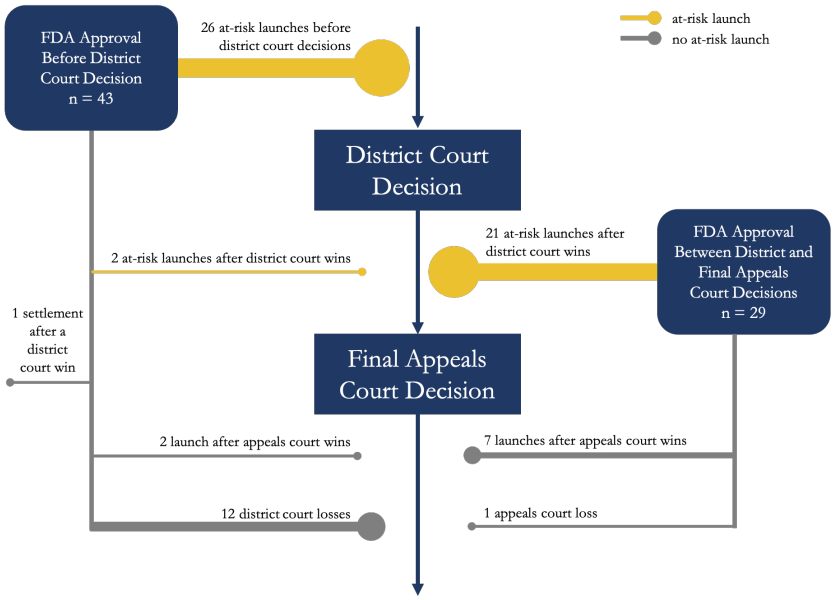


Figure 3.1: At Risk Entry Decisions

after the district court win; the litigation for one drug was settled after the generic's district court win; and no generics were launched at risk after the 14 district court decision losses, which would necessarily be blocked by the court by an injunction.[g] Of the 29 drugs that received FDA approval after a district court decision, 21 were launched at risk before the appeals court decision and 8 were not. Of the drugs that were not launched at risk, 7 launched after a favorable appeals court win and 1 lost in appeals.

We present descriptive results comparing drugs on factors that may have influenced the at-risk entry decision. We test the statistical significance of variation between the groups, using the fisher's exact test due to small sample size. In table 3.1 we present results for drugs that received FDA approval before the district court decision and in table 3.2 for drugs that received FDA approval after the district court decision, but before the appeals court decision.

[g]There were two drugs, Norvasc and Aloxi, for which the generic lost at district court, but won at appeals and launched thereafter.

Table 3.1: Generic Drugs That Received FDA Approval Before a District Court Decision

	Launched Before District Court Decision		
	Yes	No	p-value
Total, n (col %)	26 (100%)	17 (100%)	
Litigation Outcome, n (col %)			
Generic Win	7 (27%)	4 (24%)	0.808
Brand Win	5 (14%)	9 (53%)	
Settled	14 (54%)	4 (24%)	
Patent Type, n (col %)			
Has Drug Substance Patent	2 (8%)	8 (47%)	0.002
Has Drug Product Patent	5 (19%)	13 (76%)	0.0001
Has Drug Substance or Product Patent	5 (19%)	13 (76%)	0.0001
# of Patents Asserted, n (col %)			
1	9 (35%)	9 (53%)	0.244
>1	17 (65%)	8 (47%)	
Drug Sales, n (col %)			
<$50 million	8 (31%)	0 (0.0%)	0.010
50−350 million	8 (31%)	7 (41%)	
>$350 million	10 (38%)	10 (59%)	
Form			
Oral	22 (85%)	14 (82%)	0.849
Topical or Injection	4 (15%)	3 (18%)	
Months between FDA approval and district court decision, n (col %)			
<6	3 (12%)	12 (71%)	0.000
>= 6	8 (88%)	5 (29%)	
Exclusivity Status, n (col %)			
Retained	22 (85%)	12 (71%)	0.280
Forfeited	4 (15%)	5 (29%)	
Generic firm size, n (col %)			
Large (20+ ANDAs)	24 (92%)	17 (100%)	0.252
Medium (6-19 ANDAs)	1(4%)	0 (0%)	
Small (<6 ANDAs)	1(4%)	0 (0%)	

Generics that launched at risk after receiving final FDA approval before the district court decision were more likely to win or settle the patent litigation compared to generics that did not launch at risk. The correlation between launching at risk and losing patent litigation was not statistically significant.[h] Still, the correlation may imply that generic manufacturers can forecast the outcome of the litigation to some degree. Drugs launched at-risk were more likely to have under $50 million in sales and to receive FDA approval more than six months before the date of the district court decision. Drugs that were not launched at risk were more likely to have a drug substance or drug product patent than those that were launched at risk, suggesting that patent strength factors into the decision to launch at risk. The number of patents, however, was not statistically different between those that did or did not launch at risk. Firm size, dosage form, and exclusivity status were about the same across the two groups.

Table 3.2 assesses whether certain measured factors were related to the generic's decision to launch at risk for generics that received FDA approval after the district court decision. The generic's decision about whether to launch at risk was not associated with the outcome of the litigation. The generic almost always won or settled the litigation (28 of the 29 cases), indicating the chance of losing an appeal is low and other factors must be more of an influence the generic's decision.

Generic drugs launched at risk before the appeals court decision were approved closer to the date of the appeals court decision. The experience of Toprol-XL also indicates that the timing of FDA approval is an important factor. Sandoz received FDA approval for the 50mg version just two months before the appeals court decision, and chose not to launch at risk. However, Sandoz received FDA approval of the 25mg version twelve months before the appeals court decision, and Sandoz did launch the 25mg version at risk. If Sandoz had received FDA approval of the 50mg version earlier, Sandoz likely would have launched it at risk. Similarly, five other drugs also received FDA ap-

[h] The test for statistical significance compared wins and settlements to losses.

