**Distribution Agreement**

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Xin Yan Date

Order of Entry Effect and Effects of Drug Relabeling in the Pharmaceutical Industry

By

Xin Yan
Doctor of Philosophy

Economics

_____

Maria Arbatskaya, Ph.D.
Advisor

_____

Matthew Higgins, Ph.D.
Advisor

_____

Christina DePasquale
Committee Member

_____

David Howard, Ph.D.
Committee Member

Accepted:

_____

Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

_____

Date

# Order of Entry Effect and Effects of Drug Relabeling in the Pharmaceutical Industry

By

Xin Yan
M.A. Emory University, 2017
M.A. Boston University, 2012
B.A. University of Wisconsin - Madison, 2011

Advisor: Maria Arbatskaya, Ph.D.
Advisor: Matthew Higgins, Ph.D.

An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in Economics
2018

Abstract

Order of Entry Effect and Effects of Drug Relabeling in the Pharmaceutical Industry

By Xin Yan

The first chapter studies order-of-entry effects (OEE) in the pharmaceutical industry. Overall, I find evidence of first-mover advantage (FMA). On average, first movers obtain approximately a 23 percentage point higher market share than followers during their first five years in the market. Interestingly, followers who enter the market within two years of the first mover mitigate the FMA. These "fast followers" demonstrate that the speed of entry matters. Followers who enter the market more than two years after the first mover suffer a late-mover disadvantage. This disadvantage increases with the time between the initial entrant and late-mover.

The second chapter provides causal evidence relating to the impacts of FDA drug relabeling on consumer demand. We find that, on average, demand declines by 16.9 percent within two years of a relabeling event. Given the disaggregate nature of our data we capture all plausible substitution patterns by treating physicians. Critically, after accounting for this substitution demand declines by 4.7 percent, which represents consumers that prematurely leave the market. Results are robust to variation across types of relabeling, market sizes, levels of competition and degrees of cross-molecular substitution. If the consumers that leave the market should be treated, then our findings have implications for welfare and policy.

# Order of Entry Effect and Effects of Drug Relabeling in the Pharmaceutical Industry

By

Xin Yan
M.A. Emory University, 2017
M.A. Boston University, 2012
B.A. University of Wisconsin - Madison, 2011

Advisor: Maria Arbatskaya, Ph.D.
Advisor: Matthew Higgins, Ph.D.

A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in Economics
2018

Acknowledgments

I would like to express my greatest gratitude to my advisors, Dr. Maria Arbatskaya and Dr. Matthew J. Higgins for their patient guidance, support and valuable comments during my Ph.D. studies. I could not have completed these studies without their mentorship.

I am grateful to my dissertation committee members: Dr. Christina DePasquale and Dr. David Howard for their generous help. I am also grateful to Dr. Chirantan Chatterjee for his helpful discussions and comments on my research. My thanks also goes to Dr. Sara Markowitz for her help during the program.

My thanks also goes to Dr. Blake Allison, Dr. Samiran Banerjee, Dr. Kaiji Chen, Dr. David Jacho-Chavez, Dr. Zhongjian Lin, Dr. Esfandiar Maasoumi, Dr. Ian McCarthy, Dr. Hugo Mialon, Dr. Sue Mialon, Dr. Elena Pesavento, Dr. Vivian Zhanwei Yue, Dr. Tao Zha and other faculty members in the Department of Economics at Emory University for their dedicated teaching and research advising throughout my Ph.D. career. I would also like to thank Stephanie Gray for her great help during my study, job search, and paper editing. I would like to thank Brenda Baxter, Marie Browne and the other Economics staff members for their assistance as well.

Finally, I would like to thank my mother Haini Hou for her consistent support, love, and understanding. I am deeply grateful to my beloved wife, Xiaoyun Wang. Her endless support, love, and the birth of my son, Yumo Yan, encouraged me to finish my Ph.D. This dissertation is also for my father, Ning Yan, for his love and spiritual support.

# Contents

# List of Figures

# List of Tables

# Preface

My dissertation consists of two chapters focusing on pharmaceutical economics, which is at the intersection of health economics and industrial organization. Specifically, my research agenda is focused on firm behavior and the impact of regulation on consumer choice. A prescription drug's life-cycle is naturally divided into the pre-approval and post-approval stages. In the post-approval stage, while firms focus on the market performance of new products, the policymakers are focused on efficacy and safety issues. My first chapter focuses on the variations in firm performance depending on the order of entry, and my second chapter explores the impact of safety regulation on the aggregate demand.

The first chapter titled "If You Ain't First, Are You Last?: Mitigating the First Mover Advantage" is motivated by an old topic in the field of industrial organization — the order of entry effects (OEE). This paper explores the relationship between the speed of entry and the performance of subsequent followers. Specifically, I extend the current literature in two ways. First, using a newly updated and comprehensive data-set for the U.S. pharmaceutical industry between 1997 to 2011, I find evidence of a first-mover advantage (FMA). On average, first movers obtain a 23 percentage point higher market share than followers over the first five years in the market. Second, fast followers who enter within two years of the first mover do not show significantly lower performance, suggesting that the timing of entry matters. In particular, I find that the follower's disadvantage increases with entry lag for those who enter the market after two years of the market opening. Accounting for the costs of advertising and promotions, I construct measures of net sales and find that the first movers and fast followers continue to enjoy an advantage over slow followers.

Prescription drug labels are highly regulated. Manufacturers are required to provide information about the safety of drugs and effective use of products to consumers. After products are approved by the Food and Drug Administration (FDA), new data often emerges about the safety of drugs, and the FDA may require manufacturers to relabel their products. My second chapter explores safety labeling changes and how they causally impact the aggregate demand. This paper, titled "Estimating the Effects of Adverse Regulatory Events: Evidence from Drug Relabeling," is a joint work with Matthew J. Higgins and Chirantan Chatterjee. It provides causal evidence of the impact FDA drug relabeling has on aggregate demand for pharmaceuticals. We find that aggregate demand declines by 16.9 percent within two years of a relabeling event. After accounting for plausible substitution patterns by treating physicians and competitor actions, the aggregate

demand still declines by 4.7 percent. This decline plausibly represents consumers that prematurely leave the market. The overall effect appears to be driven by 'high-intensity' markets or those with significant relabeling activity. Results are robust to variation across types of relabeling, market sizes, levels of competition and degrees of cross-molecular substitution. Importantly, if the consumer that leave the market should be treated, then my findings have implications for consumer welfare.

In summary, my dissertation extends the understanding of pharmaceutical industry in two aspects. The first chapter helps firms understand the importance that entry order and timing has on its market performance. The second chapter estimates the impact of safety regulations on the aggregate demand in the post-approval stage, which helps both firms and policymakers understand how physicians and consumers behave to negative product news.

## Chapter I

# If You Ain't First, Are You Last?: Mitigating the First Mover Advantage[1]

**Abstract**

This paper studies the order-of-entry effect (OEE) in the pharmaceutical industry. Overall, I find evidence for first-mover advantage (FMA). On average, first movers obtain approximately a 23 percentage point higher market share than followers during their first five years in the market. Importantly, followers who enter the market within two years of the first mover mitigate the FMA. These "fast followers" demonstrate that the speed of entry matters. Followers who enter the market more than two years after the first mover suffer a late-mover disadvantage. This disadvantage increases with the time between the initial entrant and the late mover.

**Keywords:** Order of Entry, First Mover Advantage, Fast Follower, Switching Cost

**JEL Classication:** I10, L10, L20

[1] Acknowledgement: I thank Matthew Higgins, Maria Arbatskaya, David Howard, and Chirantan Chatterjee as well as seminar participants at Emory University for their valuable comments and engaging discussions. I also thank Murray Aitken, Courtney Yarbrough, and IMS Health Incorporated for their generous support and access to their data. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities. The statements, findings, conclusions, views, and opinions contained and expressed in this article are based in part on data obtained under license from the following IMS Health Incorporated or affiliate information service(s): IMS Midas$^{TM}$, IMS Lifecycle$^{TM}$ IMS National Disease and Therapeutic Index$^{TM}$ IMS National Prescription Audit$^{TM}$ IMS Health Incorporated, or its affiliates.

# 1 Introduction

Firms that are the first to enter a market enjoy a significant first mover advantage (FMA). They enjoy a higher market share and longer survival rate (Lieberman and Montgomery, 1988; Kalyanaram et al., 1995; Lieberman and Montgomery, 1998). More recently, studies have explored the effect of the order and timing of entry instead of just comparing the performance of the first mover and all followers (Kalyanaram et al., 1995; Agarwal and Gort, 2001). These studies suggest that the timing of entry plays an essential role in a firm's performance. In this paper, I not only identify order of entry effects (OEE) in the pharmaceutical industry over the recent two decades, but also extend the understanding of how different followers perform depending on the timing of entry.

One of the main mechanisms by which a first mover creates a FMA is attributed to the switching cost. When consumers face switching costs, the first firm to bring a product to market gains an advantage. A first mover can lock-in consumers, putting subsequent entrants at a disadvantage (Lieberman and Montgomery, 1988). In the pharmaceutical industry, the order of entry is especially important as the learning curve for new drugs is relatively steep for doctors. Previous studies suggest that doctors are reluctant to prescribe a drug they are not familiar with, even when their information is publicly available (Centor et al., 2006; Furberg et al., 2010). Thus, drugs that enter the market early have the opportunity to lock-in doctors, thereby contributing to the superior performance of the first movers in the market.

The pharmaceutical industry provides a nice environment to extend the understanding of OEEs. The market is important for health and is economically significant. Many policies intended to reduce spending focus on speeding the entry of competitors. Into the market, over 80 branded prescription drugs have been introduced every year from 2005 to 2014.[2] The pharmaceutical market has also experienced a rapid increase in the speed of follower's entry after the first drug's introduction into the market (DiMasi and Paquette, 2004).[3] By understanding the relationship between the order of entry and usage of a drug, policymakers gain insights into doctors' prescribing behaviors and can design better public policies. This paper not only helps pharmaceutical firms understand the return on their investment, but also helps policymakers understand how patient's/doctor's choices of drugs may depend on the order of their entry.

I start my analysis by constructing a data-set that allows me to explore these issues within comprehen-

[2] Among the drugs approved between 1987 and 2011, only 203 of them are first-in-class drugs, which means that the majority are drugs entering after a first mover (i.e., they are "followers"). This includes various dosages of a single brand.

[3] The mean time from the first-in-class drug's entry to the first follower drug approval has decreased from 5.5 years in the 1980s to 2.8 years in the early 1990s (DiMasi and Paquette, 2004).

sive and well-defined therapeutic categories. Specifically, the disaggregate nature of my data allows me to explore both the early stage of the sales life-cycle for both the market as a whole and specific drugs, along with the exact sequence and timing of drug introductions. Importantly, I am able to control for the two most important marketing tools used in the pharmaceutical industry – detailing and direct-to-consumer advertising (DTCA). Finally, I collect the side-effects and drug interactions for each drug to control for the potential quality differences of drugs within the same therapeutic category. Vagaries in the trial and FDA approval process add an element of randomness to the order of entry, which allows me to quantify the OEE.[4]

I find that the first mover obtains approximately a 23 percentage point higher market share over the first five years when compared to a follower in the U.S. market. However, if a follower enters the market within two years of the first mover ("fast follower"), it does not suffer any disadvantage in capturing the market share compared to the first mover. This critical two-year window of opportunity for followers is explained in two ways. First, I find that fast followers tend to be drugs in Phase III of clinical trials, the final stage before approval, when the first movers are approved. Second, I show that the average market reaches maturity (around 80 percent of the market peak sales) approximately two years after the market opening. My evidence suggests that fast followers that enter prior to the first mover's peak sales disrupt the first mover's ability to control a market. Evidence for this two-year window of opportunity for fast followers is strengthened by a series of alternative robustness and sensitivity checks.

Finally, I explore the importance of the FMA on net sales and profits.[5] Fast followers appear to mitigate the FMA on net sales. However, the first mover gains greater net sales and a higher profit compared to a slow follower. The approval process for new drugs is solely controlled by the FDA, whereas firms control the development process. A firm may try to increase the speed of entry by accelerating clinical trials. This is not costless and could impact the FMA. Through a series of robustness tests, I demonstrate that as long as the first mover's R&D expenditure is less than five times the R&D expense of a slow follower, their FMA is preserved.

The paper proceeds as follows. Section 2 reviews important features of the drug development process and discusses the research setting. Section 3 provides a discussion of the previous literature on the topic of

[4]The choice to start any R&D work is obviously endogenously determined by the firm. The firm may be able to accelerate the process of research and development. However, the clinical trial process takes around 8-12 years on average (Heilman, 1995) and the pass/fail decision at each stage of a clinical trial is largely exogenously determined by the FDA, with approximately a 10 percent success rate from the beginning of Phase I of a clinical trial to the drug's approval.

[5]Net sales are defined as real sales revenue net the promotional cost and approximated production cost. Profits are defined as net sales minus approximated R&D cost. Both of these terms will be further explained in Sections 5.4 and 7.6.

the OEE. Section 4 provides the data description and empirical specification. Main results about the OEE are presented in Section 5. Robustness and sensitivity analyses are presented in Section 6. Section 7 discusses the implications of this research and concludes the paper.

## 2 U.S. Pharmaceutical Regulatory Environment

The U.S. pharmaceutical industry is highly regulated. Every new drug has to go through a series of tests to ensure its safety and efficacy before approval.[6] The FDA's approval process and the lengthy research and development process provide an environment in which the entry action is largely exogenously determined.

Aside from the pre-clinical phases where research focuses on chemical synthesis or animal testing, the FDA clinical trial approval process for prescription drugs is divided into four phases. The first three phases are considered the pre-approval stage. After the final approval is obtained from the FDA, the drug is granted an exclusivity period for trade. Together with patent protection granted during the chemical development stage, drugs receive an intellectual property protection period.[7] The lengthy R&D process largely reduces the possibility of free-riding on technology spillovers for the same therapeutic use. Even if a marketed drug is discovered with new indications, the drug has to complete all phases of a clinical trial from investigational drug applications to a New Drug Application (NDA) for the new use. This prevents other firms from replicating the existing product within a short time period.

Next, the pharmaceutical market provides a well-defined environment, such that every product on the market meets a standard (safety and efficacy) and is categorized into different markets based on therapeutic classifications. This study uses the Anatomical Therapeutic Chemical (ATC) Classification System to classify the active ingredients of drugs according to their therapeutic properties (Organization et al., 1996) in order to define particular markets in the pharmaceutical industry. In particular, I use the ATC 4-digit class since drugs in the same class perform in a very similar way to treat the same medical condition. Drugs within the same ATC-4 digit class can be considered close substitutes.[8] Moreover, followers are often labeled as

[6] This practice dates back to 1938 when the U.S. Food, Drug, and Cosmetic Act (FD&C) subjected new drugs to a safety evaluation before they could access the market for the first time. After a worldwide drug disaster in 1961 (FDA), the FDA enacted the 1962 Drug Amendments, which explicitly states that new drug approvals should be based not only upon proof of safety, but also on a drug's efficacy.

[7] A new drug is eligible for exclusivity for five years or more based on the 21 C.F.R. 314.108, 316.31, 316.34, and Sections 505A, 505E, and 505(j)(5)(B)(iv) of the FD&C Act. The patent for certain supplements is granted by the United States Patent and Trademark Office during the development of the drug, which may take up to twenty years to conclude (FDA).

[8] The Anatomical Therapeutic Chemical (ATC) Classification System is used for the classification of the active ingredients in a drug according to the organ or system on which it acts and the drug's therapeutic, pharmacological, and chemical properties. The

"me-too" drugs since they have similar function and treat the same disease (Grabowski, 2002; Hollis, 2004). Previous studies (e.g., Andrade et al., 2016) have also used the ATC-4 classification to explore the competition of me-too drugs.

Finally, I choose to investigate branded drugs because the number of followers increase over time, and competing drugs already in the late stage development tend to continue towards entering the market. Once a drug is in the late stage of clinical trials, the high R&D sunk cost and promising returns reduce the voluntary drop-out rate (DiMasi et al., 2016). However, competing drugs in the early R&D stage may behave differently. Not only are firms interested in whether R&D investment is worthwhile, they also worry about whether the market will be saturated with too many followers.

## 3 Order and Timing of Entry Effect

The OEE have been studied primarily in the context of the FMA. The FMA is defined by a first mover who enters the market early and generates a persistent advantage in firm performance such as market share (Lieberman and Montgomery, 1988). Gradually, order of entry studies have evolved into exploring the timing of the entry. In particular, Kalyanaram et al. (1995) find that firm performance can be very different based on the order of entry among followers. Moreover, Golder and Tellis (1993) as well as Szymanski et al. (1995) investigate the pharmaceutical industry and show that the order of entry negatively relates to the late mover disadvantage. Agarwal and Gort (2001) also find that the FMA decreases for a fast follower. Other studies explore empirical and theoretical approaches to explain the trade-off between a firm's lead time and performance (e.g., Huff and Robinson, 1994; Cohen et al., 1996). A more recent study explores the possibility that a follower may actually perform better than a first mover (Shenkar, 2010b).

In the pharmaceutical industry, the studies closely related to this paper are presented in Table 1, which shows that an early entrant into the market has a superior advantage (Bond and Lean, 1977; Hurwitz and Caves, 1988; Berndt et al., 1996; Roberts, 1999; Kalyanaram, 2008). Specifically, Hurwitz and Caves (1988) analyze two therapeutic classes and find that pioneer drugs are able to maintain a superior market share even after ten years from their introduction into the market. Bond and Lean (1977) explore the market share for 29 pioneer drugs and still found these drugs' market share to be over 50 percent shortly after patent expiration. In studies focusing on the 1990s, Berndt et al. (1996) and Kalyanaram (2008) suggest that the follower

system is controlled by the World Health Organization Collaborating Center for Drug Statistics Methodology (WHOCC). The ATC 4-digit code indicates the chemical/therapeutic/pharmacological subgroup.

has a disadvantage in market share compared to the first mover. These previous studies mainly focus on the U.S. market in the pre-2000 period; yet, many policies have been implemented in the last two decades. These include the deregulation of DTCA in 1997, which increases access to the medical information that may lessen switching costs (Wilkes et al., 2000). Another related policy is Medicare Part D (2003), which increased the market size and attracted more entrants (Blume-Kohout and Sood, 2013). These changes in the pharmaceutical industry may result in different findings for the OEE than seen in previous studies because consumer search costs and competition levels have changed. This paper incorporates both detailing and DTCA and seeks to extend the existing body of literature by studying the current OEE in the pharmaceutical industry.[9]

Not only has there been dramatic policy changes, the pharmaceutical market has also experienced a rapid increase in the speed of entry of drugs over the last two decades (Lilien and Yoon, 1990; Agarwal and Gort, 2001). For example, Berndt et al. (1995) show that the entry timing negatively correlates with the market share in the anti-ulcer drug market. Andrade et al. (2016) analyze followers in France between 2001 to 2007 and find that the first mover enjoys superior market share. This paper uses followers with different times of entry to explore whether their disadvantage changes depending on the time of entry and also explores the time window of opportunity for followers in the pharmaceutical market.

The competitive advantage generated by the first mover can be explained by the mechanism that the early entrant is likely to generate a switching cost (Lieberman and Montgomery, 1988). As most consumers are risk averse, the uncertainty about new products enhances the switching cost, which decreases the likelihood of a consumer switching to new products (Burnham et al., 2003). Many researchers demonstrate both empirically (Grabowski and Vernon, 1992; Serra-Sastre and McGuire, 2013) and theoretically (Villas-Boas, 2004) that switching costs play an important role in sustaining an early mover's advantage. This specifically applies to the pharmaceutical market as drugs are experience goods. The first mover accesses the market early and locks-in the patients/doctors before followers have the opportunity to enter the market. The awareness of the first mover is widespread after a certain amount of time, which makes it harder for late entrants to build their market share by convincing doctors/patients to switch.[10] Coscelli and Shum (2004) found, using

[9] Another reason for re-evaluating the FMA in the pharmaceutical market is that insurers (and pharmacy benefit managers) play a much larger role in steering patients and physicians to particular drugs than when the earlier papers were written. Through the use of formularies, insurers are able to quickly shift market share between rival drugs. Thus, the FMA may have diminished in the recent two decades.

[10] Even though patients may be inexperienced with a certain class of drugs, doctors (especially specialists) are experienced. Therefore, for both chronic and acute conditions, there are switching costs for experienced patients and for new patients.

prescription level information from the Italian anti-ulcer market, that the introduction of a new drug into an established market has a great disadvantage, which they attribute to the uncertainty of quality over existing drugs.

I extend the understanding of the role of switching costs within the OEE by exploring a new drug's diffusion and promotion effectiveness. A drug's diffusion in a new class helps researchers determine the fraction of inexperienced consumers in the market. This would help understand the difficulty of switching patients at different times a market opens. Promotional spending is one of the most important tools used by firms to create product awareness in the pharmaceutical market. It is found to have a significant impact on increasing sales (e.g., Sridhar et al., 2014). This study focuses on those prescription drugs where the main decision maker is the doctor. As detailing is the main force used to increase drug prescriptions, I use its effectiveness to determine the ease of switching from one drug to another. By exploring promotion effectiveness among groups with different orders of entry, this paper helps understand the mechanism that leads to the advantages enjoyed by first movers.

# 4 Data

I am fortunate to have access to the IMS Health database for the national sales data for prescription drugs sold within the U.S., which provides me with a range of comprehensive data-sets. This paper focuses only on branded drugs sold in the U.S. Thus, I artificially select the drugs classified as "Original Brands" or "Licensed Brands." The timespan of data in this paper is from the second quarter of 1997 to the first quarter of 2011, which cover the time period of available data. The FDA approval date for each prescription drug is collected from the FDA website using data from the Orange Book and the Center for Drug Evaluation and Research (CDER). For my study, there are 213 drugs from 97 ATC 4-digit markets, which were all introduced after the second quarter of 1997. The IMS Health data lists the drugs' sales data in standardized units (SU), which provides comparable patient dosages by equating tablets, capsules, and liquids.

Table 2 summarizes the variables used in the estimation. Using the IMS Health data, I construct variables including the wholesale price, market share, and net sales.[11] Observed data for each drug is limited to the first five years from the first drug's approval date in order to avoid the possible entrance into the market of generic versions, which largely erodes the sale of the focal branded drug. The market sales quantity is the

[11] It is important to note that this wholesale price excludes adjustments for rebates.

summation of sales quantity of all branded drugs within class $i$ at time $t$. Market price is the average price for all branded drugs within class $i$ at time $t$ measured in real 2009 U.S. dollars. Market promotion is the sum of all detailing expenditures (in million USD) within class $i$ at time $t$. Market DTCA constitutes all DTCA expenditures within class $i$ at time $t$. Market side effects are the number of average commonly-observed side effects for all branded drugs within class $i$ at time $t$. *Major, Moderate*, and *Minor* interactions represent the average number of major, moderate, and minor drug interactions for each drug within class $i$ at time $t$.

[Table 2]

# 5 Order of Entry Effect on Market Share

To understand the market, I use the market share as the measure of the relative drug usage. I construct the market share based on the quantity sold of each drug as a fraction of the entire sales quantity of the market. Thus, the market share is derived based on the equation for each drug $i$ in the focal market $I$ at time $t$:

$$Market\ Share_{it} = \frac{Sales\ SU_{it}}{\sum_i^I Sales\ SU_{it}},$$

where $Sales\ SU_{it}$ is the sales quantity for drug $i$ at time $t$. To understand market share patterns among players with different orders of entry,[12] I construct graphs showing the trends in market share after the market opening (or first drug's introduction) for the first movers and all followers.[13] Figure 1 shows the market share of the sales quantity for the two groups.

[Figure 1]

This figure shows that the first movers on average are able to gain a superior market share. The followers on average only capture around 30 percent of the market share, even after a few years. This might suggest the existence of a first mover advantage in the industry and I posit:

*Hypothesis 1: The follower has a lower market share compared to the first mover.*

Following prior literature on the OEE estimation,[14] I propose the following empirical specification developed from the log-linear model, which is widely used in the marketing literature (e.g., Cooper, 1993):

[12] I divide the drugs into 21 groups based on entry time; further analysis is in Section 5.2. There are two cases where two branded drugs were introduced in the same quarter as the first mover. To reduce the profound effect from the co-first mover, these two unique cases were dropped from the sample.

[13] The market share and other related variables are set to missing values before the introduction of the focal drug.

[14] The approval process is further explained in Section 2. To resolve further concerns on the endogeneity issue of the order of entry for followers, I provide further robustness checks in Section A1.8.

$$Y_{it} = \beta_0 + \beta_1 Follower_i + \beta_2 Price_{it} + \beta_3 Lagged\ Promotion\ Stock_{it}$$
$$+\beta_4 Lagged\ DTCA\ Stock_{it} + \gamma X_{it} + FE_{it} + \varepsilon_{it}. \quad (1)$$

The data is in panel form and uses the quarterly information of each drug. The dependent variable, $Y_{it}$, represents the market share of drug $i$ at time $t$. The variable $Follower_i$ determines whether drug $i$ is the first mover or follower in the focal ATC 4-digit class (the variable equals 0 if it is the first mover and equals 1 otherwise). The main variable of interest is $Follower_i$, coefficient $\beta_1$ will measure if a first mover has a superior advantage on market share. Since the dependent variable is market share, which is a continuous variable between 0 and 1, the fixed effect fractional Logit estimation method is used (Papke and Wooldridge, 2008).

The specification in Equation (1) also includes key control variables: *Price, Lagged Promotion Stock,* and *Lagged DTCA Stock*, which will be log transformed in the estimation. Price is derived from the IMI data and defined as $Price_{it} = \frac{Sales\ Real\ Revenue_{it}}{Sales\ SU_{it}}$ for drug $i$ at time $t$.

The most important controls in order to isolate the OEE on the market share of a drug are marketing and advertising. In the pharmaceutical industry, marketing and advertising can be separated into two types – promotion to doctors, which is measured by *Promotion*, and advertising to patients, which is measured by *DTCA*. My data allows me to control for effects from both factors. The promotional spending includes detailing, journal advertising, and mail promotion, all of which a pharmaceutical firm will use to promote their products to health professionals. The DTCA expenditure includes the expenditure used to advertise to patients through channels such as television and Internet. In the specification, *Lagged Promotion Stock* and *Lagged DTCA Stock* are the summation of lagged and discounted promotion and DTCA expenditures, respectively.[15]

$X_{it}$ is a vector of control variables that include *Side Effect, Major Interaction, Moderate Interaction, Minor Interaction, Vintage,* and *Brands*. One of the major concerns in measuring the OEE is the quality differences between the first mover and followers. Even though the therapeutic class is a well-defined categorization, drugs within the same class still possess heterogeneous characteristics. To reduce the biases

[15] $Lagged\ Promotion\ Stock_t = \beta Promotion_{t-1} + \beta^2 Promotion_{t-2} + \beta^3 Promotion_{t-3}$, where $\beta$ is the discount factor and is set to 0.7 in the estimation.

$Lagged\ DTCA\ Stock_t = \beta DTCA_{t-1} + \beta^2 DTCA_{t-2} + \beta^3 DTCA_{t-3}$, where $\beta$ is the discount factor and is set to 0.7 in the estimation. Following Leone (1995), where the discount rate varies between 50 and 70 percent.

caused by heterogeneous quality between first movers and followers, I collect the number of commonly-observed side effects, and the major, moderate, and minor drug interactions of each drug.[16] The OEE could be better identified if drugs are largely homogeneous after accounting for the quality differences, in order to control for other observed effects on the dependent variable. I also construct the variable *Vintage*, which represents the age (in quarters) of drug $i$ at time $t$ since its introduction into the market. This is an important variable to control a drug's life-cycle. *Brands* represent the number of branded drugs in the market at time $t$, which will be used to control for the competition level in the market.

ATC therapeutic classes provide well-defined markets for this analysis. As such, I include market fixed effects to adjust for market differences.[17] For robustness purposes, ATC 3-digit fixed effect are also used; results are not significantly different. $\varepsilon_{it}$ captures the errors.

### 5.1 Order of Entry Effect on Market Share with Differentiation among Followers

As mentioned in Section 1, the speed of entry has rapidly increased over the last two decades (DiMasi and Paquette, 2004). Figure 2 summarizes the frequency of entry timing by followers into a market (in quarters since the market opening). Among the followers, there are between two to four drugs typically introduced into the market every quarter within 30 quarters (7.5 years) of the market opening.

[Figure 2]

To analyze the effect of the speed of entry on market performance, I divide the entry order into three groups: 1) first movers (97 drugs); 2) fast followers, which are drugs introduced within eight quarters after the market opening (21 drugs); and 3) slow followers, which are drugs entering the market after eight quarters of the market opening (95 drugs). Table 3 summarizes the number of drugs within each defined group and the average speed of entry for drugs introduced in the first five years of market opening. Fast followers enter the market, on average, within one year of the market opening, while slow followers enter, on average, around the fourth year after market opening.

[Table 3]

Moreover, given the three groups of players (first movers, fast followers, and slow followers), I also construct graphs showing the trends in an average firm's market share after the market opening (or the first drug's introduction). Figure 3 shows the market share of the sales quantity given by these three groups. Not

[16] The quality-related data of each drug is collected from the website *www.Drugs.com*.

[17] Fixed effects are at the ATC-4 market level.

every market has fast followers, and I divide the markets based on the existence of fast followers. Figure 3 shows a drug's average market share in the ATC 4-digit markets with fast followers. In Figure 3, first movers, on average, are able to gain a superior market share over slow followers. Fast followers, after approximately eight quarters of the first drug's introduction, hold a similar proportion of the market compared to first movers. Slow followers capture only around 10 percent of the market share. This figure provides suggestive evidence that the market share for the first mover and fast followers converges over time, while the slow follower lingers.

[Figure 3]

Fast followers are defined as followers entering the market within two years of the market opening for three reasons. First, there is a natural time gap or structural break in the data (see Figure 2). Second, the drugs that enter the market within two years of the market opening were likely to be in Phase III clinical trials before the first mover was approved (DiMasi and Paquette, 2004). Phase III clinical trials constitute a large proportion of a drug's research and development cost (DiMasi et al., 2016). Since a drug in the Phase III stage has a high rate of success in obtaining approval and entails a significant development cost, a firm is unlikely to voluntarily discontinue production in this phase. I choose the period of two years to distinguish between drugs that are already in a Phase III clinical trial (fast follower) or in an earlier stage of the development process (slow follower).[18] Third, I will show in Section 5.5 that markets reach near-maturity, on average, at around the eighth quarter after the market opening, which means any drug introduced after two years of the market opening is most likely competing for a treated patient. Accordingly, I choose the two years to be the cut-off between the fast follower and slow follower.

Thus, with the differentiated followers defined, each follower may perform differently:

*Hypothesis 2: Compared to the first mover, the fast follower has the same market share, but the slow follower has a lower market share.*

To estimate the OEE across different groups of followers, I use the following specification:

[18] I calculate the two years based on two points: 1) Around 90 percent of the market have a follower already in the Phase III clinical trial stage before the first drug in the market is approved (DiMasi and Paquette, 2004); and 2) The average time to complete Phase III is around 30 months (DiMasi et al., 2016). Thus, the mean time for a drug to move from the start of clinical trial Phase III to approval is around 27 (30*90%) months. Together, with the gap shown in Figure 2 between the 8th and 9th quarters, I choose two years (8 quarters or 24 months) to be the cut-off point.

Figure 2 shows that there are several other natural breaks from the introduction of drugs at the 30th, 40th, and 50th quarters after the market opening. According to previous research (DiMasi et al., 2016), the average time from the start of clinical trials to approval is around 96 months (32.5 quarters). It is then likely that a drug introduced after 30 quarters of the market opening has not yet started the clinical trial when the first mover is approved. Interestingly, I find that the behavior of these drugs does not differ significantly from that of the drugs introduced between 8 quarters and 30 quarters since the market opening. Thus, I did not divide a drug class into more than three groups.

$$Y_{it} = \beta_0 + \beta_{1f} Fast\ Follower_i + \beta_{1s} Slow\ Follower_i + \beta_2 Price_{it} + \beta_3 Lagged\ Promotion\ Stock_{it}$$
$$+\beta_4 Lagged\ DTCA\ Stock_{it} + \gamma X_{it} + FE_{it} + \varepsilon_{it}. \quad (2)$$

The variables of interest are separated into three groups: *First Mover, Fast Follower, and Slow Follower*. These variables will replace the variable $Follower_i$ from the estimation in Equation (1). The variable $Fast\ Follower_i$ is a dummy variable equal to one if drug $i$ was introduced into the market within eight quarters of the market opening, zero otherwise. $Slow\ Follower_i$ is defined as a dummy variable equal to one if drug $i$ was introduced into the market after eight quarters of the market opening, zero otherwise. The coefficients $\beta_{1f}$ and $\beta_{1s}$ measure, compared to the first mover, whether the fast follower and slow follower have a different level of market share, respectively.

## 5.2 Entry Time Effect on Market Share

Previous research limits the order of entry to the first mover and follower, or first mover to different orders of followers (Hurwitz and Caves, 1988; Grabowski and Vernon, 1992; Roberts, 1999). In order to understand the entire picture of the followers' performance, I allow for variation in time on followers to estimate the effect of entry timing on market share. Therefore, the next step is to estimate the OEE among different followers introduced into the market within the first twenty quarters (five years) of the market opening.

Knowing the OEE from Equation (1), I explore the speed of entry effect on market share using the following specification:

$$Y_{it} = \beta_0 + \beta_1 Entry\ Time_i + \beta_2 Price_{it} + \beta_3 Lagged\ Promotion\ Stock_{it}$$
$$+\beta_4 Lagged\ DTCA\ Stock_{it} + \gamma X_{it} + FE_{it} + \varepsilon_{it}. \quad (3)$$

The dependent variable $Y_{it}$ still represents the market share of drug $i$ from the focal ATC 4-digit class at time $t$. The variable $Entry\ Time_i$ determines the timing of the entry of drug $i$ in the focal ATC 4-digit class. The variable $Entry\ Time_i$ is separated into twenty-one categories based on the timing of entry: first mover, drugs introduced in the 1st quarter after the entry of the first mover, drugs introduced in the 2nd quarter,

drugs introduced in the 3rd quarter, and so on, up to drugs introduced after the 20th quarter (including the 20th quarter). This estimation helps us to understand the entry effect of each follower entering the market within the first five years of the market opening compared to the first mover. All other variables are the same as in Equation (1).

### 5.3 Average Entry Timing Effect on Market Share

The distribution of followers in the sample used in this paper is shown in Figure 2. The advantage persistence changes for the first mover over time due to changes in competition intensity as noted in previous literature (Roberts, 1999). Therefore, in addition to the OEE, I also explore the impact of time elapsed from the market opening for a follower's market share compared to the first mover. I explore this issue using the following specification:

$$Y_{it} = \beta_0 + \beta_1 Elapsed\ Time_i + \beta_2 Price_{it} + \beta_3 Lagged\ Promotion\ Stock_{it}$$
$$+\beta_4 Lagged\ DTCA\ Stock_{it} + \gamma X_{it} + FE_{it} + \varepsilon_{it}. \quad (4)$$

The dependent variable $Y_{it}$ represents the market share of drug $i$ from the focal ATC 4-digit class at time $t$. The variable $Elapsed\ Time_i$ determines the time (quarters) elapsed from the introduction of the first mover to the introduction of drug $i$ in the ATC 4-digit class. This is constructed to further understand the entry timing on average, which will be used in the estimation. The variable of interest is $Elapsed\ Time_i$. Equations (1) and (2) provide the estimation of the OEE of followers under different defined groups. This specification explores the average impact of time from the market opening for a follower's market share, which helps to understand whether it matters if followers enter slower or faster, on average. All other variables are the same as in Equation (1).

### 5.4 Order of Entry Effect on Net Sales

Aside from market share, which measures the comparative usage of drugs in the same therapeutic class by consumers, profits are another way of understanding the OEE (e.g., Roberts, 1999; Boulding and Christen, 2003). Due to data limitation on project-level R&D cost, I first construct the post-marketing net sales.

I apply the simple idea that net sales equals the revenue minus cost. The revenue comes directly from the data. From previous research (DiMasi et al., 2016), we know the cost to develop a drug is as high as 2.6

billion USD. This measure accounts for the potential failure and opportunity cost. Admittedly, the actual cost for a marketed drug is lower than the potential cost, considering the potential failure. In this section, I will only use the post-marketing net sales mainly because this estimation measures the order of entry for each marketed drug. The main cost is the expenditure to promote the drug and the production cost per unit. According to the decomposition of the cost associated with selling a drug, the profit for drug $i$ at time $t$ is estimated using the approximated formula as follows:

$$NS_{it} = Real\ Sales\ Revenue_{it} - Total\ Promotion_{it} - Production\ Cost_{it},$$

where $NS_{it}$ represents the net sales of drug $i$ at time $t$. The variable cost of production is constructed using the formula: $Production\ Cost_{it} = Marginal\ Cost_i * Sales\ SU_{it}$, where the marginal cost of drug $i$ is set to be the average price of the generic drugs in the same market. The generic drug is proven to be clinically the same as its branded version. Without the rigorous approval process and innovative contribution, the R&D cost for a generic drug is minuscule compared to its branded version. The main competition strategy for the generic version is on price. Considering enough competition in the market, generic drugs are able to push price down to the near-marginal cost.[19] Total promotion includes the promotional spending and the cost of DTCA in our sample. Both DTCA and promotion represent essential tools of firms to market their drugs and also constitute the majority of cost in the post-approval stage for each drug.

To check the data pattern of the net sales of drugs after market opening, Figure 4 shows the average net sales based on two defined groups (first mover and followers) after the market opening. The figure shows that first movers, on average, have higher net sales compared to followers even though there seems to be convergence.

[Figure 4]

Thus, I propose the hypothesis that:

*Hypothesis 3: Followers have lower net sales compared to first movers.*

Following an earlier study (Boulding and Christen, 2003) and referring to Hypothesis 3, I use the fol-

19

To construct the price of the generic drug, I select drugs under the classification of "Unbranded" from the IMS Health data-set in the focal market and derive the average real price of these drugs at each time period. The generic version of a branded drug will be available at the earliest five years after the approval of the branded drug because of the original drug's exclusivity. For simplicity, the marginal cost is assumed to be the same for each branded drug in the same market. The marginal cost of a focal market is equal to the lowest of all average generic prices across time in the focal market. If the generic price is not available within the focal ATC-4 digit market in the sample, I use the generic price in other ATC 4-digit markets within the same ATC 3-digit markets to construct the marginal cost.

lowing specification to estimate the impact of entry order on the net sales (or profit):

$$Y_{it} = \beta_0 + \beta_1 Follower_i + \gamma X_{it} + FE_i + \varepsilon_{it}. \tag{5}$$

The dependent variable $Y_{it}$ represents net sales, $NS_{it}$, of drug $i$ at time $t$, which is log transformed in the estimation. The variable of interest is still $Follower_i$ (I also further divide this variable into fast follower or slow follower). The vector of control variables, $X_{it}$, and the fixed effect, $FE_i$, represent the same covariates as shown in Equation (1).

### 5.5 Drug Diffusion in the New Market

In Sections 5.1 and 5.2, I propose two hypotheses of the OEE in the pharmaceutical market. First, first movers may enjoy a superior advantage on the market share compared to the follower. This could be because the first mover builds up brand loyalty and "locks-in" consumers before followers enter the market. Second, fast followers may also lock-in consumers before slow followers enter the market. To understand whether this is the mechanism by which the first mover and fast follower gain superior market share, I explore the speed of drug diffusion in a new market.

A new drug's diffusion measures how quickly it infiltrates a market. The adoption speed by doctors of new drugs is heterogeneous, determined both by doctors' preferences and market characteristics. Once a new drug is adopted by doctors, subsequent drugs have to compete with an existing treatment, which may be more difficult. Since the therapeutic class is well defined and the potential market size is determined within the population, the market size (number of patients) usually remains unchanged with the introduction of additional drugs. Previous studies find that the adoption of a new drug is relatively easier than prescribing a follower in an existing market (Dybdahl et al., 2005; Garjón et al., 2012; Huskamp et al., 2013). This may help explain why early entrants (first mover and fast follower) enjoy a superior market share and profitability compared to slow followers.

To understand whether early entrants take over the majority of the market, I construct Figure 5, which represents the average market sales in the first eight years since the market opening. The figure shows that sales increase sharply over the first two years and then starts to slow down. Market sales reach their peak at around the 13th quarter (3.25 years) and fluctuate afterward before reaching absolute peak sales at around the 22nd quarter (5.5 years) since the market opening. Between the 13th quarter to the 22nd quarter after

market opening, there is only a marginal increase. If peak sales identify the average market size, then the first two years is essential for the diffusion of drugs. This diffusion pattern suggests that an early entrant could gain market share more easily than late entrants because it is less likely they will need to compete with existing treatments.

[Figure 5]

More specifically, Table 4 presents the average market sales at the end of a two-year time period. We can see from Row *B* that the average market sales are around 26 million SU at the eighth quarter if we consider all markets. Row *C* shows that sales grow to 32 million SU after 30 quarters of the market opening. Sales at the eighth quarter reach around 80 percent of the market size, as shown in Row *D*. Note that this number is relatively similar in markets with and without fast followers.

[Table 4]

The diffusion of new products in a novel market is discussed in previous studies with summary statistics or survival analysis (Dybdahl et al., 2005; Garjón et al., 2012; Huskamp et al., 2013). According to the FDA, there is a limited number of discontinued branded drugs in the pharmaceutical industry (only eight drugs between 2000 and 2010 and none are a first-in-class drug). Thus, to estimate the diffusion speed of new drugs in a novel market, I explore new market growth, which is measured as the effect of market vintage (time-length from market introduction to current period) on market sales using the following regression specification:

$$Y_{it} = \beta_0 + \beta_1 Market\ Vintage_{it} + \beta_2 Market\ Price_{it} + \beta_3 Lagged\ Market\ Promotion\ Stock_{it} + \beta_4 Lagged\ DTCA\ Promotion\ Stock_{it} + \gamma X_{it} + FE_{it} + \varepsilon_{it}. \quad (6)$$

The data is in panel form and uses the quarterly information of each market. The dependent variable $Y_{it}$ represents sales of market $i$ at time $t$. The variable of interest is $Market\ Vintage_{it}$ (I later add the second degree $Market\ Vintage_{it}^2$ in robustness analysis as shown in Table A.10). The main variables include $Market\ Price_{it}$, measured by the average price in market $i$ at time $t$; $Lagged\ Market\ Promotion\ Stock_{it}$, which is calculated using the same strategy as *Lagged Promotion Stock* by using the sum of all promotional spending in market $i$ at time $t$; and $Lagged\ Market\ DTCA\ Stock_{it}$, which is calculated using the same strategy as *Lagged DTCA Stock* by using the sum of all promotional spending in market $i$ at time $t$. These three variables are log transformed in the estimation. The other control variables in the vector, $X_{it}$, include *Brands*

and *Generics*, which control for the number of branded and generic drugs in the market. I also include the average number of commonly-observed side effects, and the major, moderate, and minor drug interactions for drugs in market $i$ to control for the potential quality differences between markets. I also include ATC 3-digit fixed effect $FE_{it}$, and $\varepsilon_{it}$ captures the errors.

### 5.6 Endogeneity Issue

In each specification, the variables *Price*, *Promotion*, and *DTCA* may suffer from an endogeneity problem, which means that: 1) the price/promotion may cause the market share/position to change; and 2) there are some unobserved characteristics correlated with price/promotion. This problem has been well-established in previous studies (Berndt et al., 1995; Narayanan et al., 2004). Consistent with the literature (Chatterjee et al., 2018), I use two sets of instrumental variables for *Price*, which are related to the price of the focal drug but are less likely to be correlated with the error term. To exogenize the price of the focal drug, I use the mean and median of the price over other drugs in the same ATC 2-digit class. The idea behind looking at these instruments is that firms should have similar pricing strategies within the same therapeutic class; therefore, the instruments are likely to be correlated with the price of the focal drug. Even though the instrument could affect consumer utility through competition on prices, it is unlikely that other product characteristics would have a direct impact on consumer utility for the focal product. Therefore, these instruments are likely to be correlated with the focal drug price and are less likely to be correlated with unobserved product characteristics. Since the regression method used in this paper is largely the logistic regression method, which is a non-linear function, the estimation is conducted using the control function approach (Wooldridge, 2015) rather than the standard instrumental variable approach. In Equation (6), the endogeneity issue of *Market Price* is also taken into account using this approach.

Regarding the variables *Promotion* and *DTCA*, using the contemporaneous investment to control for the impact of promotional and DTCA expenditures on drug sales may lead to an endogeneity problem, primarily through reverse causality. Since the contemporaneous investment is decided by a firm's expected sales, such behavior would lead to a reverse causal relationship from sales to promotion and DTCA investment. To resolve this potential issue, I use the lagged promotional stock and lagged DTCA stock. Studies in the marketing literature (Van Heerde et al., 2007; Zhao et al., 2011) show that promotion/advertisement has a carry-over value, and previous investment is decided prior to the current period, which means the carry-over value is less likely to be caused by current sales. Therefore, using *Lagged Promotion Stock* and

*Lagged DTCA Stock* is potentially a better way to estimate the effect of promotion and DTCA on drug sales, without causing an endogeneity problem. In Equation (6), the endogeneity issue of *Market Promotion* and *Market DTCA* is also taken into account using this approach.

# 6 Main Results for Order of Entry Effect

## 6.1 Baseline Results – Effects from OEE

I start by estimating the OEE as a first mover compared to any follower on the market share, and the results in Table 5 represent the estimation of Equation (1). Model 1 shows that followers have a 23.9 percentage point (showed in the marginal effect listed at the bottom of the table) lower market share compared to the first mover. Model 2, after exogenizing the price, still shows a similar result (a 23.4 percentage point lower market share). Referring to the estimates of the price, the coefficient shows a negative and significant sign. Even though both the lagged promotion stock and lagged DTCA stock are able to increase the market share significantly, promotion appears to be more effective than DTCA. It is not surprising given that previous studies have suggested that promotion to doctors is more effective in market stealing while DTCA is more effective in market expansion (Narayanan et al., 2004; Brekke and Kuhn, 2006).

[Table 5]

The first mover in any industry usually captures a higher market share, and this result remains true in the pharmaceutical market, according to the results in Table 5. After exogenezing price and promotion, the result still holds. The first mover has a significant advantage in market share over followers for drugs introduced after 1997. The result is slightly higher than in a previous study, where the first mover enjoys a 6 to 20 percentage point advantage in market share over followers, depending on the industry (Golder and Tellis, 1993). In terms of other similar studies, Hurwitz and Caves (1988) found that a pioneer drug's market share remained over 50 percent even after patent expiration. This could be because the study focused on the pre-1984 period when competition was less intensive.[20] Moreover, in terms of a more recent study, the estimates here are more comparable with the results of Kalyanaram (2008), who suggests percentage ranges between 37-73 percent. My findings show that the follower's market share is around 60 percent of the first mover.

[20]The Hatch-Waxman Act, enacted in 1984, accelerated the approval of generic drugs. The policy greatly increased the competition in the pharmaceutical industry.

### 6.2 The Effect of a Follower's Entry Speed

Knowing that the first mover has a higher market share compared to the follower, a more interesting question is to explore the difference among followers. Rather than simply group the product into two categories as defined in Section 5.1, I define 21 groups in Equation (3), thus allowing for a greater variation in the entry speed. The results in Table 6 represent the estimation using Equation (3). Model 1 shows that drugs introduced within the first 7 quarters of a market opening are insignificantly different in the market share compared to the first mover. Every drug introduced after the 7th quarter of the market opening has a significantly lower market share compared to the first mover. Marginal effects demonstrate that followers (those drugs that enter the market after the 7th quarter of the market opening) have a lower market share. The magnitude of this disadvantage on market share ranges from 10 to 44 percentage points when compared to the first mover.

The result in Table 6 provides evidence demonstrating that the OEE depends on the timing of entry. If a drug enters the market fast enough after the market opening (within the first two years), it is able to mitigate the first mover advantage. However, the slow follower suffers in terms of the market share. From Table 5, we know the first mover enjoys a superior advantage in market share. Table 6 provides additional evidence that the follower's market share, compared to the first mover, depends on entry time.

[Table 6]

With the result shown in Table 6 and based on the pattern in Figure 2, I wonder whether there is a time window where followers can enter the market and mitigate the first mover advantage. Thus, in Table 7, I group followers into two simple categories: 1) Fast follower – those drugs introduced within eight quarters of the market opening; and 2) Slow follower – those drugs introduced after eight quarters of the market opening. Table 7 represents the estimation results of the OEE on market share based on three defined groups – first mover, fast follower, and slow follower.

The result in Table 7 suggests that the fast follower, on average, does not have any market share disadvantage compared to the first mover over the first five years. The slow follower, however, has a 32.1 percentage point lower market share, on average, compared to the first mover. This suggests that the fast follower is able to capture a comparatively similar level of market share to that of the first mover, while slow followers cannot do so. This result reconfirms the pattern we see from Figure 3 and may suggest that an entrant is able to build brand loyalty within two years, which leads to a disadvantage in consumer usage for

slow followers.

[Table 7]

These results suggest a very interesting situation that while the first mover enjoys an advantage on firm performance, Tables 6 and 7 show that as long as the follower moves fast, it is able to capture a similar market share compared to the first mover. The existence of the time window for followers to gain this opportunity provides an important market feature in the pharmaceutical industry. We know from Section 2 that followers in the pharmaceutical industry can-not free-ride on technology, like generic firms. Thus, the follower really should consider the speed of entry as an important indicator of future firm performance, even if the approval decision is largely determined by the FDA. On the demand side, market share response from the consumer demonstrates that there is a lock-in effect. Whether this effect is driven by consumers or physicians, it suggests that consumers may not be treated with the best medication available.

### 6.3 The Impact of Timing of Entry on Market Share

We know from Section 6.2 that as time elapses from the introduction of the first mover to the market, the follower seems to have a lower market share. Thus, I implement Equation (4) to estimate the impact of time elapsed from the follower's entry to market opening on market share and show the result in Table 8. Model 1 in Table 8 shows that on average, a one-quarter delay for a follower leads to a 1.0 percentage point lower market share. Model 2 of Table 8 restricts the sample to only fast followers. The results suggest followers are not greatly impacted in terms of market share, no matter when they enter the market, as long as their entry is within two years of the market opening. Interestingly, Model 3 shows that after eight quarters of the market opening, a one-quarter delay in the approval of a drug leads to a 1.1 percentage point lower market share, on average, for slow followers.

[Table 8]

Together with the results in Tables 5 to 7, Table 8 provides additional evidence that the entry timing closely relates to the post-approval market performance of the drug. In particular, the result suggests that with every quarter delay of entry, the follower, on average, will suffer more in terms of the market share. But, as long as the follower enters the market within two years of the market opening, it is able to mitigate the disadvantage.

### 6.4 Order of Entry Effect on Net Sales

While there is no doubt that the market share represents an essential part of firm performance, net sales are the real concern for the firm. Thus, I use the post-approval net sales and measure whether the order of entry has an effect on it. Using the net sales constructed in Section 5.4, Table 9 shows the impact of the entry speed on a firm's net sales. Model 1 shows that the first mover has, on average, 37.1 percent higher net sales than followers. Model 2 divides the firms into three groups and suggests that the fast follower does not bear a disadvantage in terms of net sales when compared to the first mover. Slow followers suffer 41.7 percent lower net sales compared to the first mover.

[Table 9]

The first mover and the fast follower both have similar levels of net sales; but, the slow follower is at a marked disadvantage. Results show that the first mover has an advantage over the slow follower on both the market share and net sales. Nonetheless, the fast follower does not suffer a significant disadvantage on either market share or net sales. This provides even stronger suggestive evidence that the slow follower suffers not only in terms of the market share as shown in Table 4, but also on net sales.

### 6.5 New Drugs Diffusion

One wonders what the underlying mechanism that drives these results is. According to the theory on FMA, there are three main approaches in which a first mover (early entrant) can gain a superior advantage over followers: 1) technological leadership; 2) preemption of scarce resources; and 3) switching costs and buyer choice under uncertainty (Lieberman and Montgomery, 1988). In this paper, I choose to study those branded drugs that have an exclusive, patent-protected innovation and FDA-granted exclusivity. This reduces the possibility of technological leadership of any first movers in the pharmaceutical industry. In addition, branded drugs are generally distributed to a third party pharmacy, which therefore does not demand the firm's scarce resources. Moreover, Ostini et al. (2012) describe the prevalent existence of a prescribing inertia phenomenon in the pharmaceutical industry. These factors suggest that the mechanism driving the FMA in the pharmaceutical industry might be switching costs.

To explore the formation of switching costs in the pharmaceutical industry, I measure the time trend on aggregate sales in the therapeutic class. I show the results in Table 10, which represents the estimated results using Equation (6). This shows the speed of new drug diffusion, which indirectly represents how many

patients go from untreated to treated. After controlling for the effect of price and promotion, the estimated coefficient for the variable *Market Vintage* is positive and significant in the first three years of market opening. The result in Model 1 suggests that market sales increased by 10.0 percent when *Market Vintage* increased by one quarter in the first year of market opening. The result in Model 2 suggests that the market sales increased by 4.8 percent every quarter in the second year of market opening. Similarly, results in Model 3 suggest that market sales increased by 2.1 percent every quarter in the third year of market opening. Interestingly, the speed of drug diffusion decreases and becomes insignificant after three years of market opening.

[Table 10]

The results in Table 10 show that the first three years is the most important time period for new drug diffusion. Even though the market size continues to expand significantly in the first three years, the rate of market expansion decreases over time. This means that marginal patients taking the medication from this class is limited after two years of market opening.[21] Given the results shown in Section 6.2, slow followers have a disadvantage compared to the first mover while the fast follower does not. Together, these results suggest that as long as the followers enter the market within two years of the first mover, they can distort the dominating status of the first mover and possess a similar advantage. After three years of market opening, there is not a significant amount of new patients/doctors to reach a threshold such that a new drug has to compete with an existing one.

Due to new drug diffusion, there would be a limited number of new patients a drug could treat after a certain time, which creates an advantage for the first mover and fast follower. Interestingly, previous studies also suggest two years to be an important threshold for doctors to adopt new drugs (Garjón et al., 2012; Cha and Yu, 2014; Regnier and Ridley, 2015).[22] Together with the results in this section, all this evidence suggests that the formation of the early mover advantage is mainly due to the establishment of brand loyalty (switching cost). The complete formation of brand loyalty takes around two years, on average, in each therapeutic class. Thus, if a follower enters the market within two years of the market opening, it mitigates the FMA and performs as good as a first mover.

[21] To check the robustness of the definition of a fast follower, I also provide an estimation for different definitions of fast followers and show the results in Section 6.3.

[22] Garjón et al. (2012) find that the longest time doctors take to adopt a new drug is around 23 months. Regnier and Ridley (2015) also use two years as the threshold to estimate the market share with different entry orders. Another report analyzed the pharmaceutical industry and suggested that if the first mover's lead time over a follower is less than two years, the advantage could be ignored (Cha and Yu, 2014).

## 6.6 Order of Entry on Approximated Profit

### 6.6.1 Profit Approximation

Apart from the market share and net sales, profit is the most important measure of firm performance. Due to data limitation, I will approximate profit using the available data; so, these results should be viewed only as suggestive. Profit is constructed using the same strategy for net sales, with an approximation for the cost of R&D and follows the form:

$$\Pi_{it} = Real\ Sales\ Revenue_{it} - Total\ Promotion_{it} - Production\ Cost_{it} - R\&D\ Cost_{it},$$

where $\Pi_{it}$ represents the approximate profit for drug $i$ at time $t$. The R&D cost and the advertising to consumer cost are approximated using promotional expenditure. As mentioned above, the economic R&D cost accounts for some redundant measures; thus, I use the accounting cost of R&D to approximate the R&D cost in the profit calculation. The R&D cost is highly connected with the promotional expenditure, and the cost is set to be half of the promotional cost according to previous research (Gagnon and Lexchin, 2008). Every other part is the same as shown in Section 5.5 in the construction of net sales.

### 6.6.2 The Impact of Entry Speed on Profit

Using the approximate profit constructed using the method explained in Section 6.6.1, I present the summary of results in Table 11, showing the disadvantage of a follower on profit compared to a first mover. Column 2 represents the ratio between the approximated R&D cost and the promotional expenditure for the first mover. Column 3 represents the ratio between the approximated R&D cost and promotional expenditure for the follower (regardless of the fast follower or the slow follower).

Based on previous studies (Gagnon and Lexchin, 2008), the R&D expenditure equals about half of the promotional spending on average. Thus, I first set the cost of R&D equal to half of the promotional spending and estimate the OEE using Equation (5). Row A shows that the follower has a 40.7 percent lower profit compared to the first mover, on average. However, Row E shows that the fast follower could mitigate the first mover advantage not only on market share, but also on profit. Row I suggests a slow follower has a 45.4 percent lower profit compared to a first mover.

[Table 11]

### 6.6.3 The Summary of the Impact of Entry Speed on Profit

First movers face larger uncertainty compared to followers. Although the approval decision is determined by the FDA, a firm might try to accelerate the development process with additional capital input. The decision to accelerate the R&D process, however, is not costless. Thus, I artificially increase the R&D cost in the construction of profit for first movers to determine the extent to which a first mover in profit holds. These results are also presented in Table 11.

All followers' R&D cost (regardless of whether it is a fast follower or slow follower) is set to equal half of their promotional expenditure. For example, Row B shows that when a follower's R&D cost is the same as its promotional expenditure, it still enjoys a 40.7 percent higher profit compared to a first mover. Rows E to H show that a fast follower does not suffer on profit regardless of the first mover's R&D expense. Rows I to L show that as the first mover's R&D expenditure increases, a slow follower's disadvantage on profit decreases. In particular, the slow follower does not suffer on profit compared to a first mover when the first mover's R&D expenditure equals to 2.5 times its promotional spending. This potentially means that as long as a first mover's R&D cost is less than five times of the follower's R&D cost, it is able to enjoy a superior profit compared to a slow follower.

## 7 Implications and Discussions

This paper provides insights relating to the OEE for the pharmaceutical industry. One of the main findings in this paper suggests that being first is crucial in the pharmaceutical market: The first mover enjoys superior market share and profitability. More importantly, I find that if one cannot be a pioneer in the market, being a fast follower is also beneficial. A fast follower carries a similar level of market share and profitability compared to a first mover.

The phenomenon can be explained by the establishment of the switching cost by the early entrant. Switching costs cause inertia among doctors in prescribing drugs, which leads to the sustainable market share captured by the early entrant. I find that this premium time period for the fast follower is within two years of the first mover's introduction. This time window reflects the diffusion and the adoption of new drugs to near capacity.[23] This is consistent with the theoretical argument presented by Suarez et al. (2015) that the

[23] On average, the market reaches approximately 80 percent of its size in the first two years, and this allows the first mover and fast followers to influence most doctors.

best strategy for followers is to enter the market before it peaks. Moreover, practitioners (Cha and Yu, 2014) claim that the two-year time window is critical in the pharmaceutical industry. This finding also coincides with the method used in previous research to explore predicted market shares (Regnier and Ridley, 2015). In reality, Merck discontinued two Hepatitis-C drugs in 2018 from its R&D pipeline because the market had already peaked.

These findings help managers better predict the return on investment in the ex-ante stage, as R&D costs are relatively high during a drug's development (the clinical trial stage costs roughly 70 percent of the total R&D cost), and the clinical trial stage lasts for 7-12 years (DiMasi et al., 2016). First, while one may think the first drug has to go through a restrictive review process, the FDA actually has beneficial policies for novel drugs, which suggests being first is beneficial regardless.[24] Second, if the R&D process for a drug is in the mid or late stage (e.g., Phase II or III), the optimal strategy for a follower is to get to the market as quickly as possible (preferably within two years of the market opening). Third, if the market is already established and the firm is still at the early R&D stage of developing a drug (Phase I or earlier), it may as well reroute the resources to other classes of drugs that may be more profitable.

Furthermore, this study provides suggestions for whether to start the R&D oneself or acquire a drug in its late stage of clinical trials. Based on the findings of this study, a fast follower is usually in Phase III of clinical trials when the first-in-class drug is approved.[25] This fact allows us to potentially identify fast followers and help firms better predict the market performance of a drug. Therefore, if a firm wants to avoid failure in clinical trials and enjoy an early entrant advantage, it may as well acquire a drug in its late stage of clinical trials, which has a high probability to be a fast follower.[26]

As for policymakers, the obvious insight from this study is that an early entrant could lock-in consumers, leading to prescription inertia, which is not ideal for the healthcare system for two reasons. First, the early entrant locks-in of the consumers prevent them from accessing potentially better treatments provided by slow followers. Second, a first mover could gain excess market power if no fast followers enter the market. Two possible suggestions for resolving these issues are viable. First, the policymaker may want to incen-

[24] According to the statistics from the Center for Drug Evaluation and Research (CDER), 95 percent of the novel drugs (first-in-class drugs are a subset of novel drugs) were approved in 2016 and 73 percent of these novel drugs benefited from at least one of the FDA's programs expediting drug development and review (e.g., Fast Track designation, Breakthrough Therapy designation, priority review designation, and accelerated approval).

[25] According to the FDA, the success rate from Phase III to approval is around 60 percent, while the success rate from Phase I to approval is around 6 percent.

[26] Among all mergers and acquisitions in the pre-approval stage in the pharmaceutical market, the events in Phases II and III constitute around 65 percent in 2015 (Thomson Reuters).

tivize more entries within the time window without lowering the quality standard in order to increase the competition level and choices in the market. Such a policy would provide more choices for the consumer in the first place. Second, future policy may need to aim at decreasing the switching cost by consumers (provide more information regarding the efficacy and safety of the new drug as well as conduct more comparison studies between new and old drugs), which also creates a more competitive market.