Table 3.2: Generic Drugs That Received FDA Approval After a District Court Decision

	Launched Before Final Appeals Court Decision		
	Yes	No	p-value
Total, n (col %)	21 (100.0%)	8 (100.0%)	
Litigation Outcome, n (col %)			
Generic Win	13 (62%)	7 (88%)	0.196
Brand Win	0 (0.0%)	1 (13%)	
Settled	6 (29%)	0 (0.0%	
Patent Type, n (col %)			
Has Drug Substance Patent	5 (24%)	4 (50%)	0.185
Has Drug Product Patent	9 (43%)	7 (88%)	0.031
Has Drug Substance or Product Patent	9 (43%)	7 (88%)	0.031
# of Patents Disputed, n (col %)			
1	7 (33.0%)	1 (13%)	0.278
>1	14 (67.0%)	7 (88%)	
Drug Sales, n (col %)			
<$50 million	4 (19%)	1 (13%)	0.690
50−350 million	13 (62 %)	3 (38%)	
>$350 million	4 (19%)	4 (50%)	
Form			
Oral	15 (71%)	7 (88%)	0.384
Topical or Injection	6 (29%)	1 (12%)	
Months between FDA approval and final appeal, n (col %)			
<6	3 (14%)	4 (50%)	0.046
>= 6	18 (86%)	4 (50%)	
Exclusivity Status, n (col %)			
Retained	14 (67%)	3 (38%)	0.165
Forfeited	7 (33%)	5 (62%)	
Generic firm size, n (col %)			
Large (20+ ANDAs)	19 (90%)	7 (88%)	0.822
Medium (6-19 ANDAs)	0 (0%)	0 (0%)	
Small (<6 ANDAs)	2 (10%)	1 (12%)	

proval less than seven months before the appeals court decisions and were not launched at risk.[i] The generic had forfeited its exclusivity period for five of the eight drugs that were not launched at-risk, including for the two drugs that received FDA approval more than ten months before the appeals

[i] These include generic versions Toprol-XL (100mg and 200mg), Actonel, Intermezzo, Quillivant XR, and Vescep

court decision. The generic's decision calculus is different for a generic firm that has forfeited its exclusivity period. While an at-risk launch still brings a risk of large damages, the generic's profit prospects are substantially lowered. Additionally, three of these drugs with forfeited exclusivity periods were not launched for many months after the appeals court decision, suggesting that the legal process was not the force preventing them from launching.[j]

For drugs that received FDA approval after a district court decision, the frequency of the generic launching at risk was 72% (21/29). However, drugs that were not launched at risk were not included in our data if the patent litigation was settled before the appeals court decision was reached, which may produce a censorship bias. If only drugs associated with litigation that reached an appeals court decision are included, the likelihood of the generic launching at risk falls to 59% (13/22).

Similar to drugs approved before the district court decision, the generic was less likely to launch at risk if the drug was protected by a drug substance or drug product patent. The number of patents, drug sales, firm size, and dosage form were not statistically different across the two groups.

3.5.2 Damages Paid by Generic Manufacturers

Finally, we examined the magnitude of damages paid by generics that launched at risk and then lost a court decision. Five of these six cases resulted in a settlement over the damages to be paid either during a separate damages trial or during the appeals process. The paid damages was publicly reported, at least to some degree, in three of the six cases:[k]

[j] In the case of Actonel, Teva was the first filer but forfeited its right to the exclusivity period for failing to obtain timely FDA approval. Three non-first filers received FDA approval two days before Teva and launched their versions at risk. Getting beat to market may have changed Teva's decision about whether to enter at risk.

[k] The amount was not publicly reported after settlements of litigation related to the drugs Amrix, Famvir, and Xopenex. Terms of the Amrix settlement were not disclosed. The Famvir settlement obligated Teva to "make a one-time payment to Novartis in addition to an ongoing royalty on U.S. sales of generic" Famvir. See Teva Pharmaceutical Industries Limited, Form 6-K, February 15, 2010. The Xopenex settlement released Mylan from a $18 million jury damage award, provided a license for Mylan to continue generic sales, and included other confidential details.[8]

1. Apotex launched a generic version of Plavix on August 8, 2006.[17] After antitrust authorities rejected a proposed settlement between Apotex and Sanofi (the brand), Apotex lost district and appeals court decisions regarding the patent's alleged invalidity.[134] The rejected settlement specified that, if the authorities rejected the settlement and Apotex were to lose the litigation, damages would be set to 50% of Apotex's net sales, and the district court accepted Sanofi's summary judgment motion calculating this amount.[118] On October 18, 2011, the appeals court rejected the district court's decision to grant prejudgment interest, but otherwise affirmed its decision. On February 8, 2012, Apotex paid Sanofi $444.4 million in damages, post-judgment interest, and costs.[41]

2. Teva and Sun launched generic versions of Protonix on December 24, 2007 and January 30, 2008, respectively.[23,126] A jury rejected the generics' claims of alleged noninfringement and invalidity of Protonix's active ingredient patent on April 23, 2010 and the district court judge confirmed the jury verdict in a July 15, 2020 opinion. On June 13, 2013, the parties agreed to pay a total of $2.15 billion to settle the litigation.[105] Teva agreed to pay $800 million in 2013 and another $800 by October 2014. Sun agreed to pay $550 million in 2013.