This paper also points out a potential weakness of the entry by followers. Since market size does not significantly increase after three years of the market opening, it suggests that most untreated patients have received treatment.[27] According to the data of this study, many follow-on drugs enter after generics, which is unlikely to increase the price competition of the market.[28] Thus, the clinical benefit of additional follow-on drugs requires future research.[29]

# 8 Conclusion

This paper quantifies the OEE in the pharmaceutical industry. On average, over the first five years, I find that the first mover enjoys a significantly higher market share (23 percentage points higher) than followers. This is not surprising and is consistent with previous findings (e.g., Golder and Tellis, 1993). In addition to the advantage gained by the early entrants on market share, first movers and fast followers also enjoy an advantage on profitability compared to the late movers. The estimation results suggest that first movers have a 45 percent higher net sales compared to slow followers. This advantage on market share suggests that an early entrant constitutes a higher proportion of a particular drug's usage for all consumers. The advantage on net sales reconfirms that the early entrant enjoys a better return. Together, these two parts demonstrate that the early entrant (both the first mover and the fast follower) has a competitive advantage compared to the slow follower.

More importantly, using the differential timing of entry, I find that fast followers, which access the market within two years of the market opening, do not suffer any significant disadvantage over the first mover in terms of market share or profit. Slow followers, which access the market more than two years after

[27] Table 10 suggests that market sales do not increase significantly after the 12th quarter (third year) of the market opening, on average.

[28] This is also suggested by previous studies that the followers provide more differentiated products than better clinical benefits and more price competition (Lu and Comanor, 1998; Ekelund and Persson, 2003).

[29] Note that the FDA sometimes uses the existing drugs on the market, like in Oncology market, as active comparators to test the effectiveness of a new drug, and determines whether it should be approved. This may even suggest that if the quality of late movers is superior than first movers, then the pure FMA can be even stronger. Nonetheless, the FDA compares only the new drug with the placebo effect in most other therapeutic classes.

the market opening, bear a disadvantage in both the market share and profit. Two reasons can lead to such a phenomenon. First, the first mover and fast follower are able to capture most doctors before the entrance of a slow follower. Second, the first mover and fast follower could attract consumers more easily through market strategies, such as promotion. In addition, I find that the disadvantage on market share increases with the time elapsed from the introduction of the first drug into the market.

## Reference


Agarwal, R. and Gort, M., 2001. First-Mover Advantage and the Speed of Competitive Entry, 1887–1986. *The Journal of Law and Economics*, 44(1):161–177.

Andrade, L. F., Sermet, C., and Pichetti, S., 2016. Entry Time Effects and Follow-on Drug Competition. *The European Journal of Health Economics*, 17(1):45–60.

Berndt, E. R., Bui, L., Reiley, D. R., and Urban, G. L., 1995. Information, Marketing, and Pricing in the US Antiulcer Drug Market. *The American Economic Review*, 85(2):100–105.

Berndt, E. R., Bui, L. T., Lucking-Reiley, D. H., and Urban, G. L., 1996. *The Roles of Marketing, Product Quality, and Price Competition in the Growth and Composition of the US Antiulcer Drug Industry*. University of Chicago Press.

Blume-Kohout, M. E. and Sood, N., 2013. Market Size and Innovation: Effects of Medicare Part D on Pharmaceutical Research and Development. *Journal of Public Economics*, 97:327–336.

Bond, R. S. and Lean, D. F., 1977. *Sales, Promotion, and Product Differentiation in Two Prescription Drug Markets*. Staff Report to the Federal Trade Commission.

Boulding, W. and Christen, M., 2003. Sustainable Pioneering Advantage? Profit Implications of Market Entry Order. *Marketing Science*, 22(3):371–392.

Brekke, K. R. and Kuhn, M., 2006. Direct to Consumer Advertising in Pharmaceutical Markets. *Journal of Health Economics*, 25(1):102–130.

Briesacher, B. A., Soumerai, S. B., Zhang, F., Toh, S., Andrade, S. E., Wagner, J. L., Shoaibi, A., and Gurwitz, J. H., 2013. A Critical Review of Methods to Evaluate the Impact of FDA Regulatory Actions. *Pharmacoepidemiology and Drug Safety*, 22(9):986–994.

Bunniran, S., McCaffrey, D. J., Bentley, J. P., and Bouldin, A. S., 2009. Pharmaceutical Product Withdrawal: Attributions of Blame and Its Impact on Trust. *Research in Social and Administrative Pharmacy*, 5(3):262–273.

Burnham, T. A., Frels, J. K., and Mahajan, V., 2003. Consumer Switching Costs: A Typology, Antecedents, and Consequences. *Journal of the Academy of Marketing Science*, 31(2):109–126.

Centor, R., Marchetti, P., Donnell, R., and Poses, R., 2006. How Can Physicians Stay Current on Prescription Drugs? https://www.medscape.com/viewarticle/543641.

Cha, M. and Yu, F., 2014. Pharmas First-to-Market Advantage. https://www.

mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/pharmas-first-to-market-advantage.

Chatterjee, C., Higgins, M., and Yan, X., 2018. Effects of Adverse Regulatory Events: Evidence from Drug Relabeling. *Working Paper*.

Cheah, E. T., Chan, W. L., and Chieng, C. L. L., 2007. The Corporate Social Responsibility of Pharmaceutical Product Recalls: an Empirical Examination of US and UK Markets. *Journal of Business Ethics*, 76(4):427–449.

Cohen, M. A., Eliasberg, J., and Ho, T.-H., 1996. New Product Development: the Performance and Time-to-Market Tradeoff. *Management Science*, 42(2):173–186.

Cooper, L. G., 1993. Market-Share Models. *Handbooks in Operations Research and Management Science*, 5:259–314.

Coscelli, A. and Shum, M., 2004. An Empirical Model of Learning and Patient Spillovers in New Drug Entry. *Journal of Econometrics*, 122(2):213–246.

DiMasi, J. A., Grabowski, H. G., and Hansen, R. W., 2016. Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs. *Journal of Health Economics*, 47:20–33.

DiMasi, J. A. and Paquette, C., 2004. The Economics of Follow-on Drug Research and Development. *Pharmacoeconomics*, 22(2):1–14.

Dorsey, E. R., Rabbani, A., Gallagher, S. A., Conti, R. M., and Alexander, G. C., 2010. Impact of FDA Black Box Advisory on Antipsychotic Medication Use. *Archives of Internal Medicine*, 170(1):96–103.

Dranove, D. and Olsen, C., 1994. The Economic Side Effects of Dangerous Drug Announcements. *The Journal of Law and Economics*, 37(2):323–348.

Dusetzina, S. B., Higashi, A. S., Dorsey, E. R., Conti, R., Huskamp, H. A., Zhu, S., Garfield, C. F., and Alexander, G. C., 2012. Impact of FDA Drug Risk Communications on Health Care Utilization and Health Behaviors: A Systematic Review. *Medical Care*, 50(6):466.

Dybdahl, T., Andersen, M., Kragstrup, J., Kristiansen, I. S., and Søndergaard, J., 2005. General Practitionersâ Adoption of New Drugs and Previous Prescribing of Drugs Belonging to the Same Therapeutic Class: A Pharmacoepidemiological Study. *British Journal of Clinical Pharmacology*, 60(5):526–533.

Ekelund, M. and Persson, B., 2003. Pharmaceutical Pricing in a Regulated Market. *the Review of Economics and Statistics*, 85(2):298–306.

Freedman, S., Kearney, M., and Lederman, M., 2012. Product Recalls, Imperfect Information, and Spillover

Effects: Lessons from the Consumer Response to the 2007 Toy Recalls. *Review of Economics and Statistics*, 94(2):499–516.

Furberg, C. D., Furberg, B. D., and Sasich, L. D., 2010. *Knowing Your Medications*. Potata Inc.

Gagnon, M.-A. and Lexchin, J., 2008. The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States. *PLOS Medicine*, 5(1):1.

Garjón, F. J., Azparren, A., Vergara, I., Azaola, B., and Loayssa, J. R., 2012. Adoption of New Drugs by Physicians: A Survival Analysis. *BMC Health Services Research*, 12(1):56.

Golder, P. N. and Tellis, G. J., 1993. Pioneer Advantage: Marketing Logic or Marketing Legend? *Journal of Marketing Research*, 158–170.

Grabowski, H., 2002. Patents, Innovation and Access to New Pharmaceuticals. *Journal of International Economic Law*, 5(4):849–860.

Grabowski, H. G. and Vernon, J. M., 1992. Brand Loyalty, Entry, and Price Competition in Pharmaceuticals after the 1984 Drug Act. *The Journal of Law and Economics*, 35(2):331–350.

Heilman, R., 1995. Drug Development History," Overview," and What are GCPs? *Quality assurance (San Diego, Calif.)*, 4(1):75–79.

Hollis, A., 2004. Me-Too Drugs: is There a Problem. *WHO Report*.

Huff, L. C. and Robinson, W. T., 1994. The Impact of Leadtime and Years of Competitive Rivalry on Pioneer Market Share Advantages. *Management Science*, 40(10):1370–1377.

Hurwitz, M. A. and Caves, R. E., 1988. Persuasion or Information? Promotion and the Shares of Brand Name and Generic Pharmaceuticals. *The Journal of Law and Economics*, 31(2):299–320.

Huskamp, H. A., O'Malley, A. J., Horvitz-Lennon, M., Taub, A. L., Berndt, E. R., and Donohue, J. M., 2013. How Quickly Do Physicians Adopt New Drugs? The Case of Second-Generation Antipsychotics. *Psychiatric Services*, 64(4):324–330.

Kales, H. C., Zivin, K., Kim, H. M., Valenstein, M., Chiang, C., Ignacio, R. V., Ganoczy, D., Cunningham, F., Schneider, L. S., and Blow, F. C., 2011. Trends in Antipsychotic Use in Dementia 1999-2007. *Archives of General Psychiatry*, 68(2):190–197.

Kalyanaram, G., 2008. The Order of Entry Effect in Prescription (Rx) and Over-The-Counter (OTC) Pharmaceutical Drugs. *International Journal of Pharmaceutical and Healthcare Marketing*, 2(1):35–46.

Kalyanaram, G., Robinson, W. T., and Urban, G. L., 1995. Order of market entry: Established Empirical Generalizations, Emerging Empirical Generalizations, and Future Research. *Marketing Science*,

14(3):G212–G221.

Lieberman, M. B. and Montgomery, D. B., 1988. First-mover Advantages. *Strategic Management Journal*, 9(S1):41–58.

Lieberman, M. B. and Montgomery, D. B., 1998. First-Mover (Dis) Advantages: Retrospective and Link With the Resource-Based View. *Strategic Management Journal*, 1111–1125.

Lilien, G. L. and Yoon, E., 1990. The Timing of Competitive Market Entry: An Exploratory Study of New Industrial Products. *Management Science*, 36(5):568–585.

Lu, C. Y., Zhang, F., Lakoma, M. D., Madden, J. M., Rusinak, D., Penfold, R. B., Simon, G., Ahmedani, B. K., Clarke, G., Hunkeler, E. M., et al., 2014. Changes in Antidepressant Use by Young People and Suicidal Behavior after FDA Warnings and Media Coverage: Quasi-experimental Study. *British Medical Journal*, 348:g3596.

Lu, Z. J. and Comanor, W. S., 1998. Strategic Pricing of New Pharmaceuticals. *The Review of Economics and Statistics*, 80(1):108–118.

Narayanan, S., Desiraju, R., and Chintagunta, P. K., 2004. Return on Investment Implications for Pharmaceutical Promotional Expenditures: the Role of Marketing-Mix Interactions. *Journal of Marketing*, 68(4):90–105.

Organization, W. H. et al., 1996. *Guidelines for ATC Classification and DDD Assignment*. World Health Organization.

Ostini, R., Hegney, D., Jackson, C., and Tett, S. E., 2012. Knowing How to Stop: Ceasing Prescribing when the Medicine is No Longer Required. *Journal of Managed Care Pharmacy*, 18(1):68–72.

Papke, L. E. and Wooldridge, J. M., 2008. Panel Data Methods for Fractional Response Variables with an Application to Test Pass Rates. *Journal of Econometrics*, 145(1):121–133.

Regnier, S. A. and Ridley, D. B., 2015. Forecasting Market Share in the US Pharmaceutical Market.

Rizzo, J. A., 1999. Advertising and Competition in the Ethical Pharmaceutical Industry: The Case of Antihypertensive Drugs. *The Journal of Law and Economics*, 42(1):89–116.

Roberts, P. W., 1999. Product Innovation, Product-Market Competition and Persistent Profitability in the US Pharmaceutical Industry. *Strategic Management Journal*, 655–670.

Serra-Sastre, V. and McGuire, A., 2013. Information and Diffusion of New Prescription Drugs. *Applied Economics*, 45(15):2049–2057.

Shah, N. D., Montori, V. M., Krumholz, H. M., Tu, K., Alexander, G. C., and Jackevicius, C. A., 2010.

Responding to an FDA WarningâGeographic Variation in the Use of Rosiglitazone. *New England Journal of Medicine*, 363(22):2081–2084.

Shenkar, O., 2010b. *Copycats: How Smart Companies Use Imitation to Gain a Strategic Edge*. Harvard Business Press.

Smalley, W., Shatin, D., Wysowski, D. K., Gurwitz, J., Andrade, S. E., Goodman, M., Chan, K. A., Platt, R., Schech, S. D., and Ray, W. A., 2000. Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action. *Journal of the American Medical Association*, 284(23):3036–3039.

Sridhar, S., Mantrala, M. K., and Albers, S., 2014. *Pharmaceutical Detailing Elasticities: A Meta-Analysis*. Springer.

Suarez, F. F., Grodal, S., and Gotsopoulos, A., 2015. Perfect Timing? Dominant Category, Dominant Design, and the Window of Opportunity for Firm Entry. *Strategic Management Journal*, 36(3):437–448.

Szymanski, D. M., Troy, L. C., and Bharadwaj, S. G., 1995. Order of Entry and Business Performance: An Empirical Synthesis and Reexamination. *The Journal of Marketing*, 17–33.

Tversky, A. and Kahneman, D., 1992. Advances in Prospect Theory: Cumulative Representation of Uncertainty. *Journal of Risk and Uncertainty*, 5(4):297–323.

Van Heerde, H., Helsen, K., and Dekimpe, M. G., 2007. The Impact of a Product-Harm Crisis on Marketing Effectiveness. *Marketing Science*, 26(2):230–245.

Villas-Boas, J. M., 2004. Consumer Learning, Brand Loyalty, and Competition. *Marketing Science*, 23(1):134–145.

Wilkes, M. S., Bell, R. A., and Kravitz, R. L., 2000. Direct-to-Consumer Prescription Drug Advertising: Trends, Impact, and Implications. *Health Affairs*, 19(2):110–128.

Wilkinson, J. J., Force, R. W., and Cady, P. S., 2004. Impact of Safety Warnings on Drug Utilization: Marketplace Life Span of Cisapride and Troglitazone. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 24(8):978–986.

Wooldridge, J. M., 2015. Control function methods in applied econometrics. *Journal of Human Resources*, 50(2):420–445.

Zhao, Y., Zhao, Y., and Helsen, K., 2011. Consumer Learning in a Turbulent Market Environment: Modeling Consumer Choice Dynamics after a Product-Harm Crisis. *Journal of Marketing Research*, 48(2):255–267.

Figure 1: Market Share of Brand Drugs

This graph represents the average of the market share of each brand drug based on their entry timing. The first mover is the first drug introduced in each ATC 4-digit class. The follower accesses the market after the first mover. The market share is calculated based on the sales quantity measured in a standardized unit. The Y-axis represents the market share. The X-axis represents the quarters since market opening. Drugs are limited to those introduced within the first five years of market opening.

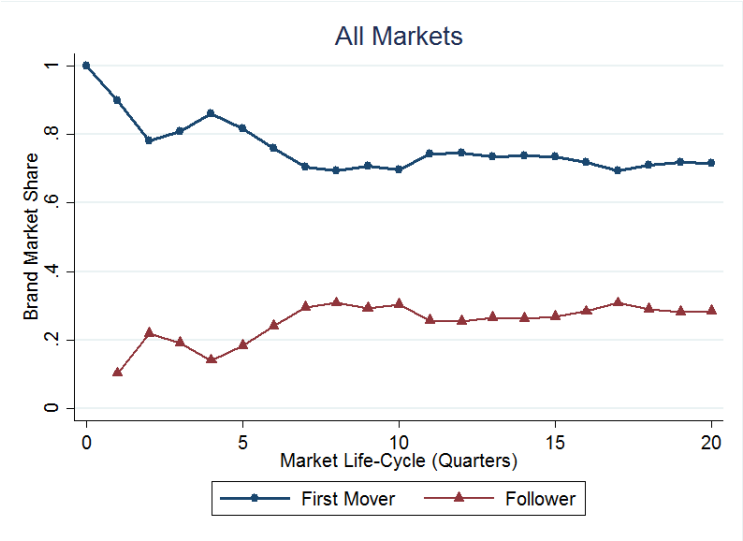


Figure 2: Entry Timing Distribution

This graph represents the entry timing frequency. The Y-axis represents the fraction of brand drugs introduced in each quarter. The X-axis represents the timing of entry of a drug since market opening, which is measured in quarters. Drugs are limited to all of the followers and exclude the first mover. Fast followers are defined as the drugs introduced within eight quarters of the market opening. Slow followers are defined as every other drug besides first mover and the fast followers.

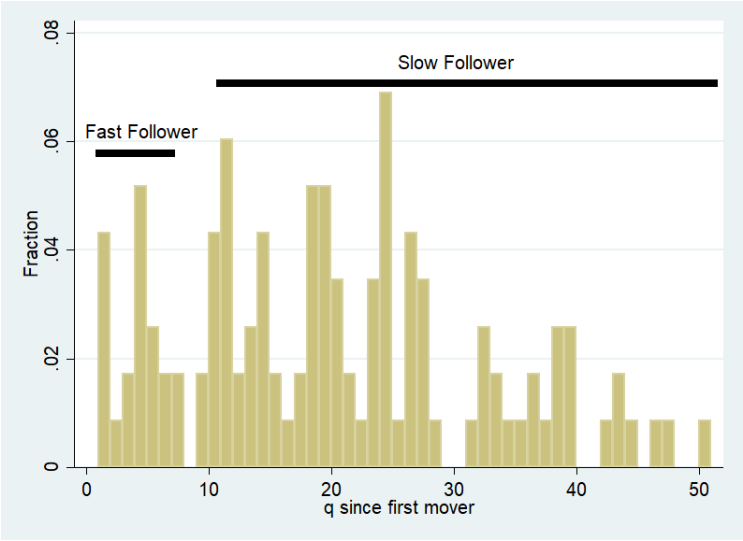

Figure 3: Market Share of Brand Drugs in Specific Markets

This graph represents the average market share of each branded drug based on their entry timing. This only represents the markets with a fast follower, and only some markets have a fast follower (this includes a total of 18 markets). The first mover is the first drug introduced in each ATC 4-digit class. The fast follower is the drug introduced within two years (eight quarters including the eighth quarter) after the first drug's introduction. The slow follower accesses the market at least two years after the market opening (excluding the eighth quarter). The market share is calculated based on the sales quantity measured in a standardized unit. The Y-axis represents the market share of branded drugs. The X-axis represents the quarters since the market opening.

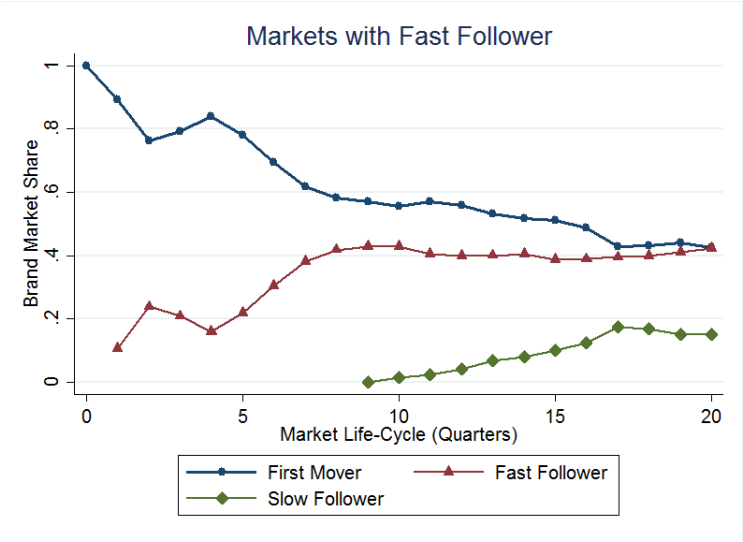


Figure 4: Net Sales of Brand Drugs

This figure represents the net sales in the logarithm of brand drugs based on their entry timing. The first mover is the first drug introduced in each ATC 4-digit class. The follower is any drug entering the market after the first mover. The Y-axis represents the logarithm of the net sales measured in millions of U.S. dollars. The X-axis represents the quarters since the market opening. This figure represents all markets.

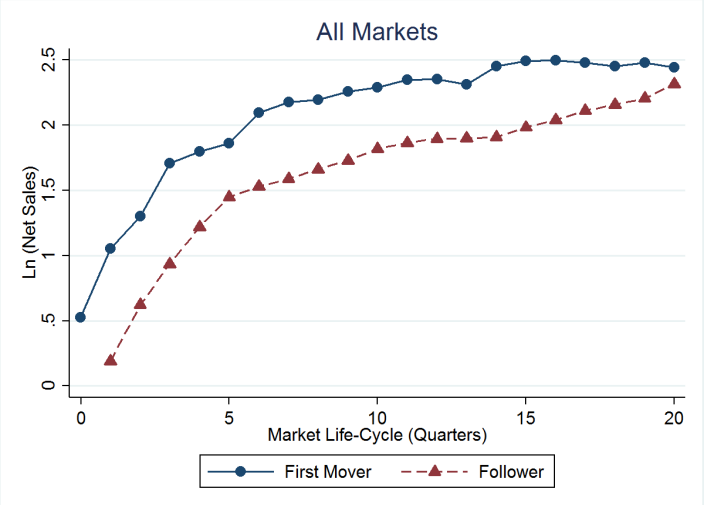

Figure 5: Average Market Sales

This graph represents the average market size after the market opening. The Y-axis represents the total market sales measured in millions of standardized units. The X-axis represents the time (quarter) since the market opening. Data is restricted to the first eight years (32 quarters) of the market opening.

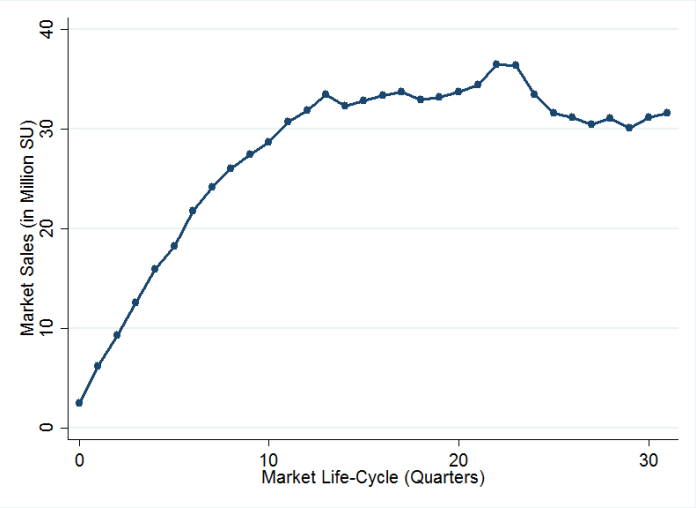


Table 1: Literature of OEE in the Pharmaceutical Industry

These four studies focus on the OEE and are closely related to my study. The column "Time Horizon" represents the time period in which the study's estimation was based on. The column "Estimation Time Period" represents the exact time period used in the estimation regarding the drug's life-cycle. The column "Therapeutic Class" describes the drug class used in the estimation. The main finding of each study is summarized in the row labeled "Finding."

| Literature | Time Horizon | Estimation Time Period | Therapeutic Class |
|---|---|---|---|
| Kalyanaram (2008) | 1998-1999 | 2-year period after 15 years (or 1 year) of FDA approval | RX-SSRI, PPI, Antihistamines; OTC-anti-ulcer, smoking-cessation |
| Finding | Follower's market share range between 37%-73% of the first mover. | | |
| Berndt et al. (1996) | 1977- 1993 | 16 Years since market opening | Anti-ulcer drug class |
| Finding | $\frac{Follower's\ Market\ Share}{Pioneer\ Market\ Share} = \frac{1}{\sqrt{Follower's\ Order}}$ | | |
| Hurwitz and Caves (1988) | 1978-1983 | Various years since patent expiration | 29 drug markets |
| Finding | Pioneer's average market share was around 63%. | | |
| Bond and Lean (1977) | 1956-1971 | 15 Years since market opening | Two therapeutic classes |
| Finding | Both first entrants have the largest market share after 10 years. | | |

Table 2: Summary Statistics

This table provides summary statistics for variables used in this paper. Market share is constructed by sales quantity over the entire market sales of all branded drugs. *Sales quantity* is measured in millions of standardized units. *Net sales* is measured in real 2009 U.S. dollars (million). *Price* is in real 2009 U.S. dollars per standardized unit. *Promotion* includes detailing, journal promotion, and mail promotion (in million USD). *DTCA* constitutes all DTCA for each drug. *Side effect* is the number of commonly-observed side effects for the drug. *Major, Moderate*, and *Minor Interactions* represent the number of major, moderate, and minor drug interactions of the drug. *Market Sales Quantity* is the sum of sales quantity of each ATC 4-digit market measured in millions of standardized units. *Market Price* is the average price for branded drugs in each ATC 4-digit market measured in real 2009 U.S. dollars. *Market Promotion* is the sum of all promotional expenditure (in million USD). *Market DTCA* constitutes all DTCA expenditure in a ATC 4-digit market. The *Market Side Effect* is the number of average commonly-observed side effects for drugs in a market. The observations in this table present the total sample from 1997 to 2011 for the first five years after each drug's introduction.

| Variables | Obs. | Mean | Median | Std. Dev. | Min | Max |
|---|---|---|---|---|---|---|
| Market Share | 3,064 | 0.57 | 0.66 | 0.41 | 0.00 | 1.00 |
| Sales Quantity | 3,064 | 17.15 | 1.13 | 43.60 | 0.00 | 392.35 |
| Net Sales | 3,064 | 40.68 | 6.88 | 99.40 | 0.00 | 989.25 |
| Follower | 3,064 | 0.50 | 0.00 | 0.50 | 0.00 | 1.00 |
| Fast Follower | 3,064 | 0.11 | 0.00 | 0.31 | 0.00 | 1.00 |
| Slow Follower | 3,064 | 0.39 | 0.00 | 0.49 | 0.00 | 1.00 |
| Entry Time | 3,064 | 4.09 | 0.00 | 6.46 | 0.00 | 20.00 |
| Price | 3,064 | 282.02 | 19.32 | 756.67 | 0.16 | 9960.00 |
| Promotion | 3,064 | 3.72 | 0.61 | 7.01 | 0.00 | 53.39 |
| Lagged Promotion Stock | 3,064 | 5.16 | 0.74 | 10.64 | 0.00 | 94.62 |
| DTCA | 3,064 | 2.71 | 0.00 | 8.85 | 0.00 | 93.92 |
| Lagged DTCA Stock | 3,064 | 2.28 | 0.00 | 7.57 | 0.00 | 72.79 |
| Side Effect | 3,064 | 10.89 | 4.00 | 15.21 | 0.00 | 76.00 |
| Major Interaction | 3,064 | 38.86 | 5.00 | 74.17 | 0.00 | 416.00 |
| Moderate Interaction | 3,064 | 280.06 | 172.00 | 274.76 | 0.00 | 918.00 |
| Minor Interaction | 3,064 | 29.14 | 8.00 | 39.60 | 0.00 | 172.00 |
| Vintage | 3,064 | 9.29 | 9.00 | 5.80 | 0.00 | 20.00 |
| Elapsed Time | 3,064 | 9.31 | 0.00 | 12.11 | 0.00 | 51.00 |
| Brands | 3,064 | 2.71 | 2.00 | 2.27 | 1.00 | 11.00 |
| Market Sales Quantity | 2,891 | 26.02 | 1.83 | 54.70 | 0.00 | 596.66 |
| Market Price | 2,891 | 196.81 | 12.09 | 508.40 | 0.15 | 4199.02 |
| Market Promotion | 2,891 | 4.85 | 0.80 | 9.89 | 0.00 | 103.94 |
| Lagged Market Promotion Stock | 2,891 | 7.12 | 1.10 | 14.73 | 0.00 | 139.86 |
| Market DTCA | 2,891 | 4407.00 | 0.00 | 13.73 | 0.00 | 140.94 |
| Lagged Market DTCA Stock | 2,891 | 6299.96 | 0.00 | 19.04 | 0.00 | 182.21 |
| Market Side Effect | 2,891 | 8.05 | 6.00 | 8.84 | 0.00 | 38.00 |
| Market Major Interaction | 2,891 | 44.15 | 10.00 | 70.10 | 0.00 | 339.00 |
| Market Moderate Interaction | 2,891 | 229.67 | 166.00 | 247.54 | 0.00 | 918.00 |
| Market Minor Interaction | 2,891 | 23.97 | 7.33 | 34.42 | 0.00 | 172.00 |
| Market Vintage | 2,891 | 22.45 | 21.00 | 14.73 | 0.00 | 55.00 |

Table 3: Speed of Entry

This table shows the average speed of each entrant. The header represents the entry position. The first row shows the time (in quarters) after the first mover, fast follower, and slow follower enter into the market (market opening). The second row represents the number of drugs that are introduced into the market under each speed of entry. The last row represents the average time (in quarters) since the market opening for each entry position. There are 97 unique ATC 4-digit markets in the sample. Data is restricted to the drugs introduced in the first five years for each market.

| Position | First Mover | Fast Follower | Slow Follower |
|---|---|---|---|
| Time since Market Opening (in Quarters) | 0 | 1-8 | 9-20 |
| Number of Entrants | 97 | 21 | 45 |
| Average Speed (Quarters since Market Opening) | 0 | 3.81 | 14.67 |

Table 4: Market Sales Over Time

This table shows the average sales of a market at a specific time period. The header shows the market in three types: 1) all markets; 2) markets with fast followers; and 3) markets without fast followers. Row A shows the number of markets in the sample. Row B represents average market sales at the eighth quarter (two years) since the market opening. Row C represents average market sales between the ninth quarter and twentieth quarter since the market opening. Row D represents the number in row B divided by the number in row C.

| | Market | All Markets | Markets with FF | Markets without FF |
|---|---|---|---|---|
| A | Number of Markets | 97 | 18 | 79 |
| B | Average Market Sales of 8 Quarters Since Market Opening | 26.06 | 48.81 | 19.82 |
| C | Average Market Sales of 9-30 Quarters Since Market Opening | 32.28 | 60.24 | 24.73 |
| D | Percentage to Maturity | 80.73% | 81.03% | 80.15% |

Table 5: The Order of Entry Effect on Market Share

Model 1 presents the results from Equation (1). Model 2 presents the results where price is exogenized. All models are estimated using the fractional Logit method. The constant is included in all regressions but excluded from the tables. Controls include *Side Effect, Major Interaction, Moderate Interaction, Minor Interaction, Vintage,* and *Brands*. Errors are clustered at the market level and are in parentheses. P-value: $^{*}0.10,^{**}0.05,^{***}0.01$. Data is restricted to the drug introduced in the first five years of market opening. The marginal effects for key variables are reported at the bottom of the table.

| DV = Market Share | Model 1 | Model 2 |
|---|---|---|
| Follower | -1.726*** | -1.699*** |
| | (0.370) | (0.372) |
| ln (Price) | -0.662* | -1.240* |
| | (0.378) | (0.650) |
| ln (Lagged Promotion Stock) | 0.112*** | 0.115*** |
| | (0.040) | (0.042) |
| ln (Lagged DTCA Stock) | 0.108** | 0.105* |
| | (0.054) | (0.055) |
| Controls | Y | Y |
| Market Fixed Effect | Y | Y |
| N | 3,064 | 3,064 |
| pseudo $R^2$ | 0.468 | 0.469 |
| **Marginal Effects: Follower** | **-0.239** | **-0.234** |

Table 6: The Order of Entry Effect on Market Share by Timing of Entry

Model 1 presents estimates for Equation (3). Model 1 is estimated using the fractional Logit method. Price is also exogenized. The first mover is omitted. The constant is included in all regressions but excluded from the tables. Controls include *Side Effect, Major Interaction, Moderate Interaction, Minor Interaction, Vintage,* and *Brands*. Errors are clustered at the market level and are in parentheses. P-value: $^{*}0.10, ^{**}0.05, ^{***}0.01$. Data is restricted to the drug introduced in the first five years of market opening. The marginal effects for key variables are reported on the right column of the table.

| DV = Market Share<br>Time since Market Opening | Model 1 | Marginal Effects |
|---|---|---|
| 1 Quarter | -0.915 | |
| | (0.662) | |
| 2 Quarters | -0.654 | |
| | (1.348) | |
| 3 Quarters | -1.555** | **-0.172** |
| | (0.645) | |
| 4 Quarters | -1.170 | |
| | (1.446) | |
| 5 Quarters | 0.085 | |
| | (1.570) | |
| 6 Quarters | -2.026 | |
| | (1.376) | |
| 7 Quarters | -0.115 | |
| | (0.755) | |
| 9 Quarters | -0.885** | **-0.098** |
| | (0.420) | |
| 10 Quarters | -2.796** | **-0.286** |
| | (1.134) | |
| 11 Quarters | -2.179*** | **-0.234** |
| | (0.503) | |
| 12 Quarters | -3.133*** | **-0.310** |
| | (0.630) | |
| 13 Quarters | -2.873*** | **-0.291** |
| | (0.878) | |
| 14 Quarters | -2.343*** | **-0.249** |
| | (0.450) | |
| 15 Quarters | -10.739*** | **-0.436** |
| | (0.788) | |
| 16 Quarters | -2.389* | **-0.253** |
| | (1.260) | |
| 17 Quarters | -1.954** | **-0.213** |
| | (0.882) | |
| 18 Quarters | -6.486*** | **-0.419** |
| | (1.355) | |
| 19 Quarters | -4.127*** | **-0.363** |
| | (1.510) | |
| 20 Quarters | -4.076*** | **-0.360** |
| | (0.649) | |
| ln (Price) | -1.085*** | |
| | (0.414) | |
| ln (Lagged Promotion Stock) | 0.116*** | |
| | (0.043) | |
| ln (Lagged DTCA Stock) | 0.088 | |
| | (0.056) | |
| Controls | Y | |
| Market Fixed Effect | Y | |
| N | 3,064 | |
| pseudo $R^2$ | 0.515 | |

Table 7: The Order of Entry Effect on Market Share by Speed to Market

Model 1 presents the estimates for Equation (2) using three defined groups (first mover-omitted category, fast follower, and slow follower). Price is also exogenized. All models are estimated using the fractional Logit method. The constant is included in all regressions but excluded from the tables. Controls include *Side Effect, Major Interaction, Moderate Interaction, Minor Interaction, Vintage,* and *Brands*. Errors are clustered at the market level and are in parentheses. P-value: $^{*}0.10,^{**}0.05,^{***}0.01$. Data is restricted to the drug introduced in the first five years of market opening. The marginal effects for key variables are reported at the bottom of the table.

| DV = Market Share | Model 1 |
|---|---|
| Fast Follower | -1.064 |
| | (0.778) |
| Slow Follower | -2.363*** |
| | (0.459) |
| ln (Price) | -0.680** |
| | (0.327) |
| ln (Lagged Promotion Stock) | 0.107*** |
| | (0.038) |
| ln (Lagged DTCA Stock) | 0.109* |
| | (0.058) |
| Controls | Y |
| Market Fixed Effect | Y |
| N | 3,064 |
| pseudo $R^2$ | 0.477 |
| **Marginal Effects:** | |
| **Slow Follower** | -0.321 |

Table 8: The Speed of Entry on Market Share

Model 1 presents the results from Equation (4) for the first mover and all followers. Model 2 presents the estimation for the first mover and fast followers. Model 3 presents the estimation for the first mover and slow followers. Price is also exogenized. All models are estimated using the fractional Logit method. The constant is included in all regressions but excluded from the tables. Controls include *Side Effect, Major Interaction, Moderate Interaction, Minor Interaction, Vintage,* and *Brands*. Errors are clustered at the market level and are in parentheses. P-value: $^{*}0.10, ^{**}0.05, ^{***}0.01$. Data is restricted to the drug introduced in the first five years of market opening. The marginal effects for key variables are reported at the bottom of the table.

| DV = Market Share | Model 1<br>Follower | Model 2<br>Fast Follower | Model 3<br>Slow Follower |
|---|---|---|---|
| Elapsed Time | -0.100*** | -0.273 | -0.106*** |
| | (0.026) | (0.253) | (0.027) |
| ln (Price) | -0.760** | -1.066* | -1.311*** |
| | (0.369) | (0.581) | (0.327) |
| ln (Lagged Promotion Stock) | 0.071* | 0.103 | 0.034 |
| | (0.041) | (0.063) | (0.038) |
| ln (Lagged DTCA Stock) | 0.131** | 0.092* | 0.130** |
| | (0.055) | (0.054) | (0.062) |
| Controls | Y | Y | Y |
| Market Fixed Effect | Y | Y | Y |
| N | 3,064 | 1,831 | 2,771 |
| pseudo $R^2$ | 0.454 | 0.483 | 0.518 |
| **Marginal Effects:**<br>**Elapsed Time** | **-0.012** | | **-0.010** |

Table 9: The Order of Entry Effect on Net Sales

Models 1 and 2 present the same specification using Equation (5). Model 1 represents the OEE on net sales based on two groups of firms: first mover and follower. Model 2 presents the results of the OEE based on three groups of firms: first mover, fast follower, and slow follower. All models are estimated using the OLS method. The constant is included in all regressions but excluded from the tables. Controls include *Side Effect, Major Interaction, Moderate Interaction, Minor Interaction, Vintage,* and *Brands*. Errors are clustered at the market level and are in parentheses. P-value: $^{*}0.10,^{**}0.05,^{***}0.01$. Data is restricted to the drug introduced in the first five years of market opening.

| DV = ln (Net Sales) | Model 1 | Model 2 |
|---|---|---|
| Follower | -0.371** | |
| | (0.175) | |
| Fast Follower | | -0.206 |
| | | (0.367) |
| Slow Follower | | -0.417** |
| | | (0.176) |
| Controls | Y | Y |
| Market Fixed Effect | Y | Y |
| N | 3,064 | 3,064 |
| Adjusted $R^2$ | 0.704 | 0.705 |

Table 10: The Effect of Vintage on Market Size

Models 1 to 6 present estimates from Equation (6). The model is estimated using the OLS method. The constant is included in all regressions but excluded from the tables. Controls include *Brands* and *Generics*. Errors are clustered at the market level and are in parentheses. P-value: $^{*}0.10, ^{**}0.05, ^{***}0.01$.

| DV = ln (Market Sales) | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 |
|---|---|---|---|---|---|---|
| Time since Market Opening (Quarters) | 0-4 | 5-8 | 9-12 | 13-16 | 17-20 | 21 & up |
| Market Vintage | 0.100*** | 0.048*** | 0.021** | 0.025 | 0.003 | 0.000 |
| | (0.034) | (0.010) | (0.010) | (0.021) | (0.007) | (0.005) |
| ln (Market Price) | -0.245 | -0.209 | 0.498 | 0.166 | -0.030 | -0.288*** |
| | (0.458) | (0.156) | (0.558) | (0.116) | (0.094) | (0.084) |
| ln (Lagged Market Promotion Stock) | 0.053*** | 0.024 | 0.115 | 0.004 | 0.004 | 0.152*** |
| | (0.020) | (0.015) | (0.093) | (0.017) | (0.019) | (0.055) |
| ln (Lagged Market DTCA Stock) | 0.012 | -0.004 | 0.004 | 0.029** | 0.009 | 0.028* |
| | (0.021) | (0.010) | (0.008) | (0.013) | (0.006) | (0.016) |
| Controls | Y | Y | Y | Y | Y | Y |
| Market Fixed Effect | Y | Y | Y | Y | Y | Y |
| N | 348 | 308 | 293 | 272 | 256 | 1,416 |
| Adjusted $R^2$ | 0.941 | 0.996 | 0.994 | 0.997 | 0.999 | 0.963 |

Table 11: Summary of Profit Approximation

This table summarizes the results from Equation (5). Rows A to D represent the OEE on profit based on two groups of firms: first mover and follower. Rows E to L represent the OEE on profit based on three groups of firms: first mover, fast follower, and slow follower. Column 2 represents the ratio between R&D cost and promotion expenditure used to approximate the R&D cost in the profit calculation for first movers. Column 3 represents the same ratio for followers (Rows A to D), fast followers (Rows E to H), and slow followers (Rows I to L). Column 4 of Rows A to D represent the profit of follower compared to first mover. Column 4 of Rows E to H represent the profit of fast follower compared to first mover. Column 4 of Rows I to L represent the profit of slow follower compared to first mover. P-value: $^{*}0.10,^{**}0.05,^{***}0.01$.

| | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| | | R&D Cost/Promotion | | Disadvantage |
| | | First Mover | Follower | Profit |
| A | Follower | 0.5 | 0.5 | -0.407*** |
| B | | 1 | 0.5 | -0.356* |
| C | | 2 | 0.5 | -0.273 |
| D | | 2.5 | 0.5 | -0.226 |
| E | Fast Follower | 0.5 | 0.5 | -0.238 |
| F | | 1 | 0.5 | -0.193 |
| G | | 2 | 0.5 | -0.113 |
| H | | 2.5 | 0.5 | -0.067 |
| I | Slow Follower | 0.5 | 0.5 | -0.454*** |
| J | | 1 | 0.5 | -0.402** |
| K | | 2 | 0.5 | -0.318* |
| L | | 2.5 | 0.5 | -0.271 |

# Appendix

## A1 Robustness and Sensitivity Check

### A1.1 OEE from Alternative Definitions of Entry Speed

In Section 6, I only focus on the drugs introduced within the first five years of the market opening and I divide the drugs into three groups: first movers, fast followers, and slow followers. When considering the distribution of the entry timing of the followers (see Figure A.1), I find that there is another natural break at the thirtieth quarter after the market opening. In this section, I divide the followers into another classification of groups: fast followers (drugs that enter the market between the 1st to 8th quarters after the market opening), slow followers 9-30 (drugs that enter the market between the 9th to 30th quarters after the market opening), and laggards 31-51 (drugs that enter the market after the 31st quarter of the market opening).

[Figure A.1]

In addition to the pattern shown in the distribution of the entry time of the follower, these natural breaks potentially identify the clinical trial stage the drugs were in the midst of when the market initially opened (signified by the introduction of the first mover in the market). Fast followers are likely to be those drugs in the third stage of clinical trials when the first mover was approved (as explained in Section 5.2). Slow followers 9-30 are likely to be those drugs that were in either the first or second stage of clinical trials. Laggards 31-51 are those drugs that had not yet entered into clinical trials when the first mover received its FDA approval.[30] The followers' information in each of the three groups is summarized in Table A.1.

[Table A.1]

Using the specification in Equation (1) and using the four defined groups (first mover, fast follower,

[30] According to DiMasi et al. (2016), the average time from the start of a clinical trial to drug approval takes approximately 96.8 months, which is around 32.27 quarters. As such, the average follower as I defined here is likely to be the drugs that were in a clinical trial (Phase I or Phase II) when the first mover was approved. Laggards would be those drugs that were not in the clinical trial stage when the first mover was approved.

slow movers 9-30, and laggard 31-51), the results in Table A.2 show there is a slight difference in the OEE between the late mover and the laggard defined in this section.

[Table A.2]

In the estimation results shown in Table A.2, the slow follower 9-30 captures a 32.2 percentage point lower market share when compared to the first mover, and the laggard 31-51 has a 30.1 percentage point lower market share compared to the first mover. Nonetheless, the test indicates that there is no significant difference between the slow follower 9-30 and the laggard 31-51.

### A1.2 Order of Entry Effect with Alternative Timeframe

In the main results discussed in Section 6, I limit the sample to the first five years of each drug to avoid the entrance of generic drugs. It would be interesting to know how long the advantage could be sustained for the early entrant, if I extend the length of the estimation period. In Tables A.3 and A.4, I present additional results demonstrating that the OEE still persists over longer time horizons. Models 4 to 6 in Table A.3 present results showing the first mover advantage under different time horizons. Model 4 shows the result of the first mover advantage on market share for the first six years of the drug. It still shows that the first mover is able to capture a 22.3 percentage point higher market share compared to the follower. Models 5 and 6 further demonstrate that the first mover captures a superior market share in the first seven and eight years of a drug's introduction, respectively. Aside from the first mover advantage on market share, Models 1 to 3 show that the fast follower mitigates the follower's disadvantage on market share compared to the first mover in the first five to eight years. Similar to Table 7, these results reconfirm the finding that as long as a drug is introduced within two years of the market opening, it does not suffer a follower's disadvantage on market share.[31]

[Table A.3]

Considering the other measure – net sales – similar to Table 9, Table A.4 presents the results of the OEE on net sales with various timeframes. Models 4 to 6 show that the first mover enjoys a superior advantage of around 31 percentage points on net sales compared to a follower, on average. Models 1 to 3 show that the fast follower mitigates the first mover advantage in terms of net sales compared to the first mover, while the

[31] A longer time horizon for each drug or class is used in the robustness check and the new summary statistics are shown in Table A.5.

slow follower suffers and has a 37 percentage point lower net sales compared to the first mover in the first five to eight years after a drug's introduction.

[Table A.4]

Both Tables A.3 and A.4 demonstrate that the first mover advantage persists over the long run for both market share and net sales. Moreover, fast followers mitigate the first mover advantage regardless of the timeframe. Interestingly, the disadvantage suffered by slow followers tends to reduce as the time period increases, while the reduction magnitude is mild. This suggests the follower's performance tends to be better in the long run, but the first mover and the fast follower still occupy a superior position.

### A1.3 Order of Entry Effect on Market Share with Alternative Definition of Fast Follower

In Table 6, I divide the entrants based on their timing of entry in the market and show that most followers who enter in the first eight quarters of the market opening mitigate the first mover advantage when compared to the first mover. In Tables A.6 and A.7, I further redefine the fast follower and slow follower using different timeframes and explore the order of entry results.

In Table A.6, I redefine fast followers to be those drugs introduced within one year of the market opening and slow followers to be the drugs introduced after one year of the market opening. Models 1 to 3 show that fast followers mitigate the first mover advantage on market share, while slow followers suffer from being late and has a 25 percentage point lower market share compared to the first mover.

[Table A.6]

Table A.7 presents the order of entry effect on market share with a different definition of the fast follower. The fast follower in Table A.7 is defined as a drug introduced within three years of the market opening and a slow follower is defined as a drug introduced after three years of the market opening. Models 1 to 3 show that the fast follower and slow follower cannot mitigate the first mover's advantage on market share. The fast follower has a 15 percentage point lower market share compared to the first mover, while the slow follower has a 38 percentage point lower market share compared to the first mover. This provides suggestive evidence that even if the market has not reached peak sales until the third year of the market opening, it is very difficult for a drug to reach enough new patients if it is introduced in the third year of the market opening. As a result, this scenario leads to a follower's disadvantage if the drug is introduced in the third year of the market opening when compared to a first mover.

[Table A.7]

In Tables A.6 and A.7, I test the sensitivity of the choice of time period for the fast follower. Table A.6 shows that the drugs that enter within one year of the market opening do not suffer from being a follower on market share. Table A.7 shows that those drugs entering within three years of the market opening suffer from being a follower on market share. Together with our main results in Tables 5 and 6, I show that fast followers' market performance does not suffer if a drug enters the market within two years of the market opening.

### A1.4 Summary of Findings on the Order of Entry Effect

Using different timeframes for the estimation on drugs based on different timings of entry, I summarize all the results and present them in Table A.8. Looking at Row C, the follower's disadvantage decreases as the time of estimation increases. This might suggest that patients are slowly switching to other drugs in the long run or it just reflects generic entry.

Comparing Rows C, D, and E, the window of opportunity that a follower needs to enter the market without appreciable disadvantage is within two years of the market opening. Once the fast follower is defined as entering the market within three years of the market opening, the follower's disadvantage is significant. Again, the disadvantage suffered by a follower compared to the first mover decreases over time. This pattern stays the same regardless of the timeframe chosen at either the time since the drug's introduction or the time since the market opening. Comparing Rows F, G, and H, the slow follower's disadvantage is different in various timeframes. If the slow follower has a higher proportion of drugs moving into the market late, the disadvantage is higher compared to the first mover. This reconfirms the results in Section 5.3 – that the later a follower moves into the market, the worse off its disadvantage.

[Table A.8]

The sensitivity analysis reconfirms that the two year is the largest window of opportunity for followers in the pharmaceutical market, on average. As long as a drug enters the market within two years of the market opening, it is able to mitigate the first mover advantage and enjoys a similar market share compared to the first mover.

### A1.5 Sensitivity Analysis of Timing of Entry Effects

Table A.9 shows the impact of the timing of entry on market share by adding an additional second degree of the variable of interest, *Elapsed Time*. The incorporation of this variable provides further evidence of how the impact of the timing of entry on market share varies dynamically. Similar to the results shown in Table 8, the later a follower accesses the market, the worse its performance in terms of market share. The square of *Elapsed Time* shows a positive sign in Models 1 and 3, suggesting that this phenomenon could be an S-shape such that the effect of the timing of entry will have a diminishing return in the long run.

[Table A.9]

In addition to the specification used for the estimate in Table 10, the speed of new drug diffusion may have a diminishing return to time scale. Thus, I add the square of the variable *Market Vintage* to the specification and estimate the speed of diffusion in a new market. Table A.10 provides the results and reconfirms the importance of the first two years for drug diffusion in a new market.

[Table A.10]

With the additional second degree term of *Market Vintage*, the result tends to be similar to the result seen in Table 10. These results suggest that the first two years of market opening is essential for drug adoption. As fast followers enter the market within two years of market opening, it falls into the high speed adoption of new drugs, which allows it to capture a similar market share as a first mover.

### A1.6 Order of Entry Effect on the Promotion Elasticity of Demand

Aside from the effect of entry timing on the speed of drug diffusion in a new market, one might think that promotion elasticity could also signify that early entrants may have a benefit. Promotion primarily constitutes detailing, which is advertising to doctors. This potentially reflects the ease of promoting drugs mainly for two reasons. First, I look at the prescription drug market, which mainly depends on doctors' choices. I divide the drugs into the ones treating chronic diseases and the ones treating acute diseases. Drugs treating chronic diseases may rely on both the doctor's and patient's experience, while drugs treating acute diseases may be determined more by the doctor's experience. Thus, promoting a drug directly to doctors should be effective since doctors would have experience with a drug regardless of whether the patient is new

or an existing one. Second, many studies suggest that detailing increases both the market share and market size while the DTCA mainly increases only the market size.

With the average promotional spending since the drug's introduction (presented in Figure A.2), I notice the first mover and fast follower spend relatively more on promotion compared to the slow follower. This finding might suggest that the first mover and fast follower gain a superior sales advantage compared to the slow follower.

[Figure A.2]

In the estimation of the OEE on promotion effectiveness, I use a similar specification in Equation (1) and add the additional interaction term between the variables *Follower* and *Promotion*. I also redefine $Y_{it}$ as sales quantity of drug $i$ at time $t$. The model follows:

$$\begin{aligned} Y_{it} = {} & \beta_0 + \beta_1 Follower_i + \beta_2 Promotion_{it} + \beta_3 Follower_i * Promotion_{it} \\ & + \beta_4 Lagged\ DTCA\ Stock_{it} + \beta_5 Price_{it} + \beta_6 X_{it} + FE_{it} + \varepsilon_{it}. \end{aligned} \tag{7}$$

Model 1 in Table A.11 shows that the promotion effectiveness is higher for the first mover compared to the follower. In addition, I divide the followers into fast and slow followers as defined in Section 6. Table A.12, Model 1, suggests that the promotion effectiveness is not significantly different between the first mover and fast follower. However, the slow follower has a lower promotion elasticity, on average.

[Table A.11]

Both Tables A.11 and A.12 suggest that the first mover has an advantage on the promotion effectiveness compared to slow followers. The fast follower does not suffer in terms of the sales and promotion effectiveness. Interestingly, this reconfirms the main results in Section 6 that the first mover and fast follower have equal market shares, and they also have similar promotion and pricing elasticity.

[Table A.12]

Together with the results in Section 6.5, I argue that the early entrant is able to access a majority of the market (doctors and patients) within two years of market opening. After two years, while the slow followers could still reach new consumers, those numbers are small. To promote a product to a new patient/doctor is obviously easier than to promote to an experienced patient/doctor. Promotional effectiveness is lower for slow followers. These findings suggest the early entrant is able to lock-in a majority of consumers within

the first two years of market opening. Moreover, consumers (both patients and doctors) experience should increase as the time of the product on the market increases; this potentially explains the result in Section 6.3, that the later the slow followers enter the market, the worse they suffer in terms of market share.

### A1.7 Endogenous Orders of Entry

The endogeneity of entry order is always controversial. In the pharmaceutical market, firms usually spend over 10 years in the R&D process, including clinical trials, before products reach the market. The approval decision is largely considered to be exogenous to the firm behavior since the FDA is considered to be a neutral third party. However, one may still question whether firms have any control over the entry speed so as to impact the order of entry.

[Table A.13]

Thus, I use an instrumental variable approach to re-estimate the OEE and compare this result with the main result shown in Tables 4 and 6. Considering the nature of endogeneity, which determines the entry order for drugs in the choice of the firm, I use firm-level capacity as an instrumental variable to signify the ability of a drug to enter the market. To do so, I use the average (and median) time between patent approval and approval of all drugs from the same firm, excluding the focal drug. This variable measures the firm's capacity for pushing a drug to the market. Using the main specification and exogenizing order of entry (by applying the residual inclusion method), I find that the result, presented in Table A.13, does not significantly differ compared to the main result of Tables 5 and 7.[32] This potentially suggests that the order of entry is largely exogenous, on average.

[32] This is also verified by the Hausman Test.

Figure A.1: Entry Timing Distribution with an Alternative Definition

This graph represents the entry timing distribution. The Y-axis represents the fraction of brand drugs introduced in the sample. The X-axis represents the entry timing of a drug since the market opening. The entry timing period is measured in quarters. Drugs are limited to all followers and exclude the first mover. The fast followers are defined as those drugs introduced within eight quarters of the market opening. Slow followers 9-30 are defined as drugs introduced between the 9th to 30th quarter after the market opening. Laggards 31-51 are defined as drugs introduced in and after the 31st quarter after the market opening.

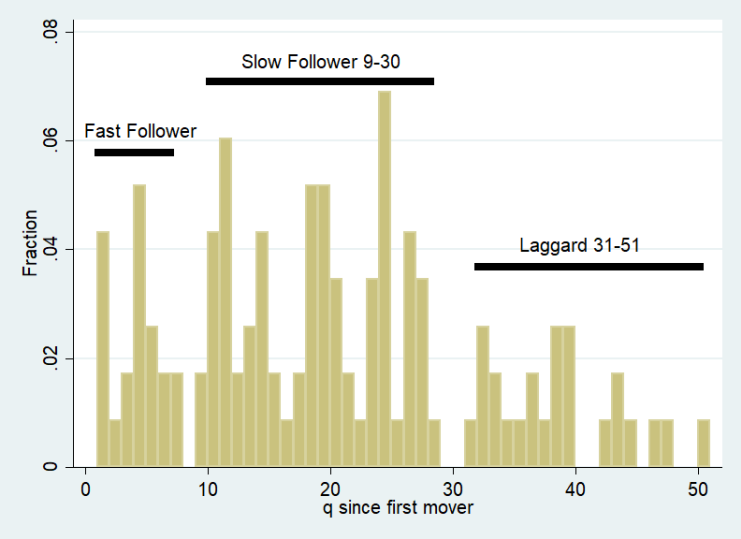


Figure A.2: Average Promotional Spending since Market Opening

This graph represents the average promotional spending after a drug's introduction. The Y-axis represents the average logarithm transformed promotional spending based on three defined groups (first mover, fast follower, and slow follower). The X-axis represents the time (quarter) since drug introduction. Promotional spending is measured in real 2009 U.S. dollars in millions.

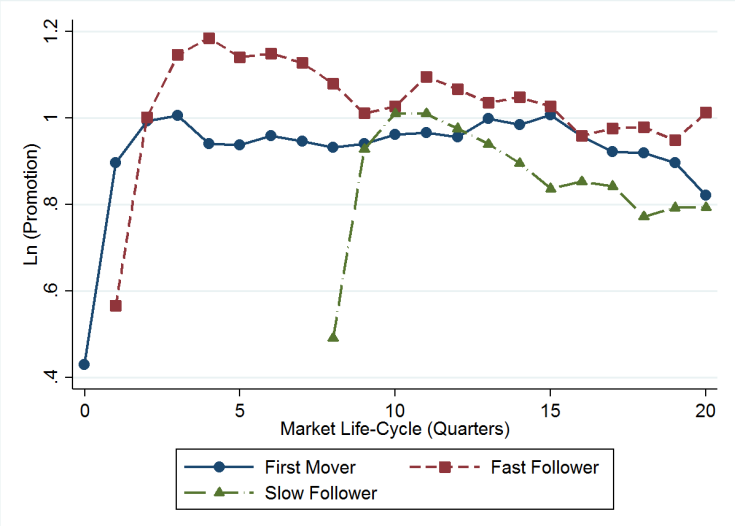

Table A.1: Speed of Entry in Four Groups

This table shows the average speed of entry for each drug classification. The first row shows the time (quarters) since the follower entered into the market (market opening). The second row represents the number of drugs that are introduced into the market under each speed of entry. The last row represents the average speed within each group. There are 97 unique ATC 4-digit drugs in the sample.

| Follower | Fast Follower | Slow Follower 9-30 | Laggard 31-51 |
|---|---|---|---|
| Time Since Market Opening (Quarters) | 1-8 | 9-30 | 31-51 |
| Number of Drugs | 21 | 71 | 24 |
| Average Speed | 3.81 | 18.30 | 38.25 |

Table A.2: The Order of Entry Effect on Market Share with Alternative Definitions of Followers

Model 1 presents an estimate using four defined groups (first mover, fast follower, slow follower 9-30, and laggard 31-51). The model is estimated using the fractional Logit method. Price is also exogenized. The first mover is omitted. The constant is included in all regressions but excluded from the tables. Controls include *Side Effect, Major Interaction, Moderate Interaction, Minor Interaction, Vintage,* and *Brands*. Errors are clustered at the market level and are in parentheses. P-value: $^{*}0.10, ^{**}0.05, ^{***}0.01$. Data is restricted to the drug introduced in the first five years of market opening. The marginal effects for key variables are reported on the right column of the table.

| DV = Market Share | Model 1 | Marginal Effects |
|---|---|---|
| Fast Follower | -1.066 | |
| | (1.177) | |
| Slow Follower 9-30 | -2.377*** | **-0.322** |
| | (0.449) | |
| Laggard 31-51 | -2.196** | **-0.301** |
| | (0.871) | |
| ln (Price) | -0.683** | |
| | (0.328) | |
| ln (Lagged Promotion Stock) | 0.109*** | |
| | (0.036) | |
| ln (Lagged DTCA Stock) | 0.109* | |
| | (0.058) | |
| Controls | Y | |
| Market Fixed Effect | Y | |
| N | 3,064 | |
| pseudo $R^2$ | 0.477 | |

Table A.3: The Order of Entry Effect on Market Share with Alternative Timeframe since Drug Introduction

Models 1 to 3 present estimates using the three defined groups (first mover, fast follower, and slow follower). Models 4 to 6 present estimates using the two defined groups (first mover and follower). Models 1 and 4 use the sample of the first six years of each drug since its introduction. Models 2 and 5 use the sample of the first seven years of each drug since its introduction, and so on. Price is also exogenized. All models are estimated using the fractional Logit method. The constant is included in all regressions but excluded from the tables. Controls include *Side Effect, Major Interaction, Moderate Interaction, Minor Interaction, Vintage,* and *Brands*. Errors are clustered at the market level and are in parentheses. P-value: $^{*}0.10,^{**}0.05,^{***}0.01$. The marginal effects for key variables are reported at the bottom of the table.

| DV = Market Share | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 |
|---|---|---|---|---|---|---|
| Time since Drug Introduction | 6 years | 7 years | 8 years | 6 years | 7 years | 8 years |
| Fast Follower | -0.905 | -0.778 | -0.696 | | | |
| | (0.649) | (0.489) | (0.440) | | | |
| Slow Follower | -2.208*** | -1.979*** | -1.781*** | | | |
| | (0.417) | (0.380) | (0.362) | | | |
| Follower | | | | -1.594*** | -1.450*** | -1.321*** |
| | | | | (0.339) | (0.321) | (0.309) |
| ln (Price) | -0.606* | -0.651* | -0.687** | -0.594 | -0.635* | -0.676* |
| | (0.328) | (0.337) | (0.335) | (0.381) | (0.386) | (0.378) |
| ln (Lagged Promotion Stock) | 0.106*** | 0.123*** | 0.133*** | 0.112*** | 0.130*** | 0.139*** |
| | (0.038) | (0.041) | (0.042) | (0.041) | (0.043) | (0.044) |
| ln (Lagged DTCA Stock) | 0.123** | 0.119** | 0.106* | 0.118** | 0.115* | 0.104* |
| | (0.060) | (0.061) | (0.058) | (0.057) | (0.059) | (0.057) |
| Controls | Y | Y | Y | Y | Y | Y |
| Market Fixed Effect | Y | Y | Y | Y | Y | Y |
| N | 3,465 | 3,820 | 4,130 | 3,465 | 3,820 | 4,130 |
| pseudo $R^2$ | 0.464 | 0.450 | 0.436 | 0.455 | 0.442 | 0.429 |
| **Marginal Effects:** | | | | | | |
| **Slow Follower** | **-0.304** | **-0.277** | **-0.254** | | | |
| **Follower** | | | | **-0.223** | **-0.205** | **-0.190** |

Table A.4: The Order of Entry Effect on Net Sales with Alternative Timeframe since Drug Introduction

Models 1 to 3 present estimates using the three defined groups (first mover, fast follower, and slow follower). Models 4 to 6 present estimated coefficients using the two defined groups (first mover and follower). Models 1 and 4 use the sample of the first six years of each drug since its introduction. Models 2 and 5 use the sample of the first seven years of each drug since its introduction, and so on. All models are estimated using the OLS method. The constant is included in all regressions but excluded from the tables. Controls include *Side Effect, Major Interaction, Moderate Interaction, Minor Interaction, Vintage,* and *Brands*. Errors are clustered at the market level and are in parentheses. P-value: $^{*}0.10,^{**}0.05,^{***}0.01$.