3. Glenmark launched a generic version of Tarka in June 2010. In, 2012, a jury ruled against Glenmark's allegations that the patents were invalid, and awarded $16.0 million in damages. On April 21, 2014, the appeals court affirmed the rulings regarding patent validity and remanded "to the district court for the reserved accounting of any post-verdict damages" – Glenmark did not appeal the damage amount. Glenmark had continued selling the remaining stock of its product for two to three months after filing its appeal, which may have resulted in an additional $9.0 million in damages (and $25 million in total). The parties settled the case on October 7, 2015, agreeing that the Tarka patent was valid and presumably agreeing on the amount of supplemental damages to be paid.[108]

Paid damages are offset, in part, by the profits earned by the generic from the at-risk launch. We estimate the generic's profits using publicly available sources and compare it to the amount of paid damages to arrive at an estimate of a net figure from the generic's point of view. We calculate the net present value of profits and damages as of the date the generic decided to launch at risk. Table 3 indicates that generic profits offset 59% to 100% or much more of the paid damages.

As described in table 3.3, if the generic has won a district court decision, the decision about whether to launch at risk depends on four parameters: the probability of losing a final appeals court decision (p); the generic's profits from waiting to launch until after the final appeals court decision (πo); the generic's profits from launching at risk (πg); and the damages the generic will owe if it launches at risk and then loses the appeal (sπb).

Empirical results above indicate that profits offset most or a large share of damages. The observed probability of the generic winning a final appeals court decision when it had already won a district court decision was 96.4%. These values indicate the generic would launch at risk as soon as possible after a district court win unless the generic's expected profits from waiting to launch until after the appeals court decision were only 2.6% less than its expected profits from launching at risk.

Table 3.3: Damages and Profits of Generics for Cases that the Generic Lost a Court Decision

	Years Between Launch and Paid Damages	Generic Profits ($M)	Paid Damages ($M)	Profits / Damages
Plavix	3.5	3,770	339.4	>100%
Protonix – Teva	5.5-6.8	664.7	1,043.8	63.7%
Protonix – Sun	5.4	316.7	312.1	101.5%
Tarka	5.3	8.4	14.2	59.2%

3.6 Discussion

The Hatch-Waxman act encouraged generic entry by reducing entry costs and creating a incentives for generic manufacturers to challenge weak or invalid patents. The frequency of 'at-risk' entry

suggests that generic manufacturers have a strong incentive to enter the market early and profits attained by at risk entry can be enough to justify the risk of damages. Our conceptual model of the at risk entry decision for generic drugs that receive final FDA approval before conclusion of patent litigation proposes that the key deterrent to at-risk entry is the expected damages owed should litigation not conclude in its favor. We compiled a dataset of 72 drugs that a generic manufacturer with first filer status received final FDA approval before a district court or appeals court decision. Of the 72 generic drugs that had the potential to launch at risk, 49 were launched at risk before the final appeals decision. For drugs that received FDA approval before the district court decision, drugs that were launched at risk were more likely to win or settle, potentially indicating that generic manufacturers may be able to anticipate a favorable litigation outcome. Drugs substance and drug product patents seemed to deter generics from launching at-risk, indicating they may be indicators of the strength of patent protection.

Our conceptual model of generic entry implies multiple policy levers to modify incentives for at-risk entry or increase protections for brand drugs facing patent challenges. The first is s, the share of brand profits lost due to generic entry that are paid in damages. If a patent is found to be valid, s should be set so that the brand firm recoups a high enough share of lost profits to incentivize continued innovation and the generic firm is discouraged from challenging strong patents. However, if the reward is too high - i.e., $s > 1$ - generic manufacturers may not ever enter at risk because the expected profits would not justify entry. Alternatively, policy makers can increase the likelihood of at-risk entry by extending or reducing the 180-day exclusivity period, thereby modifying the expected profits from entry (π_g). Modifying the 180-day exclusivity period has an ambiguous effect on long term generic prices. Essentially, the rate of at-risk entry can be modified by adjusting the carrot or the stick.

The optimal level of at-risk entry would maximize consumer welfare. Consumers have a short-term interest in paying lower prices for drugs, as well as a long-term interest in conveying appropri-

ate incentives to innovator firms to invest in research. Earlier generic entry produces welfare gains driven by considerable cost-savings for insurers, consumers, and government programs. [16,12] The decline in price after generic entry does not generally result in sizeable increases in demand, since many patients are insured and do not pay full price for prescription drugs. [16,74] Notably, in the case of at-risk generic entry where the appellate court eventually rules in favor of the brand drug, consumers still benefit. It is the generic firm, not consumers, at risk for paying damages to the brand. Consumers get to "keep" their lower prices even if the generic is later determined to have infringed a valid patent. Some have argued that Paragraph IV challenges may have also incentivized increased follow on innovation or reformulations. [16] If so, at-risk entry may further increase those incentives. The welfare effects of follow on innovation is debated and may varies by drug. [75,106,57,15]

Some have argued that if brand drugs are less profitable as a result of reduced exclusivity periods, the decreased incentive for innovation could result in less entry of new brand products in the future. [10,63] However, the Paragraph IV challenge and at-risk entry do not reduce patent length indiscriminately across all brand drugs. The Paragraph IV challenge may incentivize innovator firms to invest in patents more likely to be upheld. Evidence of targeting by generic manufacturers suggests that the Paragraph IV process enables scrutiny of patents perceived to be weak. [69] If at-risk entry does occur and courts rule in favor of the brand, the generic manufacturer must pay damages to the brand manufacturer to answer for lost profits. Thus innovation protected by strong patents should either resist early generic entry through a Paragraph IV challenge through favorable litigation outcome or be reimbursed for lost profits should a generic manufacturer enter 'at-risk'. Brand manufacturers could maintain profitability associated with the patent length of its strong patents, depending on the share of forgone profits paid in damages.