| DV = ln (Net Sales) | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 |
|---|---|---|---|---|---|---|
| Time since Drug Introduction | 6 years | 7 years | 8 years | 6 years | 7 years | 8 years |
| Fast Follower | -0.145 | -0.100 | -0.060 | | | |
| | (0.360) | (0.357) | (0.351) | | | |
| Slow Follower | -0.391** | -0.372** | -0.338* | | | |
| | (0.173) | (0.183) | (0.189) | | | |
| Follower | | | | -0.337** | -0.310* | -0.273* |
| | | | | (0.178) | (0.189) | (0.194) |
| Controls | Y | Y | Y | Y | Y | Y |
| Market Fixed Effect | Y | Y | Y | Y | Y | Y |
| N | 3,465 | 3,820 | 4,130 | 3,465 | 3,820 | 4,130 |
| Adjusted $R^2$ | 0.710 | 0.711 | 0.712 | 0.709 | 0.710 | 0.711 |

Table A.5: Summary Statistics for Robustness

This table provides summary statistics for variables used in the appendices of this paper. Market share is constructed by sales quantity over the entire market sales of all branded drugs. Sales quantity is measured in millions of standardized units. Profit is measured in real 2009 U.S. dollars (million). Promotion includes detailing, journal promotion, and mail promotion (in million USD). Price is in real 2009 U.S. dollars per standardized unit. The observations in this table present the total sample from 1997 to 2011.

| Variables | Obs. | Mean | Median | Std. Dev. | Min | Max |
|---|---|---|---|---|---|---|
| Market Share | 5,411 | 0.54 | 0.53 | 0.42 | 0.00 | 1.00 |
| Sales Quantity | 5,411 | 18.05 | 0.98 | 48.98 | 0.00 | 409.59 |
| Net Sales | 5,411 | 52.15 | 9.08 | 127.27 | 0.00 | 1033.50 |
| Follower | 5,411 | 0.42 | 0.00 | 0.49 | 0.00 | 1.00 |
| Fast Follower | 5,411 | 0.12 | 1.00 | 0.32 | 0.00 | 1.00 |
| Slow Follower | 5,411 | 0.31 | 0.00 | 0.46 | 0.00 | 1.00 |
| Fast Follower 1 | 5,411 | 0.02 | 0.00 | 0.15 | 0.00 | 1.00 |
| Slow Follower 1 | 5,411 | 0.40 | 1.00 | 0.49 | 0.00 | 1.00 |
| Fast Follower 2 | 5,411 | 0.07 | 0.00 | 0.26 | 0.00 | 1.00 |
| Slow Follower 2 | 5,411 | 0.35 | 1.00 | 0.48 | 0.00 | 1.00 |
| Price | 5,411 | 314.08 | 16.33 | 1074.02 | 0.15 | 30995.33 |
| Promotion | 5,411 | 3.30 | 0.43 | 6.90 | 0.00 | 63.18 |
| Lagged Promotion Stock | 5,411 | 4.47 | 0.49 | 9.81 | 0.00 | 94.62 |
| DTCA | 5,411 | 2.57 | 0.00 | 8.69 | 0.00 | 93.92 |
| Lagged DTCA Stock | 5,411 | 2.31 | 0.00 | 7.82 | 0.00 | 89.69 |
| Side Effect | 5,411 | 10.73 | 4.00 | 15.39 | 0.00 | 76.00 |
| Major Interaction | 5,411 | 39.09 | 5.00 | 75.99 | 0.00 | 416.00 |
| Moderate Interaction | 5,411 | 273.72 | 166.00 | 273.53 | 0.00 | 918.00 |
| Minor Interaction | 5,411 | 29.19 | 8.00 | 40.34 | 0.00 | 172.00 |
| Vintage | 5,411 | 18.40 | 16.00 | 13.64 | 0.00 | 55.00 |
| Elapsed Time | 5,411 | 6.82 | 0.00 | 10.53 | 0.00 | 51.00 |
| Brands | 5,411 | 2.72 | 2.00 | 2.25 | 0.00 | 11.00 |
| Generics | 5,411 | 6.00 | 1.00 | 12.59 | 0.00 | 111.00 |

Table A.6: The Order of Entry Effect on Market Share with an Alternative Definition of Fast Follower 1

Models 1 to 6 present an estimated coefficient using the three defined groups [first mover, fast follower 1 (drugs entering the market within one year of market opening), and slow follower 1 (drugs entering the market after one year of the market opening)]. Models 1 to 3 use the sample of the first five, six, and seven years of each drug since its introduction. Price is also exogenized. All models are estimated using the fractional Logit method. The constant is included in all regressions but excluded from the tables. Controls include *Side Effect, Major Interaction, Moderate Interaction, Minor Interaction, Vintage,* and *Brands*. Errors are clustered at the market level and are in parentheses. P-value: $^{*}0.10,^{**}0.05,^{***}0.01$. The marginal effects for key variables are reported at the bottom of the table.

| DV = Market Share | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| Time since Drug's Introduction | 5 years | 6 years | 7 years |
| Fast Follower 1 | -1.143 | -1.017 | -0.944 |
| | (0.696) | (0.672) | (0.564) |
| Slow Follower 1 | -2.059*** | -1.846*** | -1.650*** |
| | (0.423) | (0.390) | (0.357) |
| ln (Price) | -0.560 | -0.537 | -0.590 |
| | (0.374) | (0.377) | (0.385) |
| ln (Lagged Promotion Stock) | 0.111*** | 0.109*** | 0.127*** |
| | (0.039) | (0.039) | (0.042) |
| ln (Lagged DTCA Stock) | 0.117** | 0.122** | 0.118** |
| | (0.056) | (0.058) | (0.059) |
| Controls | Y | Y | Y |
| Market Fixed Effect | Y | Y | Y |
| N | 3,064 | 3,465 | 3,820 |
| pseudo $R^2$ | 0.473 | 0.458 | 0.444 |
| **Marginal Effects: Slow Follower 1** | **-0.283** | **-0.257** | **-0.233** |

Table A.7: The Order of Entry Effect on Market Share with an Alternative Definition of Fast Follower 2

Model 1 presents an estimated coefficient using the four defined groups [first mover, fast follower 2 (drugs entering the market within three years of the market opening), and slow follower 2 (drugs entering the market after three years of the market opening)]. Models 1 to 3 use the sample of the first five, six, and seven years of each drug since its introduction. Price is also exogenized. All models are estimated using the fractional Logit method. The constant is included in all regressions but excluded from the tables. Controls include *Side Effect, Major Interaction, Moderate Interaction, Minor Interaction, Vintage,* and *Brands*. Errors are clustered at the market level and are in parentheses. P-value: $^{*}0.10,^{**}0.05,^{***}0.01$. The marginal effects for key variables are reported at the bottom of the table.

| DV = Market Share | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| Time since Drug's Introduction | 5 years | 6 years | 7 years |
| Fast Follower 2 | -1.284*** | -1.088*** | -0.921*** |
| | (0.379) | (0.360) | (0.352) |
| Slow Follower 2 | -3.155*** | -2.933*** | -2.652*** |
| | (0.531) | (0.496) | (0.427) |
| ln (Price) | -0.654** | -0.619** | -0.664** |
| | (0.309) | (0.302) | (0.310) |
| ln (Lagged Promotion Stock) | 0.089** | 0.086** | 0.103** |
| | (0.041) | (0.040) | (0.041) |
| ln (Lagged DTCA Stock) | 0.133** | 0.136** | 0.129** |
| | (0.056) | (0.056) | (0.056) |
| Controls | Y | Y | Y |
| Market Fixed Effect | Y | Y | Y |
| N | 3,064 | 3,465 | 3,820 |
| pseudo $R^2$ | 0.487 | 0.473 | 0.460 |
| **Marginal Effects:** | | | |
| **Fast Follower 2** | **-0.177** | **-0.152** | **-0.130** |
| **Slow Follower 2** | **-0.406** | **-0.382** | **-0.352** |

Table A.8: Summary of Findings on Order of Entry Effect on Market Share

This table summarizes the marginal effect based on different definitions of groups within different timeframes. Row B represent the follower's disadvantage compared to the first mover under different estimation timeframes. Rows C, D, and E represent the fast follower, defined as drugs entering the market within one, two, and three years of the market opening, respectively. Rows F, G, and H represent the slow follower defined as drugs entering market after one, two, and three years of the market opening, respectively. Columns 3, 4, and 5 represent the marginal effect of a follower's (follower, fast follower, or slow follower) disadvantage compared to the first mover if the estimation timeframe is the first five, six, and seven years of the drug's introduction, respectively. P-value: $^{*}0.10$,$^{**}$ 0.05,$^{***}$ 0.01.

| | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| | | Timing of Entry (year) since Market Opening | Estimation Timeframe Since Drug Introduction | | |
| A | | | 5 years | 6 years | 7 years |
| B | Follower | 0 & up | -0.234*** | -0.223*** | -0.205*** |
| C | Fast Follower | 0-1 | -0.158 | -0.146 | -0.135 |
| D | | 0-2 | -0.147 | -0.127 | -0.101 |
| E | | 0-3 | -0.177*** | -0.152** | -0.130** |
| F | Slow Follower | 1 & up | -0.283*** | -0.257*** | -0.233*** |
| G | | 2 & up | -0.321*** | -0.267*** | -0.246*** |
| H | | 3 & up | -0.406*** | -0.382*** | -0.352*** |

Table A.9: The Speed of Entry on Market Share in a Heterogeneous Specification

Model 1 presents the results from the specification using Equation (4) with an addition of the square of the variable "*Elapsed Time*." Model 2 presents the estimation for the first mover and fast followers. Model 3 presents the estimation for the first mover and slow followers. Price is also exogenized. All models are estimated using the fractional Logit method. The constant is included in all regressions but excluded from the tables. Controls include *Side Effect, Major Interaction, Moderate Interaction, Minor Interaction, Vintage,* and *Brands*. Errors are clustered at the market level and are in parentheses. P-value: $^{*}0.10, ^{**}0.05, ^{***}0.01$. Data is restricted to the drug introduced in the first five years of market opening. The marginal effects for key variables are reported at the bottom of the table.

| DV = Market Share | Model 1<br>Follower | Model 2<br>Fast Follower | Model 3<br>Slow Follower |
|---|---|---|---|
| Elapsed Time | -0.221*** | -0.451 | -0.208*** |
| | (0.042) | (0.441) | (0.041) |
| Elapsed Time$^2$ | 0.004*** | 0.036 | 0.003*** |
| | (0.001) | (0.068) | (0.001) |
| ln (Price) | -0.687** | -1.120** | -1.200*** |
| | (0.332) | (0.531) | (0.353) |
| ln (Lagged Promotion Stock) | 0.085** | 0.109* | 0.053 |
| | (0.037) | (0.058) | (0.035) |
| ln (Lagged DTCA Stock) | 0.121** | 0.089 | 0.115* |
| | (0.058) | (0.058) | (0.066) |
| Controls | Y | Y | Y |
| Market Fixed Effect | Y | Y | Y |
| N | 3,064 | 1,831 | 2,771 |
| pseudo $R^2$ | 0.481 | 0.513 | 0.538 |
| **Marginal Effects:** | | | |
| **Elapsed Time** | **-0.025** | | **-0.021** |
| **Elapsed Time$^2$** | **0.000** | | **0.000** |

Table A.10: The Effect of Vintage on Market Size with an Alternative Specification

Models 1 to 6 present an estimated coefficient using Equation (6) by adding the variable *Market Vintage*$^2$ as an additional independent variable. Controls include *Brands* and *Generics*. Errors are clustered at the market level and are in parentheses. P-value: $^{*}0.10,^{**}0.05,^{***}0.01$.

| DV = ln (Market Sales) | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 |
|---|---|---|---|---|---|---|
| Time since Market Opening (Quarters) | 0-4 | 5-8 | 9-12 | 13-16 | 17-20 | 21 & up |
| Market Vintage | 0.182* | 0.227*** | 0.140 | 0.120 | 0.044 | 0.012 |
| | (0.095) | (0.065) | (0.261) | (0.135) | (0.204) | (0.023) |
| Market Vintage$^2$ | -0.018 | -0.014*** | -0.006 | -0.003 | -0.001 | -0.000 |
| | (0.019) | (0.005) | (0.013) | (0.005) | (0.006) | (0.000) |
| ln (Market Price) | -0.269 | -0.193 | 0.507 | 0.163 | -0.029 | -0.285*** |
| | (0.476) | (0.154) | (0.565) | (0.117) | (0.094) | (0.088) |
| ln (Lagged Market Promotion Stock) | 0.046** | 0.025* | 0.115 | 0.004 | 0.004 | 0.152*** |
| | (0.022) | (0.015) | (0.093) | (0.017) | (0.019) | (0.055) |
| ln (Lagged Market DTCA Stock) | 0.014 | -0.004 | 0.003 | 0.029** | 0.009 | 0.028* |
| | (0.021) | (0.010) | (0.008) | (0.013) | (0.006) | (0.016) |
| Controls | Y | Y | Y | Y | Y | Y |
| Market Fixed Effect | Y | Y | Y | Y | Y | Y |
| N | 348 | 308 | 293 | 272 | 256 | 1,416 |
| Adjusted $R^2$ | 0.941 | 0.996 | 0.994 | 0.997 | 0.999 | 0.963 |

Table A.11: The Order of Entry Effect on Elasticity

This table presents the estimation using Equation (7) with two defined groups (first mover and follower). All models are estimated using the OLS method. The constant is included in all regressions but excluded from the tables. Controls include *Side Effect, Major Interaction, Moderate Interaction, Minor Interaction, Vintage,* and *Brands*. Errors are clustered at the market level and are in parentheses. P-value: $^{*}0.10,^{**}0.05,^{***}0.01$. Data is restricted to the drug introduced in the first five years of market opening.

| DV = ln (Sales SU) | Model 1 |
|---|---|
| Follower | 0.119 |
| | (0.194) |
| ln (Promotion) | 0.586*** |
| | (0.104) |
| Follower * ln (Promotion) | -0.245*** |
| | (0.089) |
| ln (Price) | -0.288*** |
| | (0.069) |
| ln (Lagged DTCA Stock) | 0.140*** |
| | (0.050) |
| Controls | Y |
| Market Fixed Effect | Y |
| N | 3,064 |
| Adjusted $R^2$ | 0.879 |

Table A.12: The Order of Entry Effect on Elasticity with Alternative Definitions of Followers

This table presents the estimation using Equation (7) with three defined groups (first mover, fast follower, and slow follower). All models are estimated using the OLS method. The constant is included in all regressions but excluded from the tables. Controls include *Side Effect, Major Interaction, Moderate Interaction, Minor Interaction, Vintage,* and *Brands*. Errors are clustered at the market level and are in parentheses. P-value: $^{*}0.10, ^{**}0.05, ^{***}0.01$. Data is restricted to the drug introduced in the first five years of market opening.

| DV = ln (Sales SU) | Model 1 |
|---|---|
| Fast Follower | -0.038 |
| | (0.272) |
| Slow Follower | 0.202 |
| | (0.216) |
| ln (Promotion) | 0.637*** |
| | (0.113) |
| Fast Follower * ln (Promotion) | -0.114 |
| | (0.155) |
| Slow Follower * ln (Promotion) | -0.406*** |
| | (0.103) |
| ln (Price) | -0.283*** |
| | (0.070) |
| ln (Lagged DTCA Stock) | 0.152** |
| | (0.076) |
| Controls | Y |
| Market Fixed Effect | Y |
| N | 3,064 |
| Adjusted $R^2$ | 0.877 |

Table A.13: The Order of Entry Effect on Market Share with Exogenized Entry

Models 1 and 2 present the same specification using Equation (1). Model 1 represents the effect of the order of entry on market share based on two groups of firms: first mover and follower. Model 2 presents the results of the order of entry based on three groups of firms: first mover, fast follower, and slow follower. Order of entry and price are exogenized. All models are estimated using the fractional Logit method. The constant is included in all regressions but excluded from the tables. Controls include *Side Effect, Major Interaction, Moderate Interaction, Minor Interaction, Vintage,* and *Brands*. Errors are clustered at the market level and are in parentheses. P-value: $^{*}0.10,^{**}0.05,^{***}0.01$. Data is restricted to the drug introduced in the first five years of the market opening. The marginal effects for key variables are reported at the bottom of the table.

| DV = Market Share | Model 1 | Model 2 |
|---|---|---|
| Follower | -1.616*** | |
| | (0.432) | |
| Fast Follower | | -0.876 |
| | | (0.603) |
| Slow Follower | | -2.216*** |
| | | (0.492) |
| ln (Price) | -0.830* | -1.410*** |
| | (0.429) | (0.513) |
| ln (Lagged Promotion Stock) | 0.115** | 0.126*** |
| | (0.047) | (0.046) |
| ln (Lagged DTCA Stock) | 0.163** | 0.188** |
| | (0.066) | (0.075) |
| Controls | Y | Y |
| Market Fixed Effect | Y | Y |
| N | 3,064 | 3,064 |
| pseudo $R^2$ | 0.364 | 0.456 |
| **Marginal Effects:** | | |
| **Follower** | **-0.274** | |
| **Slow Follower** | | **-0.321** |

## Chapter II

# Estimating Effects of Adverse Regulatory Events: Evidence from Drug Relabeling[1]

**Abstract**

We provide causal evidence of the impact FDA drug relabeling has on aggregate demand for pharmaceuticals. We find that aggregate demand declines by 16.9 percent within two years of a relabeling event. After accounting for plausible substitution patterns by treating physicians and competitor actions, aggregate demand still declines by 4.7 percent. This decline plausibly represents consumers that prematurely leave the market. The overall effect appears to be driven by 'high-intensity' markets or those with significant relabeling activity. Results are robust to variation across types of relabeling, market sizes, levels of competition and degrees of cross-molecular substitution.

**Keywords:** Drug Relabeling, Adverse Regulatory Events, Demand Estimation

**JEL Classication:** I10, L10, L50

[1] Acknowledgement: (Joint with Chirantan Chatterjee and Matthew J. Higgins) We thank Maria Arbatskya, David Howard, Sara Markowitz and seminar participants at Emory University for helpful comments and suggestions. We thank IMS Health Incorporated for their generous support and access to their data. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities. The statements, findings, conclusions, views, and opinions contained and expressed in this article are based in part on data obtained under license from the following IMS Health Incorporated or affiliate information service(s): IMS Midas$^{TM}$. The usual disclaimers apply and any remaining errors are our own.

# 1 Introduction

The drug development process is long and expensive with a low probability of receiving FDA approval (Wong et al., 2018).[2] As part of the approval process drug candidates undergo clinical trials designed to test their safety and efficacy. These studies culminate with large-scale, randomized clinical trials to test a drug candidate's effectiveness. After successful completion of these trials drug candidates are submitted to the FDA for approval. The FDA maintains the Adverse Events Reporting System (FAERS) database to support its post-approval safety surveillance program. FAERS collects complaints and adverse events related to drugs and depending on the situation, the FDA will act upon this data and move to change the safety label associated with a drug. While the regulatory process underlying these safety label changes or relabeling is well defined, the overall impacts of those changes on demand is under investigated.

While prior studies have focused on various types of relabeling (e.g., Macher and Wade, 2013; Qureshi et al., 2011; Dorsey et al., 2010), most have limited their analyses to a single or limited number of therapeutic markets (e.g., Olfson and Marcus, 2008; Jacoby et al., 2005). These studies are important because we learn about the intricacies and nuances of specific markets but we are unable to draw overall conclusions about the impact of relabeling across markets. Using a dataset of drugs sold across all markets in the U.S. and U.K. we provide causal evidence relating to the impacts of FDA drug relabeling on aggregate consumer demand.[3] We find that, on average, aggregate demand declines by 16.9 percent within two years of a relabeling event. Our data allows us to capture intra- and inter-market substitution patterns as well as competitive responses. Critically, after accounting for these factors we still find that demand declined by 4.7 percent, an estimate that plausibly represents consumers that prematurely leave the market.[4]

Our results are robust across variations in types of relabeling, with impacts increasing along with relabeling severity. Prior studies have documented significant demand responses to the most severe type of

[2] In the most comprehensive analysis of clinical trial success to date, Wong et al. (2018) place the probability of a drug candidate reaching FDA approval at 13.8 percent.

[3] For ease of exposition we use the term aggregate consumer demand interchangeably with demand throughout the paper. To be precise we are referring to aggregate consumer demand. Our data is at the standard unit (e.g., pill) level and not at the individual prescription level and we have no data at the individual consumer level. We engage in back of the envelope calculations to convert our results into chronic patient prescriptions but this is only suggestive.

[4] A note on how we think about and determine the numbers of consumers that may plausibly leave the market. Our data provided by IMS Health is at the standard unit level or a measure that equates pills, tablets, liquids etc. As such, our data reflects changes in aggregate demand. Nonetheless we can translate these changes to represent numbers of prescriptions and consumers. As a conservative lower bound, we can assume that the entire decline, after accounting for substitution patterns, represents consumers that are chronic patients. This allows us to transform the decline in aggregate demand into monthly prescriptions and as a result an estimate of chronic patients. Clearly, all conditions are not chronic so as the number of acute prescriptions increases in the sample so will the number of consumers that plausibly leave the market.

relabel or a box warning (e.g., Dorsey et al., 2010). We add to this literature by accounting for plausible substitution patterns and documenting the decline in aggregate demand that represents consumers leaving the market. Surprisingly, we find fairly significant aggregate demand responses to the least severe type of relabel. Again, after accounting for plausible substitution patterns we find that consumers continue to leave the market. Unfortunately, our data is limited in that we do not know why consumers ultimately choose to leave but we proffer several plausible explanations.

Our results are also robust to variation in the levels of relabeling activity within markets, market sizes and levels of market competition. Interestingly, in markets with low levels of relabeling activity we find declines in aggregate focal drug demand completely absorbed by intra-market substitution or physicians switching patients to other drugs within that same market. In contrast, in markets with high levels of relabeling activity, after accounting for plausible substitution patterns, we find consumers leave the market. Finally, we follow prior literature (Branstetter et al., 2014, 2016) and split our sample across varying degrees of cross-molecular substitution. Cross molecule substitution (CMS) in our analysis measures the ability of patients to switch easily from one molecule to another within the same disease market induced either by the insurer or by the prescribing physician. In low CMS markets, such as those relating to the nervous system, we find that declines in aggregate focal drug demand are again absorbed by intra-market substitution. However, in high CMS markets, such as anti-infectives, we find that consumers leave the market.

There are plausible welfare implications from our findings. If consumers that leave the market should be treated, then this shift to the non-treated population could be a detriment to consumer welfare. Moreover, if consumers remain treated but are switched to drugs that are less effective, this will again be a detriment to their welfare. On the other hand, it is widely believed that some drugs are overprescribed (Lembke et al., 2018; Sacarny et al., 2016; Forgacs and Loganayagam, 2008; Price et al., 1986). If it is these consumers that exit the market then the impact on their welfare will be dampened. While we cannot make definitive welfare statements, our findings do suggest that further work is warranted. Ultimately, our findings raise policy-relevant questions about how the FDA handles adverse event reporting, safety label changes and how these changes are communicated to consumers.

The rest of the paper is organized as follows: Section 2 describes the regulatory environment; Section 3 discusses adverse regulatory events; Section 4 presents the methodology employed in the study and describes the data; empirical results are summarized in Section 5; Section 6 presents the robustness check; and Section 7 summarizes the study and highlights future research opportunities.

## 2 FDA Drug Relabeling

The pharmaceutical industry in the U.S. is highly regulated and drug candidates undergo rigorous clinical testing prior to being submitted to the FDA for approval. During this rigorous process possible risks and side effects of a drug candidate are identified. This information becomes part of the FDA approved label and drug insert that accompanies a newly approved drug. Unfortunately, some side effects do not become known until after a drug has been approved. To help with the reporting and collection of these adverse events the FDA founded MedWatch in 1993. Healthcare professionals or consumers (patients) can voluntary report to Medwatch. In more recent times this adverse events data has been made available via FAERS.[5]

During the post-approval time period the FDA monitors adverse reporting along with results from post-approval studies and peer-reviewed literature. Negative safety-related information is scrutinized and the FDA can form an investigation team to determine if a safety label update is needed. If the FDA believes a safety label change is warranted the manufacturer is notified and is required to report back to the FDA within a predetermined period. The agency works privately with a manufacturer to determine which type of safety label change will be made. At the end of the process the FDA will publish this information online while allowing firms additional time to change actual printed material.[6] Prior to 2016 product safety data was available via MedWatch but has since shifted to the FDA Drug Safety Label Change (SLC) database.

The main safety labeling changes that the FDA issues include adverse reaction, precaution, warning, contraindication, and box warning. Adverse reactions, precautions, and warnings serve to inform physicians and consumers of possible health concerns that have been clinically identified, anticipated to occur, or associated with unapproved uses. A box or "black box" warning is the most severe of type of label change and is intended to communicate potentially severe health risks resulting from taking a drug. For example, in 2004 the FDA issued box warnings for all anti-depressant drugs over the concern that these drugs could lead to suicide in patients younger than 18 years of age.[7] While these changes can be sensational, most changes are much less so. For example, Topomax® was the target of a "precaution and warning" label change due to an elevated risk of kidney stones.[8] As this example demonstrates, drugs can undergo several types of relabeling simultaneously. Additionally, a drug that has been relabeled can undergo additional safety label

[5] This data has been made available (current and historic) by quarters by the NBER: http://www.nber.org/data/fda-adverse-event-reporting-system-faers-data.html.

[6] A detailed description of the process can be found here: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm250783.pdf

[7] https://www.medpagetoday.com/psychiatry/depression/210

[8] https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=1063

changes in the future, if warranted.

## 3 Adverse Regulatory Events

We draw on several strands of literature starting with the economics of regulation. Early work in this area theorizes on the impact of regulation on consumer and firm behavior (e.g., Stigler, 1971; Peltzman, 1976; Migue, 1977). Brown et al. (1964) argued that regulation could be viewed as an information transmission process. As consumers receive new information they are able to update and change their behavior. Subsequent work built on this idea to show how information influences consumer perception of product quality (Zeithaml, 1988) and how behavior changes with positive information (Nelson, 1970). In contrast, Hartley (1994) showed how negative product information led to decreased sales. More broadly, Oberholzer-Gee and Mitsunari (2006) examined how non-related negative events, in their case the release of pollution information, decreased property values. In our context, the process of relabeling in the pharmaceutical industry can be viewed as an information transmission process that could subsequently impact consumer (or their agent's) behavior.

Our paper also draws on literatures in health economics where scholars have explored the implementation of regulatory procedures on public health (e.g., Gruenspecht and Lave, 2006). In the case of the pharmaceutical industry, Dranove (2011) stresses the importance of quality certification for efficient and optimal regulation. For drugs, this certification comes in the form of the FDA approval process. This process can be divided into pre- and post-approval stages. The pre-approval stage includes clinical testing and provides the first line of defense to ensure safety and efficacy of products. This creates a tension, however, for regulators between length of trials and getting new drugs to market. For example, adverse events have been increasing (Moore et al., 2007) and have been associated with declines in pre-approval times (Olson, 2002). This makes post-approval safety monitoring critically important. In recent times FAERS has served as an important source of data for updating safety labeling information (Wysowski and Swartz, 2005).

Based on these prior studies, adverse safety related information should improve consumer awareness about the potential safety of a drug and lead to changes in behavior. Presumably consumers and/or their agents (i.e, physicians) may shift away from a drug given a safety concern. A number of studies focused on specific therapeutic markets support this association (e.g., Dranove and Olsen, 1994; Smalley et al., 2000; Cheah et al., 2007; Olfson and Marcus, 2008; Tekin and Markowitz, 2008; Bunniran et al., 2009; Dorsey

et al., 2010; Kales et al., 2011; Dusetzina et al., 2012; Briesacher et al., 2013; Lu et al., 2014). Prior work also documents that this association could be differential; new drugs tend be impacted more than existing drugs (Wilkinson et al., 2004) and geographic variation could cause the usage of a warned drug to be different (Shah et al., 2010).

What remains unknown from this batch of prior work is what constitutes a rational, medically appropriate response? One might expect consumers, through their physicians, to be switched to other drugs as the severity of events increase. Moreover, consumers may just decide to stop treatment altogether and leave the market. Importantly, these studies are unable to distinguish between these two possibilities.[9] Prospect theory (Tversky and Kahneman, 1992; Kahneman and Tversky, 1979) provides one explanation as to why consumers may ultimately leave the market. These consumers, when confronted with new information about a drug, may vastly overestimate the probability of a negative event within their own weighting function. They may also incorrectly attribute these same negative effects to substitute drugs that physicians prescribe. As a result, they conclude that the benefit does not outweigh the risk and exit the market.

There is experimental evidence that reinforces these negative actions. For example, Bunniran et al. (2009) study blame and trust due to pharmaceutical products withdrawn as a result of safety related concerns. They found that consumers taking the withdrawn drug or those taking another drug within the same class were highly likely to blame pharmaceutical companies and the FDA. After an event trust in both institutions was also fairly low. These declines provide one plausible explanation as to why consumers may formulate and attribute the negative effects described by Tversky and Kahneman (1992) and Kahneman and Tversky (1979) to a focal drug or a substitute.

The way in which consumers appear to be responding to adverse safety events suggests that there are potential welfare implications. On the one hand, with better information patients can be more accurately and effectively treated, which should enhance welfare. On the other hand, however, if patients are irrationally switched to inferior drugs (in terms of treatment) or choose to leave the market all together, this could diminish welfare. Given the tension between moving drugs through clinical trials in a timely manner and post-approval safety events, these welfare implications are important for regulators and for the implementation of policy.

More broadly, the answer contributes additional evidence to the literature on welfare effects of regu-

[9] Given the breadth and depth of our data this is a distinction we will be able to analyze. Many prior studies lack sufficient data to capture all the intra- and inter-market substitution patterns that are possible.

lation. By its nature, regulation should be welfare enhancing but ample evidence exists that this may not always be the case. For example, the milk industry was regulated in the 1960s but that regulation was shown to be a detriment to welfare (Kessel, 1967). Bartel and Thomas (1987) found that the Occupational Safety and Health Administration did not have a significant impact on national injury rates. Similarly, Ter-Martirosyan and Kwoka (2010) found that incentive regulation caused quality degradation in the U.S. electricity industry. In healthcare, mandatory prescription regulation has not significantly improved health outcomes (Peltzman, 1987) and in hospitals regulation of quality standards has inflated costs and diminished patient welfare (Sloan and Steinwald, 1980).

Regulation can also have unintended consequence from spillovers. For example, toy recalls due to safety reasons tend to cause negative industry-wide spillover effects for similar types of toys (Freedman et al., 2012). In our setting, such spillovers would manifest in the drugs within the same market or related market as the focal drug that is relabeled due to a safety concern. Following this literature, we intend to capture both the direct and indirect (i.e., spillovers) effects of drug relabeling due to adverse safety concerns.

# 4 Empirical Strategy and Data

## 4.1 Empirical Strategy

We exploit FDA relabeling events to estimate a difference-in-differences (diff-in-diffs) specification. As we discussed above, the relabeling process involves private interaction between the FDA and focal firm and remains unknown to consumers and physicians prior to formal action. We use two groups of observations. The first group (treated) includes drugs sold in the U.S. Because FDA relabeling events only affects drugs sold in the U.S., our treated group is exposed to treatment in the post-relabel period but not in the pre-relabel period. The second group (control) is comprised of the same drugs as those in the treated group but sold in the U.K. Our identification strategy relies on the fact that the control group is not exposed to treatment in either period (see Figure 1).[10] Importantly, the U.S. FDA does not have regulatory jurisdiction over drugs sold in the U.K.

Using a traditional diff-in-diffs approach, we estimate the following model (subscripts and controls are omitted for simplicity):

[10]It is possible that drugs in the U.K. can undergo relabeling in the U.K. by the U.K. Medicines and Healthcare Products Regulatory Agency. We discuss this issue in Section 4.2.

$$y = \beta_0 + \beta_1 Relabel + \beta_2 U.S. + \beta_3 (Relabel * U.S.) + \beta_4 Price + \beta_5 (Lagged\ promotion\ stock) + \varepsilon \quad (8)$$

where $y$ is aggregate demand (i.e., drug sales). *Relabel* is a dummy variable for the post-treatment period represented by drug relabeling events and captures aggregate factors that would cause changes in $y$ even in the absence of the treatment. $U.S.$ is a dummy variable and captures possible differences between the treatment and control groups. The coefficient of interest is $\beta_3$ and it represents the impact induced by drug relabeling events on U.S. drugs relative to U.K. drugs.

## 4.2 Data

Our sample consists of all drugs sold in both the U.S. and U.K. during 2003 to 2009 as identified by IMS MIDAS™. Relabeling data for drugs sold in the U.S. was collected from the FDA MedWatch database and we restricted that data to those drugs that experienced a first-instance of a drug relabel.[11] Relabeling data for drugs sold in the U.K. was gathered from Datapharm's electronic Medicines Compendium that covers all drugs approved by the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA).[12] In order to create a clean control group we further restricted our treated drugs to include only those that experienced a relabel in the U.S. but no relabel in the U.K. within eight quarters of the U.S. relabel. Table 1 provides the distribution of relabel activity in the U.S. and U.K. For those drugs that were subsequently relabeled in the U.K. the average time until relabel was 12.95 months $after$ the relabel event in the U.S. This was shorter than 18.5 months documented by Pfistermeister et al. (2013) for a limited sample of psychiatric drugs.[13] Importantly, we could find no evidence that drug relabeling in the U.S., on average, systematically impacted contemporaneous physician prescription patterns in the U.K. (see Figure 1). This further validates our U.K. sample as a clean control for causal estimates in our study.

Next, we gathered quarterly drug-level sales, detailing (promotions), and price data from IMS MI-

[11] It is possible to have multiple different types of relabeling activity at the same time. This is not a concern for our baseline models. However, when we examine the variation across types of relabeling activity we include those observations in each type of relabeling activity. We focus on four types of relabeling events: precaution, adverse reaction, warning and box warning. There was only one first-instance of a contraindication that met our sample criteria. It was excluded from the final sample; our results do not change with this exclusion.

[12] https://www.medicines.org.uk/emc/

[13] In Table A.1 we extend the time frame for our baseline model from eight quarters to 12 and 16 quarters; our results remain robust to these longer time frames.

DAS™. Sales or quantity data is standardized by IMS into a 'standard unit' that equates pills, tablets and liquids. The data for both the U.S. and U.K. includes both hospital and retail channels. IMS MIDAS™ includes all branded and generic drugs and covers every therapeutic category. Detailing or direct-to-physician promotion data is available for all approved drugs. Financial variables from the U.K. have been converted by IMS to U.S. dollars and all financial variables have been converted to real 2009 dollars using a GDP deflator.[14] Descriptive statistics are presented in Table 2.

Note that drugs are approved for use within 4-digit anatomical therapeutic chemical (ATC) markets. The ATC classification is controlled by the World Health Organization and was designed to categorize drugs into different groups according to the organ or systems that they treat.[15] There are four different levels of classification ranging from the most aggregate (1-digit ATC) to most disaggregate (4-digit ATC). For example, 1-digit ATC market N comprises drugs for the nervous system. Within ATC N there are seven 2-digit ATC markets that contain 19 3-digit ATC markets. Each of these 3-digit ATC markets, in turn, contains 4-digit ATC markets. An advantage of our data is that it is available at the 4-digit ATC market level and can be aggregated as needed.

### 4.2.1 Dependent Variable

Our baseline dependent variable is focal drug sales (quantity) in standard units as determined by IMS. Sales are aggregated across varying dosages to the drug level since a relabeling event will impact the drug similarly across dosage types. We define *Sales* as the natural logarithm of quarterly focal drug sales plus one. In addition to the baseline focal drug level, we will consider two additional aggregate models. First, we consider sales of all drugs within the focal drugs 4-digit ATC market. Drugs within a 4-digit ATC market can be reasonably viewed as substitutes. For example, both anti-viral drugs Invirase® to Norvir® are contained in the 4-digit ATC market J5AE (protease inhibitors). Importantly, this aggregation allows us to capture intra-market substitution by physicians.

Second, we move up one more level of aggregation to the 3-digit ATC market. At this level of analysis we capture all drugs within multiple 4-digit ATC markets but contained within the same 3-digit ATC market.[16] For example, the two 4-digit ATC markets J5AE (protease inhibitors) and J5AE (nucleotide reverse

[14] It is critical to note that the price data within IMS MIDAS™ is a wholesale price. It does not include adjustments as a result of back-end rebate payments or any other discounts that may be offered to insurance or prescription benefit companies.

[15] For a more detailed discussion: https://www.whocc.no/atc_ddd_methodology/purpose_of_the_atc_ddd_system/

[16] These markets can be explored at: https://www.whocc.no/atc_ddd_index/?code=J05A.

transcriptase inhibitors) are contained within the 3-digit ATC market J5A (direct acting antivirals). This level of aggregation allows us to capture inter-market substitution by physicians.[17]

### 4.2.2 Independent Variables

Our sample includes drugs that were sold both in the U.S. and U.K. We define $U.S.$ as a dummy variable that equals one if the drug was sold in the U.S., zero otherwise. In order to implement our diff-in-diffs strategy, we define a dummy variable (*Relabel*) that equals one for all observations after a drug's first relabeling event, zero otherwise. Relabel encompasses four types of events: precaution, adverse reaction, warning and box warning.

Prior work has demonstrated the importance of detailing on physician prescription behavior (e.g., Datta and Dave, 2017; Manchanda and Honka, 2005) and reducing price elasticity (Windmeijer et al., 2006; Rizzo, 1999). However, contemporaneous detailing is a function of current sales, which could create a reverse causal relationship. To resolve this issue we use lagged promotion stock as studies have shown that promotions have a carry-over effect (e.g., Van Heerde et al., 2007; Zhao et al., 2011). Importantly, prior promotion expenditures should not be impacted by contemporaneous sales. As such we define *Lagged promotion stock* as the discounted sum of the prior three quarters detailing expenditures. We follow the literature (Leone, 1995) and use a 70 percent discount rate, however our baseline results are not sensitive to inclusion or variation in this rate.[18]

Next, we control for several drug and market characteristics that may influence sales or demand. First, we define *Vintage* as a measure of elapsed time, in quarters, from introduction. Drugs that have been on the market longer have time to build up brand loyalties with consumers and physicians even though they may become 'outdated' as newer treatments come to market. Finally, we include count variables for the *Number of brands* and *Number of generics*. The former controls for the intra-market substitution possibilities or the ability of physicians to switch patients to another drug within the same therapeutic market (often referred

[17] As a robustness check, and as a method to verify we have captured all reasonable substitution patterns, on average, we aggregate markets up one more level to the 2-digit ATC market. At this level of aggregation we capture all 3-digit ATC markets contained within a 2-digit ATC market. Each of those 3-digit ATC markets will include 4-digit ATC markets. For example, let's consider the 2-digit ATC market J04 (antimycobaterials). It contains two 3-digit ATC markets, J04A (drugs for treatment of tuberculosis) and J04B (drugs for treatment of lepra). The 3-digit ATC market J04A contains six 4-digit ATC markets: J04AA (aminosalicylic acid and derivatives), J04AB (antibiotics), J04AC (hydrazides), J04AD (thiocarbamide derivatives), J04AK (other drugs for the treatment of tuberculosis), and J04AM (combinations of drugs for the treatment of tuberculosis). The 3-digit ATC market J04B contains one 4-digit ATC market, J04BA (drugs for the treatment of lepra). Like our 3-digit ATC market level of analysis this 2-digit ATC market level of analysis can also be viewed as capturing inter-market substitution.

[18] Following Leone (1995) we vary the discount rate between 50 and 70 percent.

to 'me-to' drugs). The latter controls for cross-molecular substitution or the insurance companies ability to attempt to influence physicians to switch patients to a generic of another branded drug within a focal drug therapeutic market (Branstetter et al., 2016, 2014).[19]

### 4.2.3 Endogeneity of Price

As indicated above, for those drugs that have multiple dosages sold by the same firm we aggregate the data together to the drug-level. We define *Price* by dividing drug-level revenues by the number of drug-level SU sold. It is important to note that we are capturing wholesale price and this does not include any unmeasured discounting (rebates) by pharmaceutical companies, which is not commercially available. This price variable, however, will be highly correlated with ultimate consumer price and as such will be endogenous.[20] To address this concern we follow the literature (e.g., Hausman et al., 1994; Hausman, 1996; Nevo, 2001) and use the mean and median price of other drugs in closely related markets as instruments for the focal drug's price. Specifically, we use the mean and median price of other drugs within the same 2-digit ATC market. For example, if our focal drug is a MAO-inhibitor (4-digit ATC market C02KC) we take the mean and median price of drugs in the broader 2-digit ATC market, C02 (anti-hypertensives). Drugs within the same 2-digit ATC should, on average, be correlated due to similar marginal costs but uncorrelated with the focal drug's unobserved product characteristics. The instruments pass the usual tests and are reported in the bottom panel of each table.

# 5 Empirical Findings

## 5.1 Impact of Drug Relabeling on Demand

In Table 3 we present empirical results from Equation 1. Model 1 presents estimates at the focal drug level, Model 2 presents estimates at the 4-digit ATC market level and Model 3 presents estimates at the 3-digit ATC market level. Model 1 can be viewed as testing the casual impact of drug relabeling on aggregate focal drug demand while Model 2 captures intra-market drug substitution. In other words, Model 2 helps us

[19] As an example, assume there are three branded drugs within a market, Brand A, Brand B and Brand C along with two generic drugs, Generic B and Generic C. Cross-molecular substitution refers to an insurance company trying to convince physicians to shift patients from Brand A to either Generic B or Generic C, often by providing economic incentives to consumers.

[20] A significant body of prior research on the pharmaceutical industry uses earlier versions of the IMS Health data that we employ here. Like us, these prior researchers do not directly observe retail sales or prices. Although this is a shortcoming, the data are widely seen within the industry as the "gold standard" of pharmaceutical data.

understand if physicians switch consumers to another drug in the same 4-digit ATC market. An example of such a substitution would be a switch from the anti-viral Invirase® to Norvir®. Finally, Model 3 captures inter-market drug substitution. In this case, physicians switch patients to another drug in a different 4-digit ATC market but within the same 3-digit ATC market. In the prior example, both Invirase® and Norvir® are in the 4-digit ATC market J5AE (protease inhibitors). In the current example, a physician would be switching a patient from either of those two drugs to Retrovir®, which is in the 4-digit ATC market J5AF (nucleotide reverse transcriptase inhibitors). All three drugs are treatments for HIV and both 4-digit ATC markets, J5AE and J5AF, are contained within the 3-digit ATC market J5A (direct acting antivirals).

The dependent variable across all three models is *Sales* and includes our full set of controls. In Model 1 we include drug and time fixed effects while in Models 2 and 3 we include market and time fixed effects. *Price* is instrumented in all models and pass the usual test statistics, which are reported in the table. Standard errors are clustered at the 2-digit ATC market level. The coefficient of interest is the interaction term (*Relabel * U.S.*); it is negative and statistically significant across models. In Model 1 we find a 16.9 percent decline in focal drug sales caused by the first instance of a drug relabel. When we aggregate within 4-digit ATC markets in Model 2 we find a 5.1 percent decline in aggregate demand. Importantly, this model accounts for aggregate demand of the focal drug that was absorbed by other drugs within that same 4-digit ATC market. In other words, physicians engaged in intra-market substitution and switched patients to another drug within the same therapeutic market. From the previous example, this would be a switch from Invirase® to Norvir® within the 4-digit ATC market J5AE.[21]

This is not the only substitution that can take place. It is possible that physicians can engage in inter-market substitution and switch consumers to another drug in a different 4-digit ATC market but still within the same 3-digit ATC market. Again, in the above example, this would be a switch from Invirase® (4-digit ATC market J5AE) to Retrovir® (4-digit ATC market J5AF) which are both in 3-digit ATC market J5A. In Model 3 we find a 4.7 percent decline in aggregate demand for drugs within a 3-digit ATC market that experienced a relabel. Critically, the result in Model 3 implies that after capturing intra- and inter-market substitution patterns aggregate demand still declined by 4.7 percent. This model also captures and controls

[21] In Tables A.1 and A.2 we test alternative treatment periods. First, in Table A.1 we consider time periods of three (Model 2) and four years (Model 3) before and after a drug relabeling. Our base model (Model 1, Table 3) is included as Model 1 for comparative purposes. Second, in Table A.2 we widen the treatment window around the actual drug relabel. As a reminder, our baseline model excludes the quarter when a relabeling event occurred. In Model 1 and Model 2 we increase that exclusion to one and two quarters, respectively, before the quarter of relabel. This increase in exclusion will help if information leaks prior to announcement. All of the robustness results are consistent with our main findings in Table 3.

for competitive responses through changes in detailing (Macher and Wade, 2013). Ultimately, this decline plausibly represents consumers that fall out of the market.

It is important to recall the process that is involved with these types of substitutions. Only a physician can switch a consumer to another drug. While we can detect *ex post* that a substitution has occurred, we do not know what precipitated the move.[22] There are several possibilities. First, consumers could become informed of the relabel and push a physician to switch them. Second, physicians could independently learn about the relabel and decide to proactively switch a consumer. Third, physicians could learn about the relabel through detailing, either by the affected company or by a competitor and then decide to switch a consumer to another drug. These three are not mutually exclusive and there is some evidence to support the third explanation (Macher and Wade, 2013).

Given that our data is at the standard unit level we do not know exactly how many consumers this represents because prescription patterns will differ across drugs and consumers. We can, however, calculate a conservative, lower bound if we assume that the loss was for chronic conditions that require daily uptake. Under this assumption, we can multiply the decline in aggregate demand from Model 3 by average sales over the two-year sample period prior to the relabeling event. This translates into an estimated decline of 7.97 million standard units or slightly over 265,000 30-day prescriptions. If all of these prescriptions were for chronic conditions then this translates into approximately 11,000 consumers that fall out of the market.[23] Again, this is likely to be a conservative, lower bound estimate because not every prescription is for a chronic condition requiring a daily dose. As the number of prescriptions for acute conditions increase so would the number of consumers that fall out of the market.

These results have interesting welfare implications but even with our data, the best we can do is conjecture about them. First, if consumers that should be medicated move from the treated to untreated population this would be a detriment to consumer welfare. As suggested above, prospect theory provides one explanation as to why consumers may fall out of the market. These consumers, when confronted with new information about their current drug, may vastly overestimate the probability of a negative event within their own weighting function. They may also incorrectly attribute these same negative effects to the substitute drugs that physicians prescribe. As a result, they conclude the benefit does not outweigh the risk and exit the

[22] This would require data on why physicians switched or changed a prescription. It would also require us to have prescription level data as opposed to what we have at the standard-unit level.

[23] Average quarterly sales (21.2 million) x 4.7% = 0.99 million standard units x 8 quarters = 7.97 million standard units. Next, 7.97 million divided by 30 = 265,707 30-day prescriptions. Finally, 265,707 divided by 24 months = 11,071 chronic patients.

market.[24] Second, if the consumers that leave the market were those that were only marginally benefitting from a drug or maybe should not have been prescribed a drug to begin with, then the negative impact on welfare may be muted. For example, ample evidence exists that suggests many medications are overprescribed (e.g., Lembke et al., 2018; Sacarny et al., 2016; Forgacs and Loganayagam, 2008; Price et al., 1986). Unfortunately, no data exists to determine which type of consumer leaves the market and why. As such, the overall impact on welfare is most likely bounded between these two extremes.

## 5.2 Heterogeneous Impacts Across Relabeling Intensity

Relabeling intensity varies across therapeutic markets (see Table A.3). In Tables 4 and 5 we explore how these differential intensities impact aggregate demand. We divide our data into two sub-samples and define 'low-intensity markets' and 'high-intensity markets'.[25] In Table 4, low-intensity markets are defined as those 4-digit ATC markets where there was only one relabeling event over our sample period. In contrast, in Table 5, we define high-intensity markets as those 4-digit ATC markets where more than one relabeling event occurred over the sample period. In Table 4, Model 1 the coefficient on the interaction term (*Relabel * U.S.*) is negative and statistically significant at the one percent level. We find a decline of 10.8 percent in aggregate demand for focal drugs in these low-intensity markets. Interestingly, however, in Model 2 and Model 3 the interaction is not statistically significant. This suggests that intra-market substitution absorbed the decline in aggregate focal drug demand. In other words, in these markets physicians were successfully able to switch consumers to another drug within that same 4-digit ATC market. To the extent that consumer or physician concerns are warranted due to a relabeling event, this is the expected outcome.

In high-intensity markets, on the other hand, results are more complex. Across all models in Table 5 the interaction term is negative and statistically significant. In Model 1 aggregate focal drug demand declined by 18.9 percent decline while in Model 2 aggregate demand declined by 6.0 percent for drugs within a focal drug's 4-digit ATC market. As before, Model 2 represents intra-market substitution or consumers being switched to other drugs within the same 4-digit ATC market. Shifting to the 3-digit ATC market that incorporates inter-market substitution patterns, Model 3, aggregate demand declined by 5.0 percent. Critically, this 5.0 percent decline in aggregate demand represents consumers that fall out of the market after controls for all plausible substitution patterns..

[24] Patients could leave the market for costs reasons too. For example, the new drug that a physician wants to switch to may be too expensive or not covered by insurance.

[25] At the 4-digit ATC market-level there are 61 markets categorized as low-intensity and 76 as high-intensity.

In Tables A.4 and A.5 we redefine low-intensity and high-intensity markets as those markets in the bottom and top quartile of relabeling activity. Results remain robust with those reported in Tables 4 and 5. In low-intensity markets, Table A.4, Model 1 aggregate focal demand declined by 10.3 percent. The interaction was not significant in Model 2 nor Model 3 again suggesting that intra-market substation absorbed the entire decline. For the high-intensity markets, Table A.5, Model 1 aggregate focal drug demand declined by 20.1 percent. In Model 2, which incorporates intra-market substitution patterns, aggregate demand declined by 13.0 percent. Finally, in Model 3 that incorporates inter-market substitution, aggregate demand declined by 8.3 percent. Again, this 8.3 percent decline in aggregate demand represents consumers that fall out of the market.

### 5.3 Heterogeneous Impacts Across Levels of Relabeling Severity

As discussed in Section 2.0 the severity of drug relabeling spans from precaution (least serious) through box warnings (most serious). Table 6 explores whether the aggregate demand response we documented varies across this continuum of severity. We split the data into three sub-samples representing precaution (Model 1), adverse reaction (Model 2) and warning/box warning (Model 3). The categorization continues to be based on the first time a drug is relabeled and allows us to isolate out the effects of any potential prior relabeling activity. Drugs that have multiple types of relabeling are counted individually in each category.[26] Across all models the interaction remains negative and statistically significant. As expected, we see an increasingly negative aggregate demand response as severity increases; aggregate demand declines by 15.6 percent, 20.3 percent and 36.3 percent in Models 1, 2 and 3, respectively.

The increasing decline in aggregate demand as severity increases should not be surprising; physicians appear to be switching consumers to other drugs as new potential risks reveal themselves. Notwithstanding the general decline, the results in Model 1 are unexpected. This appears to be a rather strong aggregate demand response given the limited severity of the relabel. If the response is medically warranted or if physicians believe there may be future problems with a relabeled drug, then we should see intra-market substitution absorb this decline.[27] We examine this in Table 7 where we split the sample and combine the two least severe relabeling events (i.e., precaution and adverse reaction) together. Again, across the models

[26] For example, if a relabeling event included both a precaution and an adverse reaction it would be included both as a precaution and adverse reaction individually.

[27] The average probability that a drug that has received a precaution receives another relabel is 72.2%. As such, physicians may be pre-emptively switching patients to another drug. However, in this case we should see the entirety of aggregate demand decline of a focal drug absorbed by intra-market substitution.

we find a negative and statistically significant coefficient on our interaction of interest. At the focal drug level, Model 1, aggregate demand declined by 14.7 percent while at the 4-digit ATC market level, which incorporates intra-market substitution, aggregate demand declined by 5.1 percent. At the 3-digit ATC market level, Model 3, which accounts for inter-market substitution aggregate demand declined by 4.0 percent and represents the consumers that leave the market.

In Table 6 Model 3, aggregate demand declined by 36.3 percent for drugs that received either a warning or box warning. This response should not be surprising given the severity of the relabeling event. In Table 8, we combine warnings and box warnings and examine their intra- and inter-market substitution patterns. Across all three models in Table 8 our coefficient on the interaction term is negative and statistically significant. At the 4-digit ATC market level that incorporates intra-market substitution patterns (Model 2), aggregate demand declined by 10.0 percent. At the 3-digit ATC market level that accounts for inter-market substitution patterns (Model 3), aggregate demand declined by 8.3 percent and again represents consumers that leave the market. As the severity of the relabeling event increases (Table 7, Model 3 versus Table 8, Model 3) the percentage of consumers that choose to leave the market increases as well.[28] Importantly, given the substitution patterns captured within Model 3, consumers appear to viewing potential substitutes in the same negative manner as the focal drug.

Finally, we combine the intensity levels of relabeling activity from the prior section and examine how it impacts the heterogeneity of relabeling severity that we considered in this section. In Tables A.8 and A.9 we replicate Tables 7 and 8 for low-intensity markets. Results are consistent with our prior findings (Table 4 and Table A.4). In Tables A.8 and A.9 we see declines in aggregate focal demand (Model 1) of 6.6 and 45.0 percent, respectively. Results in Models 2 and 3 are not statistically significant, suggesting that the entire decline in aggregate focal drug demand was absorbed by intra-market substitution.

In Tables A.10 and A.11 we replicate Tables 7 and 8 for high-intensity markets. Again, results are consistent with our prior findings for high-intensity markets (Table 5 and Table A.5). For relabeling events that involved precaution or adverse warnings in high intensity markets, aggregate demand declined by 17.3 percent (Table A.10, Model 1). At the 4-digit ATC market (Model 2) that incorporates intra-market substitution patterns, aggregate demand declined by 5.9 percent. Finally, at the 3-digit ATC market level (Model 3)

[28] In Tables A.6 and A.7 we consider alternative time periods. First, in Table A.6 we consider three and four years before and after a relabeling event (as opposed to two years in our baseline model). Second, our baseline model excludes the quarter in which a relabeling event occurred. In Table A.7 we exclude one and two quarters prior to the relabeling event (along with the quarter of the event). In both tables and across all models our results remain robust to our baseline findings.

that incorporates inter-market substitution patterns, aggregate demand declined by 4.8 percent. This again represents consumers that leave the market. The most significant declines are in high-intensity markets with warnings or box warnings (Table A.11). Aggregate demand declined by 34.3 percent at the focal drug level (Model 1), 10.4 percent at the 4-digit ATC market level (Model 2), and 15.8 percent at the 3-digit ATC market level (Model 3). Unlike low-intensity markets where intra-market substitution absorbed the decline in aggregate focal drug demand, in high-intensity markets we see significant movement by consumers out of the market.

# 6 Robustness

## 6.1 Variation Across Market Concentration and Market Size

It may be possible that variation in market size or the level of competition within markets may differentially influence physician prescribing behavior or consumer behavior. For example, business or general news stories may enhance physician or consumer awareness about a drug. We examine these issues in Table A.12. In Models 1 and 2 we separate markets into the bottom and top quartiles of sales while in Models 3 and 4 we create a HHI index and separate markets into the bottom and top quartiles, respectively. Across all models we find a negative and significant coefficient on our interaction term. Aggregate demand declined by 9.5 percent and 19.8 percent in the bottom and top sales quartiles (Models 1 and 2), respectively. However, when we consider the bottom and top quartiles of HHI, the difference becomes negligible. In Models 3 and 4, aggregate demand declined by 22.8 percent and 21.3 percent, respectively. Thus, we appear to see some variation in response across market sizes but not across levels of competition.

## 6.2 Cross-Molecular Substitution

Drugs vary in their level of cross-molecular substitution (Branstetter et al., 2016) or rates at which one drug can be substituted for another. Thus we examine two classes of drugs that, according to our discussions with physicians and prior research, should exhibit significantly different cross-molecular substitution. The first market we will consider is ATC N (nervous system), which is comprised of seven 2-digit ATC therapeutic markets: anesthetics (N01), analgesics (N02), antiepileptics (N03), anti-Parkinson (N04), psycholeptics (N05), psychoanaleptics (N06) and other nervous system drugs (N07). Within these 2-digit ATC markets we have additional 3-digit and 4-digit ATC markets. For example, within N06 resides anti-depressants (N06A)

and anti-dementia (N06D) drugs. In general, ATC N should exhibit lowers of cross-molecular substitution (Branstetter et al., 2016). In Table A.13 we find a decline in aggregate focal drug demand of 21.4 percent (Model 1), however, the coefficient of interest is not significant in Model 2 or Model 3. These markets experience greater declines in aggregate demand, in percentage terms, than we saw for the overall sample, however, the entire decline is absorbed by intra-market substitution. That is, physicians successfully switch consumers to other drugs within the same 4-digit ATC market.

The second market that we consider is ATC J (anti-infectives), which is comprised of six 2-digit ATC markets: anti-bacterials (J01), anti-mycotics (J02), anti-mycobaterials (J04), anti-virals (J05), immune sera and immunoglobulins (J06), and vaccines (J07). The 2-digit ATC market J01 includes 10 different 3-digit ATC markets comprising various classes of anti-bacterials; for example, tetracyclines (J01A) and beta-lactam anti-bacterials/penicillins (J01C). In general, these ATC markets should exhibit greater rates of CMS than ATC N. In Table A.14 we find a focal decline in aggregate demand of 24.2 percent (Model 1). In these markets, however, we also see declines of 13.8 percent and 13.5 percent in the 4-digit (Model 2) and 3-digit (Model 3) ATC markets, respectively. Thus, in markets where we observe greater rates of CMS, we also observe significant numbers of consumers leaving the market.

While we explore only two markets that represent varying levels of CMS we do find interesting results that are suggestive that the degree to which drugs are substituted ultimately impacts consumer response and their choice to leave the market. Generally, drugs within ATC N tend to be for chronic conditions as opposed to drugs within ATC J that tend to be for more acute conditions. Thus, consumers may be more willing to drop out of less-chronic markets. Interestingly, the rate at which consumers leave the market appears to be the opposite of what scholars have found with respect to drug adherence rates (e.g., Haynes et al., 2002; Jackevicius et al., 2002; Cramer et al., 2003). In one study using data from Kaiser primary non-adherence for anti-infectives was found to be 2.9 percent (Shin et al., 2012). Our combined results appear to suggest that for acute conditions primary non-adherence is lower but when confronted with negative information consumers leave the market at a higher rate than those suffering chronic conditions. In chronic markets, primary non-adherence is greater but those consumers are less likely to completely abandon the market. Overall, our results suggest that policy makers and physicians need to worry about not only non-adherence but also how consumers respond to negative news about drugs.

# 7 Discussion and Conclusions

We are not the first to analyze the impacts of drug relabeling in the U.S. However, unlike prior studies we are able to do so in a more comprehensive and causal manner. Given the breadth of our data we are able to incorporate all plausible intra- and inter-market substitution patterns across a larger number of markets. This allows us to estimate not only the causal impact of a relabeling event on a focal drug but also quantify consumers that ultimately fall out of the market. In our baseline regressions (Table 3, Model 1) we find a decline in aggregate focal drug demand of 16.9 percent at the first instance of relabeling. As Figure 1 demonstrates there is a significant decline in aggregate demand due to relabeling. Critically, after accounting for intra- and inter-market substitution patterns and potential competitor reactions we find decline in aggregate demand of 4.7 percent that plausibly represents consumers that leave the market (Table 3, Model 3). As a lower bound, this translates into approximately 11,000 consumers with chronic conditions. We believe this is the first evidence to suggest that drug relabeling is causing consumers to leave the market.

These baseline results have potential welfare implications as consumers shift from the treated to untreated population. On the one hand, if these are consumers that should be treated but are no longer treated this will be a detriment to welfare. Adding to this negative effect will be those consumers that may have been switched to another drug that turns out to be less effective. On the other hand, there is ample evidence to suggest that some types of drugs are overprescribed so if the consumers that leave the market should never have been treated in the first place then these negative welfare impacts will be dampened. Unfortunately, we have no data to suggest which types of consumers are leaving the market so we are unable to make definitive statements about welfare.

In addition to our baseline results, we find increasing impacts across all levels of relabeling severity (Table 6). Consistent with prior literature (e.g., Dorsey et al., 2010) we find the greatest impact, in percentage forms, for the most severe type of relabel. Less intuitive, however, is why we see such a significant aggregate demand response for the least severe relabel (i.e., precaution). Conditional on receiving a precaution, there is a significant probability that a drug will be relabeled again in the future. So it is plausible that physicians are preemptively switching consumers to other drugs. It is possible that physicians may also be responding to increased detailing by competitors (Macher and Wade, 2013).[29] After accounting for intra- and inter-market substitution (Table 7) we still find a 4.0 percent decline in aggregate demand, which represents consumers

[29] Here we are not referring to state substitution laws that allow for the shift from Brand A to Generic A without physician approval. Instead, we are talking about the movement from Brand A to either Brand B or Generic B.

falling out of the market. As we conjectured in the paper, prospect theory provides one explanation for why this may be occurring; consumers may be over-estimating future negative events and projecting those negative events onto substitute products. As a result, in their minds the expected costs of taking substitute products are not worth the expected benefits.

We exploit other variation in our data. For example, we break markets into "low-intensity" and "high-intensity" markets based on the level of relabeling activity within a particular 4-digit ATC market. In the case of low-intensity markets (Table 4 and Table A.4) and low-intensity markets across types of relabeling (Tables A.8 and A.9), we find that the entire decline in aggregate focal demand was absorbed by intra-market substitution. That is patients were all successfully switched to other drugs within the same 4-digit ATC market. In contrast, in the case of high-intensity markets (Table 5 and Table A.5) and high-intensity markets across types of relabeling (Tables A.9 and A.10) we find not only declines in aggregate focal drug demand but also find that consumers leave the market. This split is an important caveat to prior work, especially the work focused on box warnings (e.g., Dorsey et al., 2010; Olfson and Marcus, 2008; Jacoby et al., 2005) because it suggests the impacts are more nuanced. Ultimately, the impacts of these kinds of warnings depend on the type of market in which they occurred.