Weak patents can also extend effective exclusivity periods for brand drugs. Once notified of a Paragraph IV challenge, if a brand decides to sue the generic entrant for patent infringement, the brand is entitled to a "30-month stay" during which the FDA may not grant final approval to the

generic while patent litigation is on-going, forestalling at risk entry, even if the generic has met all technical requirements for entry to a satisfactory copy of the brand's product. For a brand manufacturer, a winning strategy may be to seek and obtain weak patents to extend nominal exclusivity, as even patents that are unlikely to be found valid or infringed upon judicial review are entitled to a delay in generic competition of 30 months or the duration of patent litigation. Without at-risk entry, weak patents would further delay generic entry until the completion of patent litigation, which could incentivize investment in questionable patents.

At-risk entry can play a constructive role because neither the patent system nor the courts are perfectly efficient. If the United States Patent and Trademark Office (USPTO) were a perfect arbiter of patent applications, a patent would be awarded if and only if it were valid and enforceable, obviating the need for patent litigation based on patent validity. Alternatively, if courts could determine validity instantaneously upon initiation of a patent challenge, there would be no need for at-risk entry. But neither the patent office nor courts can achieve this outcome. The patent office will inevitably grant patents that a court would find invalid, and courts may take years to reach a verdict on patent validity.

The optimal level of at-risk entry requires balancing short-term objectives of cost-saving results from earlier generic entry and long-term objectives of optimal investment into new drugs. Regarding the long-term objectives, a social planner should seek to optimize investment with respect to the quality and the scope of innovation. Drugs that are more innovative should be granted a greater prize, or greater profits. Specifically, letting T be the reward in the form of monopoly profits for an "ironclad" patent, we assume T is set optimally, which is to say, T is the second-best policy optimally balancing the short and long-term objectives. By "ironclad" we mean the patent is certain to be upheld. Drugs that are less innovative, as measured through patent validity and enforceability, should be rewarded at some fraction of T. Invalid patent may receive no reward.

A social planner may also value pharmaceutical investments in research and development that

may not result in strong patents. For example, regulators value clinical trials on pediatric populations for existing drugs that may not produce incremental IP for the brand firm. Such investments efforts can be rewarded though FDA exclusivities that are unaffected by at-risk entry. Newly approved brand drugs are protected through FDA exclusivity periods, during which the FDA will not approve any generic entrant, and a follow-on period of remaining patent protection, during which a Paragraph IV challenge and at-risk entry is possible. Brand drugs that experience at-risk entry still maintain high profitability during FDA exclusivities and the 30-month stay.

References

[1] 21 CFR § 314.107 (2002). Date of approval of a 505(b)(2) application or anda.

[2] 21 CFR § 355 (2002). Section (j)(2)(b) - notice of opinion that patent is invalid or will not be infringed.

[3] Anonymous (2015). Much ado about something; generic drugs - proquest. *The Economist*, 415:57–58.

[4] Antman, E. M., Anbe, D. T., Armstrong, P. W., Bates, E. R., Green, L. A., Hand, M., Hochman, J. S., Krumholz, H. M., Kushner, F. G., Lamas, G. A., et al. (2004). ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the american college of cardiology/american heart association task force on practice guidelines (committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *Journal of the American College of Cardiology*, 44(3):E1–E211.

[5] Ashenfelter, O. C., Hosken, D. S., and Weinberg, M. C. (2013). The price effects of a large merger of manufacturers: A case study of maytag-whirlpool. *American Economic Journal: Economic Policy*, 5:239–261.

[6] Ashenfelter, O. C., Hosken, D. S., and Weinberg, M. C. (2015). Efficiencies brewed: pricing and consolidation in the us beer industry. *The RAND Journal of Economics*, 46:328–361.

[7] Author, C., Ellison, S. F., Cockburn, I., Griliches, Z., Hausman, J., and Cockburn, L. (1997). Characteristics of demand for pharmaceutical products: An examination of four characteristics of demand for pharmaceutical products: an examination of four cephalosporins. *The RAND Journal of Economics*, 28:426–446.

[8] author listed, N. (2012). Mylan announces settlement agreement in litigation relating to its generic xopenex. *PR newswire*.

[9] Baicker, K., Chernew, M. E., and Robbins, J. A. (2013). The spillover effects of Medicare managed care: Medicare Advantage and hospital utilization. *Journal of Health Economics*, 32:1289–1300.

[10] Berndt, E., Conti, R., and Murphy, S. (2017). The landscape of us generic prescription drug markets, 2004-2016. *National Bureau of Economic Research Working Paper Series*.

[11] Berndt, E. R. (2002). Pharmaceuticals in u.s. health care: Determinants of quantity and price. *The Journal of Economic Perspectives*, 16:45–66.

[12] Berndt, E. R., Mortimer, R., Bhattacharjya, A., Parece, A., and Tuttle, E. (2007). Authorized generic drugs, price competition, and consumers' welfare. *Health Affairs*, 26:790–799.

[13] Berndt, E. R. and Newhouse, J. P. (2012). Pricing and reimbursement in us pharmaceutical markets. In Danzon, P. M. and Nicholson, S., editors, *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*. Oxford University Press.

[14] Blackwell, M., Iacus, S., King, G., and Porro, G. (2009). cem: Coarsened exact matching in stata. *The Stata Journal*, 9:524–546.

[15] Bokhari, F. A. and Fournier, G. M. (2013). Entry in the ADHD drugs market: Welfare impact of generics and me-too's. *Journal of Industrial Economics*, 61(2):339–392.

[16] Branstetter, L., Chatterjee, C., Higgins, M. J., Braguinsky, S., Cockburn, I., Gaynor, M., Greenstreet, D., Hamilton, B., Taylor, L., Thursby, J., Train, K., Stern, S., Harhoff, D., Haeussler, C., Aitken, M., Kubo, K., Kumar, V., Ni, J., and Weber, E. (2016). Regulation and welfare: evidence from paragraph iv generic entry in the pharmaceutical industry. *The RAND Journal of Economics*, 47:857–890.

[17] Carreyrou, J. (2006). Apotex launches generic plavix, pressuring bristol-myers, sanofi. *The Wall Street journal. Eastern edition*.

[18] Centers for Medicare and Medicaid Services (2021). Nadac (national average drug acquisition cost) | data.medicaid.gov. Available at https://data.medicaid.gov/Drug-Pricing-and-Payment/NADAC-National-Average-Drug-Acquisition-Cost-/a4y5-998d.

[19] Chandra, A., Gruber, J., and Mcknight, R. (2010). American economic association patient cost-sharing and hospitalization offsets in the elderly. *The American Economic Review*, 100:193–213.

[20] Cheng, J. (2008). An antitrust analysis of product hopping in the pharmaceutical industry. *Columbia Law Review*, 108:1471–1515.

[21] Chernew, M. E., Juster, I. A., Shah, M., Wegh, A., Rosenberg, S., Rosen, A. B., Sokol, M. C., Yu-Isenberg, K., and Fendrick, A. M. (2010). Evidence that value-based insurance can be effective. *Health Affairs*, 29:530–536.

[22] Coate, M. B. and Heimert, A. J. (2009). Merger efficiencies at the federal trade commission 1997–2007.

[23] Cohen, T. (2007). Teva launches generic Protonix, ups '07 EPS forecast | Reuters. Reuters.

[24] Commission, F. T. (2016). Teva/allergen divestiture products. Available at https://www.ftc.gov/system/files/documents/cases/160915teva-allergan-table.pdf.

[25] Conti, R. M. and Berndt, E. R. (2020). Four facts concerning competition in us generic prescription drug markets. *International Journal of the Economics of Business*, 27:27–48.

[26] Conti, R. M., Nguyen, K. H., and Rosenthal, M. B. (2018). Generic prescription drug price increases: which products will be affected by proposed anti-gouging legislation? *Journal of pharmaceutical policy and practice*, 11:29.

[27] Coronado, J., Jiménez-Martín, S., and Marín, P. L. (2014). An empirical analysis of the multimarket contact theory in pharmaceutical markets. *European Journal of Health Economics*, 15:623–643.

[28] Cutler, D., Deaton, A., and Lleras-Muney, A. (2006). The determinants of mortality. *Journal of Economic Perspectives*, 20:97–120.

[29] Dafny, L., Duggan, M., and Ramanarayanan, S. (2012). Paying a premium on your premium? consolidation in the us health insurance industry. *American Economic Review*, 102:1161–1185.

[30] Dafny, L., Ho, K., and Lee, R. S. (2019). The price effects of cross-market mergers: theory and evidence from the hospital industry. *The RAND Journal of Economics*, 50:286–325.

[31] Dave, C. V., Kesselheim, A. S., Fox, E. R., Qiu, P., and Hartzema, A. (2017). High generic drug prices and market competition: A retrospective cohort study. *Annals of Internal Medicine*, 167:145–151.

[32] Davidson, C. and Mukherjee, A. (2007). Horizontal mergers with free entry. *International Journal of Industrial Organization*, 25:157–172.

[33] Donohue, J. (2006). Mental health in the medicare part d drug benefit: A new regulatory model? *Health Affairs*, 25:707–719.

[34] Douglas, B. (1990). Multimarket contact and collusive behavior.

[35] Dow Jones Institutional News (2015). Hikma pharmaceuticals plc acquisition - Proquest.

[36] Drake, K. M. and McGuire, T. G. (2020). Generic entry before the agreed-upon date in pharmaceutical patent settlements. *Journal of Competition Law and Economics*, 16:188–219.

[37] Drake, K. M., Starr, M. A., and McGuire, T. G. (2015). Do "reverse payment" settlements constitute an anticompetitive pay-for-delay? *International Journal of the Economics of Business*, 22:173–200.

[38] Edlin, A., Hemphill, S., Hovenkamp, H., and Shapiro, C. (2013). Activating actavis. *Antitrust*, 28.

[39] Edlin, A., Hemphill, S., Hovenkamp, H., and Shapiro, C. (2015). The actavis inference: Theory and practice. *Rutgers University Law Review*, 67:586–636.

[40] Elhauge, E. and Krueger, A. (2012). Solving the patent settlement puzzle. *Texas Law Review*, 91:283–330.

[41] Faigen, N. (2010). US judge orders Apotex to pay Sanofi $442 million damages in Plavix case. *Scrip*, page 25.

[42] Farrell, J., Balan, D., Brand, K., and Wendling, B. (2011). Economics at the FTC: Hospital mergers, authorized generic drugs, and consumer credit markets. Available at https://www.ftc.gov/reports/economics-ftc-hospital-mergers-authorized-generic-drugs-consumer-credit-markets.

[43] Farrell, J., Pautler, P. A., and Vita, M. G. (2009). Economics at the ftc: Retrospective merger analysis with a focus on hospitals. *Review of Industrial Organization*, 35:369–385.

[44] Farrell, J. and Shapiro, C. (2010). Recapture, pass-through, and market definition. *Antitrust Law Journal*, 76:585–604.

[45] Federal Trade Commission (2018). Amneal impax complaint. Available at https://www.ftc.gov/system/files/documents/cases/1810017_amneal_impax_complaint_final_0.pdf.

[46] Fein, A. J. (2011). 2011-12 economic report on pharmaceutical wholesalers and specialty distributors.

[47] Firozi, P. (2018). The health 202: Here's why rural independent pharmacies are closing their doors. *The Washington Post*.

[48] Fischer, M., Leeflang, P. S., and Verhoef, P. C. (2010). Drivers of peak sales for pharmaceutical brands. *Quantitative Marketing and Economics*, 8:429–460.