Our results are robust to alternative treatment windows and to the exclusion of additional quarters prior to treatment. In addition to being sensitive to relabeling intensity, our results also vary across different levels of CMS. In markets were we expect low levels of cross-molecular substitution we find strong declines in aggregate focal drug demand (Table A.13, Model 1). The entire decline, however, is absorbed by intra-market substitution. That is, on average, consumers are switched to other drugs within the same 4-digit ATC market. We see the opposite in markets with higher levels of CMS. In that market (Table A.14) we again see similar declines in aggregate focal drug demand. However, in this market we still see aggregate demand decline by 13.5 percent after accounting for intra- and inter-market substitution patterns. This finding complements existing literatures on drug adherence. Low CMS markets tend to be chronic conditions with higher levels of non-adherence while higher CMS markets tend to be acute conditions with lower levels of non-adherence. Thus, in low CMS markets physicians need to worry about adherence while in high CMS markets they need to worry about consumers leaving the market if exposed to negative product news.

Our work is not without limitations and we are left with several important questions. First, we need to understand why physicians are switching patients and whether those reasons vary across variation in relabeling severity. Are physicians practicing defensively and shifting patients out of potential liability

concerns? Are consumers requesting to be switched? Or, are physicians succumbing to promotion influences by competitor firms (e.g., Macher and Wade, 2013)? Second, we don't know if consumers that get switched are moved to 'inferior' treatments for their respective condition. Not all drugs in all classes are perfect substitutes so to the extent that there is variation in the medical level of substitution this could have welfare implications for those consumers. Third, with our data we don't know which types of consumers leave the market. Were these consumers that should be treated? Or were they only marginally benefiting? If there is a behavioral explanation for their actions, is there a mechanism that can be devised to nudge them back into the market? We leave these questions for future work.

## Reference

Arnade, C., Calvin, L., Kuchler, F., et al., 2008. *Market Response to a Food Safety Shock: the 2006 Foodborne Illness Outbreak of E. Coli O157: H7 Linked to Spinach*.

Bakhtavoryan, R., Capps Jr, O., and Salin, V., 2014. The Impact of Food Safety Incidents across Brands: the Case of the Peter Pan Peanut Butter Recall. *Journal of Agricultural and Applied Economics*, 46(4):559.

Bartel, A. P. and Thomas, L. G., 1985. Direct and Indirect Effects of Regulation: A New Look at OSHA's Impact. *The Journal of Law and Economics*, 28(1):1–25.

Bartel, A. P. and Thomas, L. G., 1987. Predation through Regulation: The Wage and Profit Effects of the Occupational Safety and Health Administration and The Environmental Protection Agency. *The Journal of Law and Economics*, 30(2):239–264.

Beach, J. E., Faich, G. A., Bormel, F. G., and Sasinowski, F. J., 1998. Black Box Warnings in Prescription Drug Labeling: Results of A Survey of 206 Drugs. *Food and Drug Law Journal*, 53:403.

Branstetter, L., Chatterjee, C., and Higgins, M. J., 2014. Starving (or Fattening) the Golden Goose?: Generic Entry and the Incentives for Early-Stage Pharmaceutical Innovation. *NBER working paper 20532*.

Branstetter, L., Chatterjee, C., and Higgins, M. J., 2016. Regulation and welfare: evidence from paragraph IV generic entry in the pharmaceutical industry. *The RAND Journal of Economics*, 47(4):857–890.

Briesacher, B. A., Soumerai, S. B., Zhang, F., Toh, S., Andrade, S. E., Wagner, J. L., Shoaibi, A., and Gurwitz, J. H., 2013. A Critical Review of Methods to Evaluate the Impact of FDA Regulatory Actions. *Pharmacoepidemiology and Drug Safety*, 22(9):986–994.

Brown, G. W., Lu, J. Y., and Wolfson, R. J., 1964. Dynamic Modeling of Inventories Subject to Obsolescence. *Management Science*, 11(1):51–63.

Bunniran, S., McCaffrey, D. J., Bentley, J. P., and Bouldin, A. S., 2009. Pharmaceutical Product Withdrawal: Attributions of Blame and Its Impact on Trust. *Research in Social and Administrative Pharmacy*, 5(3):262–273.

Cheah, E. T., Chan, W. L., and Chieng, C. L. L., 2007. The Corporate Social Responsibility of Pharmaceutical Product Recalls: An Empirical Examination of US and UK Markets. *Journal of Business Ethics*, 76(4):427–449.

Cramer, J., Rosenheck, R., Kirk, G., Krol, W., Krystal, J., and 425, V. N. S. G., 2003. Medication Compliance Feedback and Monitoring in A Clinical Trial: Predictors and Outcomes. *Value in Health*, 6(5):566–

573.

Dalen, D. M., 1997. Regulation of Quality and the Ratchet Effect: Does Unverifiability Hurt the Regulator? *Journal of Regulatory Economics*, 11(2):139–155.

Datta, A. and Dave, D., 2017. Effects of Physician-Directed Pharmaceutical Promotion on Prescription Behaviors: Longitudinal Evidence. *Health Economics*, 26(4):450–468.

Dorsey, E. R., Rabbani, A., Gallagher, S. A., Conti, R. M., and Alexander, G. C., 2010. Impact of FDA Black Box Advisory on Antipsychotic Medication Use. *Archives of Internal Medicine*, 170(1):96–103.

Dranove, D., 2011. *Health Care Markets, Regulators, and Certifiers*, volume 2. Elsevier.

Dranove, D. and Olsen, C., 1994. The Economic Side Effects of Dangerous Drug Announcements. *The Journal of Law and Economics*, 37(2):323–348.

Dusetzina, S. B., Higashi, A. S., Dorsey, E. R., Conti, R., Huskamp, H. A., Zhu, S., Garfield, C. F., and Alexander, G. C., 2012. Impact of FDA Drug Risk Communications on Health Care Utilization and Health Behaviors: A Systematic Review. *Medical Care*, 50(6):466.

Forgacs, I. and Loganayagam, A., 2008. Overprescribing Proton Pump Inhibitors.

Freedman, S., Kearney, M., and Lederman, M., 2012. Product Recalls, Imperfect Information, and Spillover Effects: Lessons from the Consumer Response to the 2007 Toy Recalls. *Review of Economics and Statistics*, 94(2):499–516.

Grepperud, S., 2015. Optimal Safety Standards when Accident Prevention Depends upon Both Firm and Worker Effort. *European Journal of Law and Economics*, 39(3):505–521.

Gruenspecht, H. K. and Lave, L. B., 2006. The Economics of Health, Safety, and Environmental Regulation. *Handbook of Industrial Organization*, 2(7):1507–1550.

Hartley, R., 1994. *Management Mistakes & Successes*. John Wiley and Sons.

Hausman, J., Leonard, G., and Zona, J. D., 1994. Competitive Analysis with Differenciated Products. *Annales d'Economie et de Statistique*, 159–180.

Hausman, J. A., 1996. *Valuation of New Goods under Perfect and Imperfect Competition*. University of Chicago Press.

Haynes, R. B., McDonald, H. P., and Garg, A. X., 2002. Helping Patients Follow Prescribed Treatment: Clinical Applications. *Journal of the American Medical Association*, 288(22):2880–2883.

Jackevicius, C. A., Mamdani, M., and Tu, J. V., 2002. Adherence with Statin Therapy in Elderly Patients with and Without Acute Coronary Syndromes. *Journal of the American Medical Association*, 288(4):462–

467.

Jacoby, J. L., Fulton, J., Cesta, M., and Heller, M., 2005. After the Black Box Warning: Dramatic Changes in ED Use of Droperidol. *The American Journal of Emergency Medicine*, 23(2):196.

Jarrell, G. and Peltzman, S., 1985. The Impact of Product Recalls on the Wealth of Sellers. *Journal of Political Economy*, 93(3):512–536.

Kahneman, D. and Tversky, A., 1979. Prospect Theory: An Analysis of Decision under Risk. *Econometrica*, 47(2):263–292.

Kales, H. C., Zivin, K., Kim, H. M., Valenstein, M., Chiang, C., Ignacio, R. V., Ganoczy, D., Cunningham, F., Schneider, L. S., and Blow, F. C., 2011. Trends in Antipsychotic Use in Dementia 1999-2007. *Archives of General Psychiatry*, 68(2):190–197.

Kessel, R. A., 1967. Economic Effects Of Federal Regulation Of Milk Markets. *The Journal of Law and Economics*, 10:51–78.

Kitch, E. W., Isaacson, M., and Kasper, D., 1971. The Regulation of Taxicabs in Chicago. *The Journal of Law and Economics*, 14(2):285–350.

Lembke, A., Papac, J., and Humphreys, K., 2018. Our Other Prescription Drug Problem. *New England Journal of Medicine*, 378(8):693–695.

Leone, R. P., 1995. Generalizing What is Known about Temporal Aggregation and Advertising Carryover. *Marketing Science*, 14(3):G141–G150.

Lu, C. Y., Zhang, F., Lakoma, M. D., Madden, J. M., Rusinak, D., Penfold, R. B., Simon, G., Ahmedani, B. K., Clarke, G., Hunkeler, E. M., et al., 2014. Changes in Antidepressant Use by Young People and Suicidal Behavior after FDA Warnings and Media Coverage: Quasi-Experimental Study. *British Medical Journal*, 348:g3596.

Macher, J. and Wade, J., 2013. The Black Box of Strategy: Competitive Responses to and Performance from Adverse Events. *Working Paper*.

Magat, W. A. and Moore, M. J., 1995. Consumer Product Safety Regulation in The United States and the United Kingdom: The Case of Bicycles. Technical Report 1.

Manchanda, P. and Honka, E., 2005. The Effects and Role of Direct-to-Physician Marketing in the Pharmaceutical Industry: An Integrative Review. *Yale Journal Health Policy, Law and Ethics*, 5:785.

Marsh, T. L., Schroeder, T. C., and Mintert, J., 2004. Impacts of Meat Product Recalls on Consumer Demand in the USA. *Applied Economics*, 36(9):897–909.

Migue, J.-L., 1977. Controls versus Subsidies in the Economic Theory of Regulation. *The Journal of Law and Economics*, 20(1):213–221.

Moore, M. J. and Magat, W. A., 1996. Labeling and Performance Standards for Product Safety: The Case of CPSC's Lawn Mower Standards. *Managerial and Decision Economics*, 509–516.

Moore, T. J., Cohen, M. R., and Furberg, C. D., 2007. Serious Adverse Drug Events Reported to the Food and Drug Administration, 1998-2005. *Archives of internal medicine*, 167(16):1752–1759.

Nelson, P., 1970. Information and Consumer Behavior. *Journal of Political Economy*, 78(2):311–329.

Neumann, G. R. and Nelson, J. P., 1982. Safety Regulation and Firm Size: Effects of the Coal Mine Health and Safety Act of 1969. *The Journal of Law and Economics*, 25(2):183–199.

Nevo, A., 2001. Measuring Market Power in ihe Ready-to-Eat Cereal Industry. *Econometrica*, 69(2):307–342.

Oberholzer-Gee, F. and Mitsunari, M., 2006. Information Regulation: Do the Victims of Externalities Pay Attention? *Journal of Regulatory Economics*, 30(2):141–158.

Olfson, M. and Marcus, S. C., 2008. A Case-Control Study of Antidepressants and Attempted Suicide during Early Phase Treatment of Major Depressive Episodes. *Journal of Clinical Psychiatry*, 69(3):425–432.

Olson, M. K., 2002. Pharmaceutical Policy Change and the Safety of New Drugs. *The Journal of Law and Economics*, 45(S2):615–642.

Peltzman, S., 1976. Toward a More General Theory of Regulation. *The Journal of Law and Economics*, 19(2):211–240.

Peltzman, S., 1987. The Health Effects of Mandatory Prescriptions. *The Journal of Law and Economics*, 30(2):207–238.

Pfistermeister, B., Schenk, C., Kornhuber, J., Bürkle, T., Fromm, M. F., and Maas, R., 2013. Different Indications, Warnings and Precautions, and Contraindications for the Same DrugâAn International Comparison of Prescribing Information for Commonly Used Psychiatric Drugs. *Pharmacoepidemiology and Drug Safety*, 22(3):329–333.

Piggott, N. E. and Marsh, T. L., 2004. Does Food Safety Information Impact US Meat Demand? *American Journal of Agricultural Economics*, 86(1):154–174.

Price, D., Cooke, J., Singleton, S., and Feely, M., 1986. Doctors' Unawareness of the Drugs Their Patients are Taking: A Major Cause of Overprescribing? *British Medical Journal*, 292(6513):99–100.

Pruitt, S. W. and Peterson, D. R., 1986. Security Price Reactions around Product Recall Announcements.

*Journal of Financial Research*, 9(2):113–122.

Qureshi, Z. P., Seoane-Vazquez, E., Rodriguez-Monguio, R., Stevenson, K. B., and Szeinbach, S. L., 2011. Market Withdrawal of New Molecular Entities Approved in the United States from 1980 to 2009. *Pharmacoepidemiology and Drug Safety*, 20(7):772–777.

Rhee, M. and Haunschild, P. R., 2006. The Liability of Good Reputation: A Study of Product Recalls in the US Automobile Industry. *Organization Science*, 17(1):101–117.

Rizzo, J. A., 1999. Advertising and Competition in the Ethical Pharmaceutical Industry: The Case of Antihypertensive Drugs. *The Journal of Law and Economics*, 42(1):89–116.

Sacarny, A., Yokum, D., Finkelstein, A., and Agrawal, S., 2016. Medicare Letters to Curb Overprescribing of Controlled Substances Had No Detectable Effect on Providers. *Health Affairs*, 35(3):471–479.

Schwartzstein, J. and Shleifer, A., 2013. An Activity-Generating Theory of Regulation. *The Journal of Law and Economics*, 56(1):1–38.

Shah, N. D., Montori, V. M., Krumholz, H. M., Tu, K., Alexander, G. C., and Jackevicius, C. A., 2010. Responding to an FDA Warning - Geographic Variation in the Use of Rosiglitazone. *New England Journal of Medicine*, 363(22):2081–2084.

Shavell, S., 1993. The Optimal Structure of Law Enforcement. *The Journal of Law and Economics*, 36(1, Part 2):255–287.

Shin, J., McCombs, J. S., Sanchez, R. J., Udall, M., Deminski, M. C., and Cheetham, T. C., 2012. Primary Nonadherence to Medications in an Integrated Healthcare Setting. *The American Journal of Managed Care*, 18(8):426–434.

Sloan, F. A. and Steinwald, B., 1980. Effects of Regulation on Hospital Costs and Input Use. *The Journal of Law and Economics*, 23(1):81–109.

Smalley, W., Shatin, D., Wysowski, D. K., Gurwitz, J., Andrade, S. E., Goodman, M., Chan, K. A., Platt, R., Schech, S. D., and Ray, W. A., 2000. Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action. *Journal of the American Medical Association*, 284(23):3036–3039.

Souiden, N. and Pons, F., 2009. Product Recall Crisis Management: The Impact on Manufacturer's Image, Consumer Loyalty and Purchase Intention. *Journal of Product & Brand Management*, 18(2):106–114.

Stigler, G. J., 1971. The Theory of Economic Regulation. *The Bell Journal of Economics*, 3–21.

Stojanović, Ž., Dragutinović-Mitrović, R., and Zaouche-Laniau, M., 2017. Products with Nutrition and Health Claims in the Western Balkans: Labelling Behaviour, Regulation and Policy Implications. *Euro-*

*pean Journal of Law and Economics*, 43(1):107–123.

Tekin, E. and Markowitz, S., 2008. The Relationship Between Suicidal Behavior and Productive Activities of Young Adults. *Southern Economic Journal*, 300–331.

Ter-Martirosyan, A. and Kwoka, J., 2010. Incentive Regulation, Service Quality, and Standards in US Electricity Distribution. *Journal of Regulatory Economics*, 38(3):258–273.

Tversky, A. and Kahneman, D., 1992. Advances in Prospect Theory: Cumulative Representation of Uncertainty. *Journal of Risk and uncertainty*, 5(4):297–323.

Van Heerde, H., Helsen, K., and Dekimpe, M. G., 2007. The Impact of a Product-Harm Crisis on Marketing Effectiveness. *Marketing Science*, 26(2):230–245.

Wagner, A. K., Chan, K. A., Dashevsky, I., Raebel, M. A., Andrade, S. E., Lafata, J. E., Davis, R. L., Gurwitz, J. H., Soumerai, S. B., and Platt, R., 2006. FDA Drug Prescribing Warnings: Is the Black Box Half Empty or Half Full? *Pharmacoepidemiology and Drug Safety*, 15(6):369–386.

Wilkinson, J. J., Force, R. W., and Cady, P. S., 2004. Impact of Safety Warnings on Drug Utilization: Marketplace Life Span of Cisapride and Troglitazone. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 24(8):978–986.

Windmeijer, F., de Laat, E., Douven, R., and Mot, E., 2006. Pharmaceutical Promotion and GP Prescription Behaviour. *Health Economics*, 15(1):5–18.

Wong, C. H., Siah, K. W., and Lo, A. W., 2018. Estimation of Clinical Trial Success Rates and Related Parameters. https://doi.org/10.1093/biostatistics/kxx069.

Wysowski, D. K. and Swartz, L., 2005. Adverse Drug Event Surveillance and Drug Withdrawals in the United States, 1969-2002: The Importance of Reporting Suspected Reactions. *Archives of Internal Medicine*, 165(12):1363–1369.

Zeithaml, V. A., 1988. Consumer Perceptions of Price, Quality, and Value: A Means-End Model and Synthesis of Evidence. *The Journal of Marketing*, 2–22.

Zhao, Y., Zhao, Y., and Helsen, K., 2011. Consumer Learning in a Turbulent Market Environment: Modeling Consumer Choice Dynamics after a Product-Harm Crisis. *Journal of Marketing Research*, 48(2):255–267.

Figure 1: Focal Drug Demand in U.S. and U.K. Surrounding Relabel Events

The figure shows the sales quantity of focal drugs in the U.S. (treated) and U.K. (control) before and after relabeling. The relabeling event is set at t=0 where time horizon is in quarters and labeled on the x-axis. Sales are shown over eight quarters before and after the quarter of relabeling. The left y-axis are sales of drugs in the U.S., the right y-axis are sales of the same drugs in the U.K. Drug sales are in standardized units (millions) as determined by IMS Health and natural logarithms are taken.

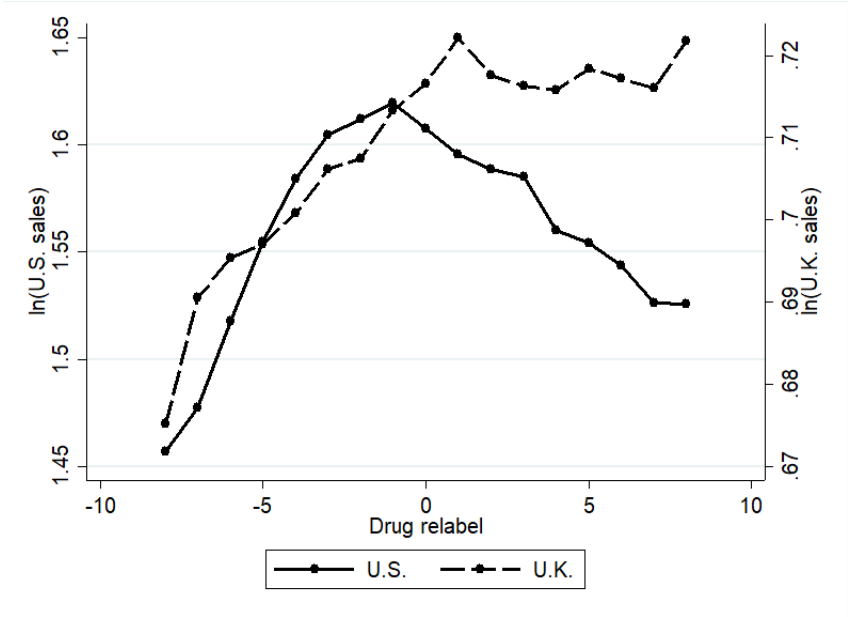


Table 1: Distribution of Relabel Activity between the U.S. and U.K.

Our sample consists of drugs sold both in the U.S. and U.K. In order to create a clean control window we excluded drugs if they were relabeled in the U.K. within eight quarters of a U.S. relabel. This table shows the variation in relabeling types across the U.S. and U.K. for our sample. Within the imposed restrictions the average elapsed time between relabeling in the U.S. and U.K. is 12.95 quarters.

| Relabeling Type | U.S. | U.K. | Average Time (Quarter) |
|---|---|---|---|
| Precaution | 226 | 166 | 13.48 |
| Adverse Reaction | 176 | 134 | 11.83 |
| Warning | 161 | 115 | 12.06 |
| Boxed Warning | 53 | 35 | 9.40 |
| Label Changes | 251 | 180 | 12.95 |

Table 2: Descriptive Statistics

Sales (quantity) are measured in million of standardized units. IMS Health has converted financial variables for U.K. drugs to U.S. dollars. All financial variables have been converted to real 2009 U.S. dollars using a GDP deflator.

| Variable | Obs | Mean | Median | Std. Dev. | Min | Max |
|---|---|---|---|---|---|---|
| U.S. | 6,519 | 0.54 | 1.00 | 0.50 | 0.00 | 1.00 |
| Sales (standard units) | 6,519 | 13.87 | 0.88 | 45.81 | 0.00 | 577.85 |
| Promotion | 6,519 | 1.73 | 0.02 | 5.40 | 0.00 | 63.18 |
| Lagged promotion stock | 6,519 | 6.84 | 0.68 | 15.46 | 0.00 | 135.17 |
| Price | 6,519 | 91.78 | 2.36 | 357.43 | 0.01 | 5352.50 |
| Relabel | 6,519 | 0.27 | 0.00 | 0.45 | 0.00 | 1.00 |
| Precaution | 6,519 | 0.22 | 0.00 | 0.42 | 0.00 | 1.00 |
| Adverse reaction | 6,519 | 0.16 | 0.00 | 0.37 | 0.00 | 1.00 |
| Warning | 6,519 | 0.11 | 0.00 | 0.31 | 0.00 | 1.00 |
| Box warning | 6,519 | 0.03 | 0.00 | 0.17 | 0.00 | 1.00 |
| Vintage | 6,519 | 23.53 | 24.00 | 11.53 | 1.00 | 56.00 |
| Number of brands | 6,519 | 7.98 | 6.00 | 6.31 | 0.00 | 32.00 |
| Number of generics | 6,519 | 13.70 | 5.00 | 23.70 | 0.00 | 149.00 |

Table 3: Effects of Relabeling on Demand

Dependent variable is the natural logarithm of sales, ln(*Sales*). The unit of analysis in Model 1 is the focal drug level, Model 2 is the 4-digit ATC market (ATC4) level and Model 3 is the 3-digit ATC market (ATC3) level. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands*, and *Number of generics*. The models are log-linear, as such the marginal effects are calculated using the equation exp($\beta$-1) where $\beta$ is the respective coefficient on our variable of interest, (*Relabel*U.S.*). Marginal effects for our variables of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

| DV = ln(Sales) | Model 1<br>Focal drug | Model 2<br>ATC4 market | Model 3<br>ATC3 market |
|---|---|---|---|
| Relabel | 0.108*** | 0.058** | 0.023 |
| | (0.032) | (0.024) | (0.020) |
| U.S. | 0.712*** | 1.796*** | 1.375*** |
| | (0.034) | (0.040) | (0.036) |
| Relabel * U.S. | -0.185*** | -0.052* | -0.048** |
| | (0.025) | (0.028) | (0.023) |
| ln(Price) | -0.610*** | -1.158*** | -0.544*** |
| | (0.053) | (0.049) | (0.049) |
| ln(Lagged promotion stock) | 0.742*** | 0.186*** | 0.151*** |
| | (0.015) | (0.009) | (0.007) |
| Controls | Y | Y | Y |
| Drug fixed effect | Y | N | N |
| Market fixed effect | N | Y | Y |
| Time fixed effect | Y | Y | Y |
| N | 6,519 | 5,946 | 4,946 |
| Adjusted $R^2$ | 0.531 | 0.765 | 0.820 |
| First stage F-statistic | 37.12 | 64.79 | 26.56 |
| Hansen J-statistic | 2.12 | 0.15 | 2.621 |
| Hansen J p-value | 0.145 | 0.698 | 0.105 |
| **Marginal effects:**<br>**Relabel * U.S.** | **-0.169** | **-0.051** | **-0.047** |

Table 4: Effects of Relabeling on Demand: Low-Intensity Markets

Dependent variable is the natural logarithm of sales, ln(*Sales*). Low-intensity markets are defined as those 4-digit ATC markets where there was only one relabeling event over our sample period. The unit of analysis in Model 1 is the focal drug level, Model 2 is the 4-digit ATC market (ATC4) level and Model 3 is the 3-digit ATC market (ATC3) level. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands*, and *Number of generics*. The models are log-linear, as such the marginal effects are calculated using the equation exp($\beta$-1) where $\beta$ is the respective coefficient on our variable of interest, (*Relabel*U.S.*). Marginal effects for our variables of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

| DV = ln(Sales) | Model 1<br>Focal drug | Model 2<br>ATC4 market | Model 3<br>ATC3 market |
|---|---|---|---|
| Relabel | 0.096* | -0.008 | -0.071 |
| | (0.052) | (0.094) | (0.089) |
| U.S. | 0.350*** | 1.640*** | 0.842*** |
| | (0.056) | (0.094) | (0.085) |
| Relabel * U.S. | -0.114*** | -0.012 | -0.015 |
| | (0.04) | (0.07) | (0.064) |
| ln(Price) | -0.522*** | -1.073*** | -0.445*** |
| | (0.055) | (0.046) | (0.072) |
| ln(Lagged promotion stock) | 0.691*** | 0.153*** | 0.166*** |
| | (0.034) | (0.021) | (0.019) |
| Controls | Y | Y | Y |
| Drug fixed effect | Y | N | N |
| Market fixed effect | N | Y | Y |
| Time fixed effect | Y | Y | Y |
| N | 1,576 | 1,576 | 749 |
| Adjusted $R^2$ | 0.655 | 0.561 | 0.638 |
| First stage F-statistic | 79.67 | 150.21 | 16.34 |
| Hansen J-statistic | 1.235 | 0.477 | 0.092 |
| Hansen J p-value | 0.267 | 0.490 | 0.761 |
| **Marginal effects:**<br>**Relabel * U.S.** | **-0.108** | | |

Table 5: Effects of Relabeling on Demand: High-Intensity Markets

Dependent variable is the natural logarithm of sales, ln(*Sales*). High-intensity markets are defined as those 4-digit ATC markets where there was more than one relabeling event over our sample period. The unit of analysis in Model 1 is the focal drug level, Model 2 is the 4-digit ATC market (ATC4) level and Model 3 is the 3-digit ATC market (ATC3) level. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands*, and *Number of generics*. The models are log-linear, as such the marginal effects are calculated using the equation exp($\beta$-1) where $\beta$ is the respective coefficient on our variable of interest, (*Relabel*U.S.*). Marginal effects for our variables of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

| DV = ln(Sales) | Model 1<br>Focal Drug | Model 2<br>ATC4 market | Model 3<br>ATC3 market |
|---|---|---|---|
| Relabel | 0.118*** | 0.072*** | 0.026 |
| | (0.037) | (0.022) | (0.02) |
| U.S. | 0.904*** | 1.874*** | 1.539*** |
| | (0.038) | (0.034) | (0.043) |
| Relabel * U.S. | -0.210*** | -0.062** | -0.051** |
| | (0.03) | (0.028) | (0.023) |
| ln(Price) | -0.846*** | -1.137*** | -0.539*** |
| | (0.099) | (0.081) | (0.076) |
| ln(Lagged promotion stock) | 0.706*** | 0.180*** | 0.129*** |
| | (0.019) | (0.008) | (0.006) |
| Controls | Y | Y | Y |
| Drug fixed effect | Y | N | N |
| Market fixed effect | N | Y | Y |
| Time fixed effect | Y | Y | Y |
| N | 4,943 | 4,370 | 4,197 |
| Adjusted $R^2$ | 0.526 | 0.833 | 0.852 |
| First stage F-statistic | 17.61 | 48.22 | 33.22 |
| Hansen J-statistic | 1.501 | 0.218 | 0.778 |
| Hansen J p-value | 0.221 | 0.64 | 0.378 |
| **Marginal effects:**<br>**Relabel * U.S.** | **-0.189** | **-0.06** | **-0.05** |

Table 6: Heterogeneous Impacts across Levels of Relabeling Severity

Dependent variable is the natural logarithm of sales, ln(*Sales*). Data is split into three sub-samples representing precaution (Model 1), adverse reaction (Model 2) and warning/box warning (Model 3). The categorization is based on the first time a drug is relabeled and allows us to isolate out the effects of any potential prior relabeling activity. The unit of analysis in Model 1 is the focal drug level, Model 2 is the 4-digit ATC market (ATC4) level and Model 3 is the 3-digit ATC market (ATC3) level. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands*, and *Number of generics*. The models are log-linear, as such the marginal effects are calculated using the equation exp($\beta$-1) where $\beta$ is the respective coefficient on our variable of interest, (*Relabel*U.S.*). Marginal effects for our variables of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * p $<$ 0.10, ** p $<$ 0.05, *** p $<$ 0.01.

| DV = ln(Sales) | Model 1 Precaution | Model 2 Adverse reaction | Model 3 Warning/Box |
|---|---|---|---|
| Relabel | 0.111*** | 0.143*** | 0.176*** |
| | (0.030) | (0.040) | (0.050) |
| U.S. | 0.838*** | 0.749*** | 0.607*** |
| | (0.039) | (0.041) | (0.051) |
| Relabel * U.S. | -0.170*** | -0.227*** | -0.451*** |
| | (0.027) | (0.036) | (0.059) |
| ln(Price) | -0.759*** | -0.528*** | -0.709*** |
| | (0.069) | (0.039) | (0.070) |
| ln(Lagged promotion stock) | 0.725*** | 0.790*** | 0.756*** |
| | (0.017) | (0.022) | (0.026) |
| Controls | Y | Y | Y |
| Drug fixed effect | Y | Y | Y |
| Market fixed effect | N | N | N |
| Time fixed effect | Y | Y | Y |
| N | 5,183 | 3,166 | 2,236 |
| Adjusted $R^2$ | 0.517 | 0.579 | 0.430 |
| First stage F-statistic | 29.39 | 65.76 | 37.76 |
| Hansen J-statistic | 0.81 | 5.821 | 1.451 |
| Hansen J p-value | 0.368 | 0.055 | 0.228 |
| **Marginal effects: Relabel * U.S.** | **-0.156** | **-0.203** | **-0.363** |