[49] Food and Drug Administration (2019). Generic competition and drug prices | FDA. Available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/generic-competition-and-drug-prices.

[50] Food and Drug Administration (2020). Frequently asked questions on patents and exclusivity | FDA. Available at https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity.

[51] Food and Drug Administration (2021a). About drugs@fda. Available at https://www.fda.gov/drugs/drug-approvals-and-databases/about-drugsfda.

[52] Food and Drug Administration (2021b). Approved drug products with therapeutic equivalence evaluations (orange book) | FDA. Available at https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book.

[53] Frank, R. G. (2007). The ongoing regulation of generic drugs. *New England Journal of Medicine*, 357:1993–1996. doi: 10.1056/NEJMp078193.

[54] Frank, R. G. and Salkever, D. S. (1996). Generic entry and the pricing of pharmaceuticals. *Journal of Economics & Management Strategy,*, 6:75–90.

[55] Gagnon, M.-A. and Volesky, K. D. (2017). Merger mania: mergers and acquisitions in the generic drug sector from 1995 to 2016. *Globalization and Health*, 13:62.

[56] Gifford, K., Winter, A., Wiant, L., Dolan, R., Tian, M., and Kff, R. G. (2020). How state medicaid programs are managing prescription drug costs: Results from a state medicaid pharmacy survey for state fiscal years 2019 and 2020. Available at https://www.kff.org/medicaid/report/how-state-medicaid-programs-are-managing-prescription-drug-costs-results-from-a-state-medicaid-pharmacy-survey-for-state-fiscal-years-2019-and-2020/.

[57] Gogtay, J. A. and Malhotra, G. (2013). Reformulation of existing antiretroviral drugs. *Current Opinion in HIV and AIDS*, 8(6):550–555.

[58] Goldman, D. and Lakdawalla, D. (2011). Chapter thirteen - intellectual property, information technology, biomedical research, and marketing of patented products. In Pauly, M. V., Mcguire, T. G., and Barros, P. P., editors, *Handbook of Health Economics*, volume 2, pages 825–872. Elsevier.

[59] Goodell, S., Druss, B. G., and Walker, E. R. (2011). Mental disorders and medical comorbidity. Robert Wood Johnson Foundation. Available at https://www.rwjf.org/en/library/research/2011/02/mental-disorders-and-medical-comorbidity.html.

[60] Goodman-Bacon, A. (2020). Difference-in-differences with variation in treatment timing *.

[61] Grabowski, H. (2004). Are the economics of pharmaceutical research and development changing? productivity, patents and political pressures. *PharmacoEconomics*, 22:15–24.

[62] Grabowski, H. G. and Kyle, M. (2007). Generic competition and market exclusivity periods in pharmaceuticals. *Managerial and Decision Economics*, 28:491–502.

[63] Grabowski, H. G., Kyle, M., Mortimer, R., Long, G., and Kirson, N. (2011). Evolving brand-name and generic drug competition may warrant a revision of the hatch-waxman act. *Health Affairs*, 30:2157–2165.

[64] Grabowski, H. G. and Vernon, J. M. (1992). Brand loyalty, entry, and price competition in pharmaceuticals after the 1984 drug act. *Journal of Law & Economics*, 35.

[65] Greene, A. and Steadman, D. D. (2010). Analyzing litigation success rates. *Pharmaceuticals*, 212:1–24.

[66] Hartman, M., Martin, A. B., Benson, J., and Catlin, A. (2020). National health care spending in 2018: Growth driven by accelerations in medicare and private insurance spending. *Health Affairs*, 39:8–17.

[67] Hartung, D. M., Carlson, M. J., Kraemer, D. F., Haxby, D. G., Ketchum, K. L., and Greenlick, M. R. (2008). Impact of a medicaid copayment policy on prescription drug and health services utilization in a fee-for-service medicaid population.

[68] Hemphill, C. S. and Lemley, M. A. (2010). Earning exclusivity: generic drug incentives and the hatch-waxman act. *Antitrust LJ*, 77:947.

[69] Hemphill, C. S. and Sampat, B. N. (2011). When do generics challenge drug patents? *Journal of Empirical Legal Studies*, 8:613–649.

[70] Hernandez, I., Sampathkumar, S., Good, C. B., Kesselheim, A. S., and Shrank, W. H. (2019). Changes in drug pricing after drug shortages in the united states. *Annals of Internal Medicine*, 170:74.

[71] Higgins, M. J. and Graham, S. J. (2009). Balancing innovation and access: patent challenges tip the scales. *Science*, 326(5951):370–371.

[72] Hirschfeld, R., Bowden, C. L., Gitlin, M. J., Keck, P. E., Suppes, T., Thase, M. E., and Perlis, R. H. (2002). *Practice guideline for the treatment of patients with bipolar disorder*. American Psychiatric Association.

[73] Hosken, D. S., Olson, L. M., and Smith, L. K. (2018). Do retail mergers affect competition? evidence from grocery retailing. *Journal of Economics & Management Strategy*, 27:3–22.

[74] Huckfeldt, P. and Knittel, C. (2011). Pharmaceutical use following generic entry: Paying less and buying less. *NBER Working Paper Series*.

[75] Huskamp, H. A., Busch, A. B., Domino, M. E., and Normand, S. L. T. (2009). Antidepressant reformulations: Who uses them, and what are the benefits? *Health Affairs*, 28:734–745.

[76] Huskamp, H. A., Donohue, J. M., Koss, C., Berndt, E. R., and Frank, R. G. (2008). Generic entry, reformulations and promotion of ssris in the us. *Pharmacoeconomics*, 26(7):603–616.

[77] Hyman, Phelps & McNamara, P.C. (2021). Fda law blog. Available at https://www.fdalawblog.net/.

[78] IQVIA Institute (2020). Medicine spending and affordability in the united states. Technical report, IQVIA Institute for Human Data Science.

[79] James, P. A., Oparil, S., Carter, B. L., Cushman, W. C., Dennison-Himmelfarb, C., Handler, J., Lackland, D. T., LeFevre, M. L., MacKenzie, T. D., Ogedegbe, O., Smith, S. C., Svetkey, L. P., Taler, S. J., Townsend, R. R., Wright, J. T., Narva, A. S., and Ortiz, E. (2014). 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eighth joint national committee (jnc 8). *JAMA - Journal of the American Medical Association*, 311:507–520.

[80] Kaiser Family Foundation (2005). Follow the pill: Understanding the U.S. commercial pharmaceutical supply chain.

[81] Koch, T. and Ulrick, S. W. (2020). Price effects of a merger: Evidence from a physicians' market. *Economic Inquiry*, page ecin.12954.

[82] Ku, L. and Steinmetz, E. (2013). The continuity of medicaid coverage: An update.

[83] Landon, B. E., Zaslavsky, A. M., Saunders, R. C., Pawlson, L. G., Newhouse, J. P., and Ayanian, J. Z. (2012). Analysis of medicare advantage HMOs compared with traditional Medicare shows lower use of many services during 2003–09. *Health Affairs*, 31:2609–2617.

[84] Lemley, M. A. (2008). Ignoring patents what ifs and other alternative intellectual property and cyberlaw stories. *Michigan State Law Review*, 2008:19–34.

[85] Levy, J., Rosenberg, M., and Vanness, D. (2015). Us based drug cost parameter estimates using national average drug acquisition cost. *Value in Health*, 18:A7.

[86] Lichtenberg, F. R. (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*, 11:403–416.

[87] Lieberman, D. A., Polinski, J. M., Choudhry, N. K., Avorn, J., and Fischer, M. A. (2015). Medicaid prescription limits: policy trends and comparative impact on utilization. *BMC health services research*, 16(1):1–11.

[88] Lietzan, E. and Post, J. (2016). The law of 180–day exclusivity. *Food and Drug Law Journal*, 71:327–400.

[89] Lietzan, E. K. (2004). A brief history of 180-day exclusivity under the hatch-wasman amendments to the federal food, drug, and cosmetic act. *Food and Drug Law Journal*, 59:287–324.

[90] Lu, C. Y., Soumerai, S. B., Ross-Degnan, D., and Adams, A. S. (2010). Unintended impacts of a medicaid prior authorization policy on access to medications for bipolar illness. *Medical Care*, 48:4–9.

[91] Manspeizer, D. (2014). The law on damages in generic drug launches remains vague. *Mondaq business briefing*.

[92] Marino, A. M., Zábojník, J., Marinot, A. M., and Zabojnikt, J. (2006). Merger, ease of entry and entry deterrence in a dynamic model. *The Journal of Industrial Economics*, 54:397–423.

[93] Mccoy, R. G., Bunkers, K. S., Ramar, P., Meier, S. K., Benetti, L. L., Nesse, R. E., and Naessens, J. M. (2018). Patient attribution: Why the method matters hhs public access. *Am J Manag Care*, 24:596–603.

[94] McGuire, T. G. (2011). Demand for health insurance. In *Handbook of health economics*, volume 2, pages 317–396. Elsevier.

[95] Medicaid and CHIP Payment and Access Comission (MACPAC) (2018a). Medicaid payment for outpatient prescription drugs. Available at https://www.macpac.gov/wp-content/uploads/2015/09/Medicaid-Payment-for-Outpatient-Prescription-Drugs.pdf.

[96] Medicaid and CHIP Payment and Access Comission (MACPAC) (2018b). Medicaid's share of state budgets. Available at https://www.macpac.gov/subtopic/medicaids-share-of-state-budgets/.

[97] Medicaid and CHIP Payment and Access Comission (MACPAC) (2019). Medicaid drug spending trends.

[98] Meier, M. H., Deputy, B. S. A., Director, A., and Monahan, K. (2018). Overview of ftc actions in pharmaceutical products and distribution* health care division bureau of competition federal trade commission washington d.c. 20580.

[99] Minority Staff of the U.S. Senate (2018). A tangled web. Available at https://www.finance.senate.gov/imo/media/doc/A Tangled Web.pdf.

[100] Morton, F. S. (1999). Entry decisions in the generic pharmaceutical industry. *The Rand Journal of Economics*, 30:421.

[101] Nelson, S. J., Zeng, K., Kilbourne, J., Powell, T., and Moore, R. (2011). Normalized names for clinical drugs: Rxnorm at 6 years. *Journal of the American Medical Informatics Association*, 18(4):441–448.

[102] Office, U. G. A. (2016). Generic drugs under medicare: Part d generic drug prices declined overall, but some had extraordinary price increases.

[103] O'malley, J. M., Wexler, B. M., Dittmann, E. W., and Ashkenazi, I. S. (2011). Focus on pharma 30 intellectual property magazine failure to launch. *Intellectual Property Magazine*.

[104] Pachman, E., Link, B., and Ciaccia, A. (2020). Responsiveness of maximum allowable cost (mac) to generic drug inflation.

[105] Pearson, S., Decker, S., and Voreacos, D. (2010). Pfizer reaches $2.15 billion protonix accord with teva. *Bloomberg. com*.

[106] Powell, D. and Pacula, R. L. (2021). The evolving consequences of oxycontin reformulation on drug overdoses. *American Journal of Health Economics*, 7(1):41–67.

[107] Powers, M. D. and Carlson, S. C. (2001). The evolution and impact of the doctrine of willfull patent infringement. *Syracuse Law Rev.*, 51:53.

[108] Practical Law Intellectual Property & Technology (2011). $16 Million Damages Award Against At Risk Generic Affirmed: Federal Circuit. Thomson Reuters Practical Law. Available at https://uk.practicallaw.thomsonreuters.com/5-565-7726?transitionType=Default&contextData=(sc.Default)&firstPage=true.

[109] Reeves, A. (2015). Endo vaults into top 5 among generic-drug firms acquiring par for $8.05 bil - proquest. *Investor's Business Daily*.

[110] Regan, T. L. (2008). Generic entry, price competition, and market segmentation in the prescription drug market. *International Journal of Industrial Organization*, 26:930–948.

[111] Reiffen, D. and Ward, M. R. (2005). Generic drug industry dynamics.

[112] Rockoff, J. D. and Mattioli, D. (2015). Teva offers to buy mylan for $40 billion. *The Wall Street Journal*.

[113] Rosenbaum, L. (2020). Coalition of attorneys general file third lawsuit against generic drug 'price-fixing'. *Forbes*.

[114] Sacks, C. A., Wiele, V. L. V. D., Fulchino, L. A., Patel, L., Kesselheim, A. S., and Sarpatwari, A. (2020). Assessment of variation in state regulation of generic drug and interchangeable biologic substitutions. *JAMA Internal Medicine*.

[115] Salako, A., Ullrich, F., and Mueller, K. J. (2018). Update: Independently owned pharmacy closures in rural america, 2003-2018 purpose key findings.

[116] Schmitt, M. (2018). Multimarket contact in the hospital industry. *American Economic Journal: Economic Policy*, 10:361–387.

[117] Shapiro, C. (2003). Antitrust analysis of patent settlements between rivals comments and replies. *Antitrust*, 17:70–77.

[118] Shuchman, M. (2006). Delaying generic competition—corporate payoffs and the future of plavix. *New England Journal of Medicine*, 355(13):1297–1300.

[119] Simpson, J. and Taylor, C. (2008). Do gasoline mergers affect consumer prices? the marathon ashland petroleum and ultramar diamond shamrock transaction. *The Journal of Law & Economics*, 51:135–152.

[120] Somayaji, C. and Wainer, D. (2015). Teva snaps up allergan's generics arm, dumping mylan - bloomberg. *Bloomberg*.

[121] Sood, N., Shih, T., Nuys, K. V., and Goldman, D. (2017). The flow of money through the pharmaceutical distribution system.

[122] Soumerai, S. B., McLaughlin, T. J., Ross-Degnan, D., Casteris, C. S., and Bollini, P. (1994). Effects of limiting medicaid drug-reimbursement benefits on the use of psychotropic agents and acute mental health services by patients with schizophrenia. *New England Journal of Medicine*, 331(10):650–655.

[123] Soumerai, S. B., Ross-Degnan, D., Avorn, J., McLaughlin, T. J., and Choodnovskiy, I. (1991). Effects of medicaid drug-payment limits on admission to hospitals and nursing homes. *New England Journal of Medicine*, 325:1072–1077.

[124] Stagg, V. (2015). ELIXHAUSER: Stata module to calculate Elixhauser index of comorbidity. Statistical Software Components, Boston College Department of Economics.

[125] Stahl, S. M., Morrissette, D. A., Citrome, L., Saklad, S. R., Cummings, M. A., Meyer, J. M., O'Day, J. A., Dardashti, L. J., and Warburton, K. D. (2013). Meta-guidelines" for the management of patients with schizophrenia. *CNS Spectr*, 18(3):150–162.

[126] Stanton, T. (2012). Wyeth puts $960M squeeze on Sun for Protonix launch | FiercePharma. Fierce Pharma.

[127] Sun, L. and Abraham, S. (2020). Estimating dynamic treatment effects in event studies with heterogeneous treatment effects.

[128] Tenn, S. and Wendling, B. W. (2014). Entry threats and pricing in the generic drug industry. *The Review of Economics and Statistics*, 96:214–228.

[129] The Kaiser Family Foundation (2009). The crunch continues: Medicaid spending, coverage and policy in the midst of a recession.

[130] The Kaiser Family Foundation (2012). The role of medicaid for adults with chronic illnesses.

[131] The Kaiser Family Foundation (2021). State health facts. Available at https://www.kff.org/statedata/.

[132] The Lancet Oncology (2015). Generic drug market: growing and merging. *The Lancet Oncology*, 16:595.

[133] Trujillo, A. J., Garcia-Morales, E. E., Kabarriti, G., and Anderson, G. (2019). Do mergers and acquisitions improve firms' financial performance? the case of the u.s. generic drug industry funding information. *Managerial and Decision Economics*, 41:10–24.

[134] United States Court of Appeals for the Federal Circuit (2008). SANOFI-SYNTHELABO V APOTEX. case number 2007-1438.

[135] U.S. Department of Justice and The Federal Trade Commission (2010). Horizontal merger guidelines. Available at https://www.justice.gov/atr/horizontal-merger-guidelines-08192010.

[136] Vivian, J. C. (2008). Generic-substitution laws. *US Pharmacist*, 33:30–34.

[137] Walker, E. R., McGee, R. E., and Druss, B. G. (2015). Mortality in mental disorders and global disease burden implications a systematic review and meta-analysis. *JAMA Psychiatry*, 72:334–341.

[138] Witters, D. (2020). In u.s., 66% report increase in cost of prescription drugs.

[139] World Health Organization (1993). The icd-10 classification of mental and behavioural disorders.

[140] Yu, Y. and Gupta, S. (2014). Pioneering advantage in generic drug competition. *International Journal of Pharmaceutical and Healthcare Marketing*, 8:126–150.