Table 7: Effects of Precaution/Adverse Reaction Relabeling on Demand

Dependent variable is the natural logarithm of sales, ln(*Sales*). Sample includes the combination of precaution and adverse reaction. The unit of analysis in Model 1 is the focal drug level, Model 2 is the 4-digit ATC market (ATC4) level and Model 3 is the 3-digit ATC (ATC3) level. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands,* and *Number of generics.* The models are log-linear, as such the marginal effects are calculated using the equation exp($\beta$-1) where $\beta$ is the respective coefficient on our variable of interest, (*Relabel*U.S.*). Marginal effects for our variables of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

| DV = ln(Sales) | Model 1<br>Focal Drug | Model 2<br>ATC4 market | Model 3<br>ATC3 market |
|---|---|---|---|
| Relabel | 0.068** | 0.067*** | 0.021 |
| | (0.032) | (0.024) | (0.021) |
| U.S. | 0.659*** | 1.779*** | 1.440*** |
| | (0.039) | (0.042) | (0.033) |
| Relabel * U.S. | -0.159*** | -0.052* | -0.041* |
| | (0.035) | (0.028) | (0.023) |
| ln(Price) | -0.569*** | -1.175*** | -0.700*** |
| | (0.053) | (0.045) | (0.027) |
| ln(Lagged promotion stock) | 0.808*** | 0.186*** | 0.151*** |
| | (0.018) | (0.009) | (0.007) |
| Controls | Y | Y | Y |
| Drug fixed effect | Y | N | N |
| Market fixed effect | N | Y | Y |
| Time fixed effect | Y | Y | Y |
| N | 6,310 | 5,722 | 4,955 |
| Adjusted $R^2$ | 0.407 | 0.768 | 0.812 |
| First stage F-statistic | 49.62 | 70.28 | 42.9 |
| Hansen J-statistic | 0.065 | 0.09 | 2.254 |
| Hansen J p-value | 0.799 | 0.765 | 0.133 |
| **Marginal effects:**<br>**Relabel * U.S.** | **-0.147** | **-0.051** | **-0.040** |

Table 8: Effects of Warning/Box Warning Relabeling on Demand

Dependent variable is the natural logarithm of sales, ln(*Sales*). Sample includes the combination of warning and box warning. The unit of analysis in Model 1 is the focal drug level, Model 2 is the 4-digit ATC market (ATC4) level and Model 3 is the 3-digit ATC market (ATC3) level. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands,* and *Number of generics*. The models are log-linear, as such the marginal effects are calculated using the equation exp($\beta$-1) where $\beta$ is the respective coefficient on our variable of interest, (*Relabel*U.S.*). Marginal effects for our variables of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

| DV = ln(Sales) | Model 1<br>Focal Drug | Model 2<br>ATC4 market | Model 3<br>ATC3 market |
|---|---|---|---|
| Relabel | 0.176*** | 0.020 | 0.005 |
| | (0.050) | (0.034) | (0.029) |
| U.S. | 0.607*** | 1.821*** | 1.545*** |
| | (0.051) | (0.048) | (0.042) |
| Relabel * U.S. | -0.451*** | -0.105** | -0.087** |
| | (0.059) | (0.044) | (0.036) |
| ln(Price) | -0.709*** | -0.997*** | -0.533*** |
| | (0.070) | (0.059) | (0.028) |
| ln(Lagged promotion stock) | 0.756*** | 0.174*** | 0.117*** |
| | (0.026) | (0.012) | (0.012) |
| Controls | Y | Y | Y |
| Drug fixed effect | Y | N | N |
| Market fixed effect | N | Y | Y |
| Time fixed effect | Y | Y | Y |
| N | 2,236 | 2,189 | 1,991 |
| Adjusted $R^2$ | 0.430 | 0.834 | 0.812 |
| First stage F-statistic | 37.76 | 96.64 | 753.48 |
| Hansen J-statistic | 1.451 | 0.824 | 1.653 |
| Hansen J p-value | 0.228 | 0.364 | 0.199 |
| **Marginal effects:**<br>**Relabel * U.S.** | **-0.363** | **-0.100** | **-0.083** |

# Appendix

Table A.1: Baseline Results across Alternative Time Periods

Dependent variable is the natural logarithm of sales, ln(*Sales*). Model 1 replicates Model 1, Table 3. The time period of analysis is extended to three years (12 quarters) in Model 2 and four years (16 quarters) in Model 3. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands*, and *Number of generics*. The models are log-linear, as such the marginal effects are calculated using the equation exp(β-1) where β is the respective coefficient on our variables of interest, (*Relabel*U.S.*). Marginal effects for our variable of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

| DV = ln(Sales) | Model 1<br>2 years | Model 2<br>3 years | Model 3<br>4 years |
|---|---|---|---|
| Relabel | 0.108*** | 0.113*** | 0.132*** |
| | (0.032) | (0.027) | (0.025) |
| U.S. | 0.712*** | 0.696*** | 0.711*** |
| | (0.034) | (0.027) | (0.026) |
| Relabel * U.S. | -0.185*** | -0.235*** | -0.279*** |
| | (0.025) | (0.022) | (0.021) |
| ln(Price) | -0.610*** | -0.499*** | -0.506*** |
| | (0.053) | (0.033) | (0.036) |
| ln(Lagged promotion stock) | 0.742*** | 0.760*** | 0.772*** |
| | (0.015) | (0.013) | (0.012) |
| Controls | Y | Y | Y |
| Drug fixed effect | Y | Y | Y |
| Market fixed effect | N | N | N |
| Time fixed effect | Y | Y | Y |
| N | 6,519 | 9,229 | 11,842 |
| Adjusted $R^2$ | 0.497 | 0.498 | 0.484 |
| First stage F-statistic | 37.12 | 36.23 | 39.12 |
| Hansen J-statistic | 2.12 | 4.31 | 3.982 |
| Hansen J p-value | 0.145 | 0.635 | 0.679 |
| **Marginal effects:**<br>**Relabel * U.S.** | **-0.168** | **-0.209** | **-0.243** |

Table A.2: Baseline Results across Alternative Treatment Periods

Dependent variable is the natural logarithm of sales, ln(*Sales*). In our baseline model specification the quarter of relabel is excluded from analysis. Model 1 drops the quarter of relabel (t = 0) and the quarter prior (t = -1) Model 2 drops the quarter of relabel (t = 0) and the two quarters prior (t = -1, -2). Dropping prior quarters controls for any possible leakage of information. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands*, and *Number of generics.* The models are log-linear, as such the marginal effects are calculated using the equation exp($\beta$-1) where $\beta$ is the respective coefficient on our variable of interest, (*Relabel*U.S.*). Marginal effects for our variables of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

| DV = ln(Sales) | Model 1<br>T = 0, -1 | Model 2<br>T = 0, -1, -2 |
|---|---|---|
| Relabel | 0.118*** | 0.124*** |
| | (0.036) | (0.041) |
| U.S. | 0.671*** | 0.673*** |
| | (0.032) | (0.034) |
| Relabel * U.S. | -0.203*** | -0.210*** |
| | (0.027) | (0.028) |
| ln(Price) | -0.472*** | -0.470*** |
| | (0.040) | (0.042) |
| ln(Lagged promotion stock) | 0.739*** | 0.745*** |
| | (0.016) | (0.016) |
| Controls | Y | Y |
| Drug fixed effect | Y | Y |
| Market fixed effect | N | N |
| Time fixed effect | Y | Y |
| N | 6,074 | 5,661 |
| Adjusted $R^2$ | 0.501 | 0.498 |
| First stage F-statistic | 48.86 | 44.81 |
| Hansen J statistic | 3.791 | 3.457 |
| Hansen J p-value | 0.15 | 0.178 |
| **Marginal effects:**<br>**Relabel * U.S.** | **-0.183** | **-0.189** |

Table A.3: Variation in Relabeling Activity

Count of first instance relabeling activity across type and over time. If a drug has multiple relabel types they are each counted below.

| ATC | Relabel Type | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|---|---|---|
| A | Precaution | 6 | 13 | 17 | 19 | 24 | 26 | 26 |
| | Adverse Reaction | 4 | 7 | 12 | 17 | 21 | 26 | 29 |
| | Warning | 1 | 3 | 4 | 6 | 7 | 12 | 13 |
| | Boxed Warning | 0 | 0 | 0 | 0 | 3 | 5 | 5 |
| | Total Relabel | 6 | 14 | 19 | 22 | 28 | 31 | 33 |
| B | Precaution | 4 | 5 | 7 | 7 | 7 | 8 | 8 |
| | Adverse Reaction | 4 | 7 | 9 | 9 | 9 | 9 | 9 |
| | Warning | 2 | 3 | 6 | 6 | 7 | 7 | 7 |
| | Boxed Warning | 0 | 0 | 0 | 0 | 1 | 1 | 3 |
| | Total Relabel | 4 | 7 | 9 | 9 | 9 | 10 | 11 |
| C | Precaution | 10 | 15 | 20 | 26 | 30 | 36 | 39 |
| | Adverse Reaction | 11 | 15 | 19 | 22 | 22 | 24 | 26 |
| | Warning | 9 | 11 | 15 | 17 | 20 | 23 | 24 |
| | Boxed Warning | 0 | 0 | 1 | 2 | 3 | 4 | 4 |
| | Total Relabel | 16 | 23 | 27 | 31 | 34 | 40 | 42 |
| D | Precaution | 1 | 5 | 7 | 7 | 7 | 7 | 7 |
| | Adverse Reaction | 0 | 3 | 4 | 4 | 5 | 5 | 5 |
| | Warning | 0 | 0 | 1 | 3 | 3 | 3 | 3 |
| | Boxed Warning | 0 | 0 | 0 | 2 | 2 | 3 | 3 |
| | Total Relabel | 1 | 5 | 7 | 8 | 8 | 8 | 8 |
| G | Precaution | 5 | 7 | 14 | 15 | 16 | 17 | 17 |
| | Adverse Reaction | 2 | 4 | 10 | 11 | 11 | 12 | 13 |
| | Warning | 0 | 0 | 1 | 1 | 5 | 9 | 11 |
| | Boxed Warning | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total Relabel | 5 | 7 | 14 | 15 | 17 | 18 | 18 |
| H | Precaution | 1 | 5 | 5 | 6 | 6 | 7 | 7 |
| | Adverse Reaction | 1 | 4 | 5 | 6 | 6 | 7 | 7 |
| | Warning | 0 | 2 | 2 | 3 | 3 | 4 | 4 |
| | Boxed Warning | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total Relabel | 1 | 5 | 5 | 6 | 6 | 7 | 7 |
| J | Precaution | 18 | 44 | 50 | 56 | 59 | 64 | 68 |
| | Adverse Reaction | 12 | 30 | 40 | 45 | 46 | 53 | 57 |
| | Warning | 6 | 16 | 22 | 30 | 41 | 53 | 56 |
| | Boxed Warning | 2 | 8 | 9 | 10 | 13 | 15 | 16 |
| | Total Relabel | 22 | 49 | 55 | 59 | 62 | 69 | 72 |

Table A.3: Variation in Relabeling Activity (continued).

| ATC | Relabel Type | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|---|---|---|
| L | Precaution | 14 | 25 | 31 | 38 | 44 | 46 | 52 |
| | Adverse Reaction | 11 | 19 | 30 | 35 | 41 | 46 | 51 |
| | Warning | 7 | 10 | 17 | 29 | 38 | 41 | 47 |
| | Boxed Warning | 4 | 5 | 6 | 16 | 21 | 21 | 25 |
| | Total Relabel | 17 | 30 | 39 | 43 | 52 | 54 | 57 |
| M | Precaution | 8 | 17 | 20 | 23 | 24 | 24 | 24 |
| | Adverse Reaction | 5 | 11 | 15 | 15 | 17 | 18 | 19 |
| | Warning | 1 | 6 | 9 | 14 | 16 | 18 | 18 |
| | Boxed Warning | 0 | 1 | 3 | 10 | 11 | 11 | 12 |
| | Total Relabel | 10 | 19 | 21 | 23 | 24 | 24 | 24 |
| N | Precaution | 12 | 24 | 32 | 40 | 45 | 47 | 51 |
| | Adverse Reaction | 7 | 14 | 18 | 27 | 35 | 38 | 39 |
| | Warning | 7 | 11 | 22 | 30 | 38 | 40 | 44 |
| | Boxed Warning | 0 | 0 | 9 | 14 | 16 | 19 | 19 |
| | Total Relabel | 14 | 28 | 36 | 44 | 52 | 55 | 56 |
| P | Precaution | 1 | 1 | 2 | 2 | 2 | 2 | 2 |
| | Adverse Reaction | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Warning | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Boxed Warning | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total Relabel | 1 | 1 | 2 | 2 | 2 | 2 | 2 |
| R | Precaution | 3 | 5 | 6 | 6 | 9 | 11 | 11 |
| | Adverse Reaction | 3 | 3 | 4 | 4 | 5 | 7 | 7 |
| | Warning | 2 | 3 | 3 | 3 | 4 | 5 | 6 |
| | Boxed Warning | 1 | 1 | 1 | 1 | 2 | 2 | 2 |
| | Total Relabel | 6 | 8 | 8 | 8 | 10 | 12 | 12 |
| S | Precaution | 6 | 8 | 9 | 11 | 11 | 11 | 11 |
| | Adverse Reaction | 0 | 1 | 3 | 4 | 4 | 4 | 4 |
| | Warning | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Boxed Warning | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total Relabel | 6 | 8 | 10 | 12 | 12 | 12 | 12 |
| T | Precaution | 2 | 2 | 3 | 3 | 5 | 5 | 5 |
| | Adverse Reaction | 0 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Warning | 0 | 0 | 0 | 1 | 2 | 2 | 3 |
| | Boxed Warning | 0 | 0 | 0 | 0 | 1 | 1 | 1 |
| | Total Relabel | 2 | 3 | 4 | 4 | 5 | 5 | 6 |

Table A.3: Variation in Relabeling Activity (continued).

| ATC | Relabel Type | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|---|---|---|
| V | Precaution | 1 | 2 | 2 | 3 | 3 | 4 | 5 |
| | Adverse Reaction | 1 | 2 | 2 | 2 | 3 | 3 | 3 |
| | Warning | 1 | 1 | 1 | 1 | 3 | 3 | 3 |
| | Boxed Warning | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Total Relabel | 1 | 2 | 2 | 3 | 4 | 4 | 5 |

ATC Therapeutic Code Definition:

**A:** Alimentary tract and metabolism

**B:** Blood and blood forming organs

**C:** Cardiovascular system

**D:** Dermatological

**G:** Genitourinary system and sex hormones

**H:** Systemic hormonal preparations, excluding sex hormones

**J:** Anti-infectives L: Anti-neoplastic and immunomodulating agents

**M:** Musculoskeletal system

**N:** Nervous system

**P:** Anti-parasitic products

**R:** Respiratory system

**S:** Sensory organs

**T:** Diagnostic agents

**V:** Various

Table A.4: Effects of Relabeling on Demand: Low-Intensity Markets (Bottom Quartile)
Dependent variable is the natural logarithm of sales, ln(*Sales*). Low-intensity markets are defined as those 4-digit ATC markets in the bottom quartile of relabeling activity over our sample period. The unit of analysis in Model 1 is the focal drug level, Model 2 is the 4-digit ATC market (ATC4) level and Model 3 is the 3-digit ATC market (ATC3) level. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands*, and *Number of generics*. The models are log-linear, as such the marginal effects are calculated using the equation exp($\beta$-1) where $\beta$ is the respective coefficient on our variable of interest, (*Relabel*U.S.*). Marginal effects for our variables of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

| DV = ln(Sales) | Model 1<br>Focal Drug | Model 2<br>ATC4 market | Model 3<br>ATC3 market |
|---|---|---|---|
| Relabel | 0.077 | 0.140** | 0.007 |
| | (0.054) | (0.059) | (0.051) |
| U.S. | 0.386*** | 1.013*** | 1.092*** |
| | (0.051) | (0.117) | (0.080) |
| Relabel * U.S. | -0.109*** | -0.104 | -0.018 |
| | (0.041) | (0.067) | (0.054) |
| ln(Price) | -0.564*** | -1.068*** | -0.740*** |
| | (0.129) | (0.097) | (0.047) |
| ln(Lagged promotion stock) | 0.971*** | 0.321*** | 0.070*** |
| | (0.024) | (0.028) | (0.016) |
| Controls | Y | Y | Y |
| Drug fixed effect | Y | N | N |
| Market fixed effect | N | Y | Y |
| Time fixed effect | Y | Y | Y |
| N | 1,264 | 1,202 | 1,170 |
| Adjusted $R^2$ | 0.725 | 0.726 | 0.599 |
| First stage F-statistic | 12.81 | 38.02 | 81.74 |
| Hansen J-statistic | 0.558 | 0.017 | 0.590 |
| Hansen J p-value | 0.455 | 0.897 | 0.442 |
| **Marginal effects:**<br>**Relabel * U.S.** | **-0.103** | | |

Table A.5: Effects of Relabeling on Demand: High-Intensity Markets (Top Quartile)

Dependent variable is the natural logarithm of sales, ln(*Sales*). High-intensity markets are defined as those 4-digit ATC markets in the top quartile of relabeling activity over our sample period. The unit of analysis in Model 1 is the focal drug level, Model 2 is the 4-digit ATC market (ATC4) level and Model 3 is the 3-digit ATC market (ATC3) level. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands*, and *Number of generics*. The models are log-linear, as such the marginal effects are calculated using the equation exp($\beta$-1) where $\beta$ is the respective coefficient on our variables of interest, (*Relabel*U.S.*). Marginal effects for our variable of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

| DV = ln(Sales) | Model 1<br>Focal Drug | Model 2<br>ATC4 market | Model 3<br>ATC3 market |
|---|---|---|---|
| Relabel | 0.157*** | 0.172*** | 0.088*** |
| | (0.051) | (0.063) | (0.028) |
| U.S. | 0.812*** | 1.809*** | 1.574*** |
| | (0.048) | (0.128) | (0.055) |
| Relabel * U.S. | -0.224*** | -0.139** | -0.087*** |
| | (0.043) | (0.064) | (0.033) |
| ln(Price) | -0.628*** | -1.209*** | -0.814*** |
| | (0.051) | (0.056) | (0.028) |
| ln(Lagged promotion stock) | 0.695*** | 0.259*** | 0.165*** |
| | (0.036) | (0.026) | (0.012) |
| Controls | Y | Y | Y |
| Drug fixed effect | Y | N | N |
| Market fixed effect | N | Y | Y |
| Time fixed effect | Y | Y | Y |
| N | 1,903 | 1,669 | 1,533 |
| Adjusted $R^2$ | 0.508 | 0.692 | 0.882 |
| First stage F-statistic | 100.28 | 147.89 | 1054.4 |
| Hansen J-statistic | 0.147 | 1.459 | 0.066 |
| Hansen J p-value | 0.701 | 0.227 | 0.798 |
| **Marginal effects:**<br>**Relabel * U.S.** | **-0.201** | **-0.130** | **-0.083** |

Table A.6: Heterogeneous Relabeling Severity Across Alternative Time Periods

Data split across types of relabeling activity and across alternative periods of analysis. Models 1-3 are extended to three years or 12 quarters before and after a relabeling event. Models 4-5 are extended to four years or 16 quarters before and after a relabeling event.

| | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 |
|---|---|---|---|---|---|---|
| | | 3 years | | | 4 years | |
| DV = ln(Sales) | Precaution | Adverse Reaction | Warning/Box | Precaution | Adverse Reaction | Warning/Box |
| Relabel | 0.075*** | 0.108*** | 0.036 | 0.083*** | 0.119*** | 0.063** |
| | (0.026) | (0.030) | (0.034) | (0.024) | (0.028) | (0.031) |
| U.S. | 0.731*** | 0.770*** | 0.566*** | 0.708*** | 0.740*** | 0.741*** |
| | (0.035) | (0.032) | (0.034) | (0.027) | (0.030) | (0.044) |
| Relabel * U.S. | -0.207*** | -0.237*** | -0.285*** | -0.238*** | -0.270*** | -0.213*** |
| | (0.023) | (0.027) | (0.041) | (0.021) | (0.026) | (0.039) |
| ln(Price) | -0.700*** | -0.473*** | -0.372*** | -0.611*** | -0.470*** | -0.698*** |
| | (0.063) | (0.039) | (0.045) | (0.043) | (0.039) | (0.072) |
| ln(Lagged promotion stock) | 0.773*** | 0.720*** | 0.698*** | 0.795*** | 0.762*** | 0.703*** |
| | (0.013) | (0.014) | (0.016) | (0.011) | (0.013) | (0.015) |
| Controls | Y | Y | Y | Y | Y | Y |
| Drug fixed effect | Y | Y | Y | Y | Y | Y |
| Market fixed effect | N | N | N | N | N | N |
| Time fixed effect | Y | Y | Y | Y | Y | Y |
| N | 8,711 | 6,428 | 5,943 | 10,877 | 8,059 | 7,587 |
| Adjusted $R^2$ | 0.487 | 0.558 | 0.433 | 0.505 | 0.549 | 0.418 |
| First stage F-statistic | 40.01 | 42.48 | 35.42 | 44.13 | 39.64 | 35.92 |
| Hansen J-statistic | 0.978 | 1.781 | 2.76 | 4.699 | 0.843 | 1.261 |
| Hansen J p-value | 0.323 | 0.619 | 0.43 | 0.454 | 0.974 | 0.261 |
| **Marginal effects: Relabel * U.S.** | **-0.186** | **-0.211** | **-0.247** | **-0.211** | **-0.236** | **-0.192** |

Table A.7: Heterogeneous Relabeling Severity Across Alternative Treatment Periods

Data split across types of relabeling activity and across alternative exclusion windows. Models 1-3 exclude the quarter of a relabeling event and prior quarter from the analysis. Models 4-6 exclude the quarter of a relabeling event and two prior quarters.

| | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 |
|---|---|---|---|---|---|---|
| | | T = 0, -1 | | | T = 0, -1, -2 | |
| DV = ln(Sales) | Precaution | Adverse Reaction | Warning/Box | Precaution | Adverse Reaction | Warning/Box |
| Relabel | 0.124*** | 0.155*** | 0.179*** | 0.134*** | 0.166*** | 0.184*** |
| | (0.038) | (0.050) | (0.054) | (0.043) | (0.056) | (0.056) |
| U.S. | 0.847*** | 0.745*** | 0.468*** | 0.848*** | 0.758*** | 0.471*** |
| | (0.042) | (0.044) | (0.047) | (0.044) | (0.047) | (0.048) |
| Relabel * U.S. | -0.191*** | -0.255*** | -0.456*** | -0.203*** | -0.273*** | -0.455*** |
| | (0.029) | (0.039) | (0.061) | (0.031) | (0.041) | (0.062) |
| ln(Price) | -0.758*** | -0.515*** | -0.408*** | -0.749*** | -0.510*** | -0.398*** |
| | (0.073) | (0.040) | (0.044) | (0.075) | (0.041) | (0.046) |
| ln(Lagged promotion stock) | 0.725*** | 0.804*** | 0.738*** | 0.734*** | 0.807*** | 0.730*** |
| | (0.018) | (0.024) | (0.026) | (0.018) | (0.025) | (0.027) |
| Controls | Y | Y | Y | Y | Y | Y |
| Drug fixed effect | Y | Y | Y | Y | Y | Y |
| Market fixed effect | N | N | N | N | N | N |
| Time fixed effect | Y | Y | Y | Y | Y | Y |
| N | 4,552 | 2,786 | 1,975 | 4,240 | 2,599 | 1,839 |
| Adjusted $R^2$ | 0.491 | 0.552 | 0.374 | 0.490 | 0.548 | 0.365 |
| First stage F-statistic | 48.17 | 55.94 | 36.8 | 21.06 | 51.52 | 33.89 |
| Hansen J-statistic | 0.934 | 2.399 | 2.316 | 0.57 | 1.641 | 3.03 |
| Hansen J p-value | 0.334 | 0.301 | 0.314 | 0.45 | 0.44 | 0.22 |
| **Marginal effects: Relabel * U.S.** | **-0.173** | **-0.225** | **-0.366** | **-0.165** | **-0.238** | **-0.365** |

Table A.8: Effects of Precaution/Adverse Selection Relabeling: Low-Intensity Markets

Dependent variable is the natural logarithm of sales, ln(*Sales*). Sample includes the combination of precaution and adverse reaction along with low-intensity markets. The unit of analysis in Model 1 is the focal drug level, Model 2 is the 4-digit ATC market (ATC4) level and Model 3 is the 3-digit ATC market (ATC3) level. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands*, and *Number of generics*. The models are log-linear, as such the marginal effects are calculated using the equation exp($\beta$-1) where $\beta$ is the respective coefficient on our variable of interest, (*Relabel*U.S.*). Marginal effects for our variables of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

| DV = ln(Sales) | Model 1<br>Focal Drug | Model 2<br>ATC4 market | Model 3<br>ATC3 market |
|---|---|---|---|
| Relabel | 0.075* | 0.024 | -0.063 |
| | (0.039) | (0.088) | (0.086) |
| U.S. | 0.333*** | 1.559*** | 0.829*** |
| | (0.052) | (0.101) | (0.088) |
| Relabel * U.S. | -0.068* | -0.020 | 0.011 |
| | (0.035) | (0.072) | (0.065) |
| ln(Price) | -0.287*** | -1.044*** | -0.584*** |
| | (0.053) | (0.045) | (0.036) |
| ln(Lagged promotion stock) | 0.804*** | 0.165*** | 0.178*** |
| | (0.034) | (0.021) | (0.020) |
| Controls | Y | Y | Y |
| Drug fixed effect | Y | N | N |
| Market fixed effect | N | Y | Y |
| Time fixed effect | Y | Y | Y |
| N | 1,564 | 1,564 | 737 |
| Adjusted $R^2$ | 0.622 | 0.558 | 0.638 |
| First stage F-statistic | 76.21 | 160.56 | 204.09 |
| Hansen J-statistic | 0.248 | 0.977 | 2.462 |
| Hansen J p-value | 0.618 | 0.323 | 0.117 |
| **Marginal effects:**<br>**Relabel * U.S.** | **-0.066** | | |

Table A.9: Effects of Warning/Box Warning Relabeling: Low-Intensity Markets

Dependent variable is the natural logarithm of sales, ln(*Sales*). Sample includes the combination of warning and box warning along with low-intensity markets. The unit of analysis in Model 1 is the focal drug level, Model 2 is the 4-digit ATC market (ATC4) level and Model 3 is the 3-digit ATC market (ATC3) level. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands*, and *Number of generics*. The models are log-linear, as such the marginal effects are calculated using the equation exp($\beta$-1) where $\beta$ is the respective coefficient on our variable of interest, (*Relabel*U.S.*). Marginal effects for our variables of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * p $<$ 0.10, ** p $<$ 0.05, *** p $<$ 0.01.

| DV = ln (Sales) | Model 1<br>Focal Drug | Model 2<br>ATC4 market | Model 3<br>ATC3 market |
|---|---|---|---|
| Relabel | 0.228* | -0.251** | -0.007 |
| | (0.117) | (0.098) | (0.118) |
| U.S. | 0.174** | 1.842*** | 1.051*** |
| | (0.072) | (0.078) | (0.095) |
| Relabel * U.S. | -0.597*** | 0.163 | 0.021 |
| | (0.148) | (0.113) | (0.120) |
| ln(Price) | -0.310*** | -0.812*** | -0.449*** |
| | (0.077) | (0.048) | (0.039) |
| ln(Lagged promotion stock) | 0.596*** | 0.183*** | 0.181*** |
| | (0.049) | (0.022) | (0.029) |
| Controls | Y | Y | Y |
| Drug fixed effect | Y | N | N |
| Market fixed effect | N | Y | Y |
| Time fixed effect | Y | Y | Y |
| N | 654 | 762 | 430 |
| Adjusted $R^2$ | 0.746 | 0.707 | 0.638 |
| First stage F-statistic | 18.28 | 410.61 | 580.23 |
| Hansen J-statistic | 0.708 | 1.67 | 1.276 |
| Hansen J p-value | 0.400 | 0.196 | 0.259 |
| **Marginal effects:**<br>**Relabel * U.S.** | **-0.450** | | |

Table A.10: Effects of Precaution/Adverse Selection Relabeling: High-Intensity Markets

Dependent variable is the natural logarithm of sales, ln(*Sales*). Sample includes the combination of precaution and adverse reaction along with high-intensity markets. The unit of analysis in Model 1 is the focal drug level, Model 2 is the 4-digit ATC market (ATC4) level and Model 3 is the 3-digit ATC market (ATC3) level. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands*, and *Number of generics*. The models are log-linear, as such the marginal effects are calculated using the equation exp($\beta$-1) where $\beta$ is the respective coefficient on our variable of interest, (*Relabel*U.S.*). Marginal effects for our variables of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

| DV = ln(Sales) | Model 1<br>Focal Drug | Model 2<br>ATC4 market | Model 3<br>ATC3 market |
|---|---|---|---|
| Relabel | 0.035 | 0.071*** | 0.019 |
| | (0.041) | (0.023) | (0.021) |
| U.S. | 0.773*** | 1.889*** | 1.630*** |
| | (0.047) | (0.034) | (0.032) |
| Relabel * U.S. | -0.190*** | -0.061** | -0.049** |
| | (0.045) | (0.027) | (0.024) |
| ln(Price) | -0.658*** | -1.176*** | -0.781*** |
| | (0.071) | (0.072) | (0.033) |
| ln(Lagged promotion stock) | 0.803*** | 0.174*** | 0.133*** |
| | (0.022) | (0.007) | (0.007) |
| Controls | Y | Y | Y |
| Drug fixed effect | Y | N | N |
| Market fixed effect | N | Y | Y |
| Time fixed effect | Y | Y | Y |
| N | 4,746 | 4,158 | 4,218 |
| Adjusted $R^2$ | 0.360 | 0.844 | 0.846 |
| First stage F-statistic | 31.25 | 54.03 | 405.85 |
| Hansen J-statistic | 0.011 | 0.218 | 1.095 |
| Hansen J p-value | 0.915 | 0.641 | 0.295 |
| **Marginal effects:**<br>**Relabel * U.S.** | **-0.173** | **-0.059** | **-0.048** |

Table A.11: Effects of Warning/Box Warning Relabeling: High-Intensity Markets

Dependent variable is the natural logarithm of sales, ln(*Sales*). Sample includes the combination of warning and box warning along with high-intensity markets. The unit of analysis in Model 1 is the focal drug level, Model 2 is the 4-digit ATC market (ATC4) level and Model 3 is the 3-digit ATC market (ATC3) level. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands*, and *Number of generics*. The models are log-linear, as such the marginal effects are calculated using the equation exp($\beta$-1) where $\beta$ is the respective coefficient on our variable of interest, (*Relabel*U.S.*). Marginal effects for our variables of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * p $<$ 0.10, ** p $<$ 0.05, *** p $<$ 0.01.

| DV = ln (Sales) | Model 1<br>Focal Drug | Model 2<br>ATC4 market | Model 3<br>ATC3 market |
|---|---|---|---|
| Relabel | 0.212** | 0.093*** | 0.041 |
| | (0.087) | (0.034) | (0.031) |
| U.S. | 0.670*** | 1.778*** | 1.675*** |
| | (0.070) | (0.052) | (0.041) |
| Relabel * U.S. | -0.420*** | -0.110*** | -0.172*** |
| | (0.091) | (0.040) | (0.038) |
| ln(Price) | -0.891*** | -0.581*** | -0.594*** |
| | (0.098) | (0.068) | (0.039) |
| ln(Lagged promotion stock) | 0.791*** | 0.132*** | 0.114*** |
| | (0.034) | (0.014) | (0.011) |
| Controls | Y | Y | Y |
| Drug fixed effect | Y | N | N |
| Market fixed effect | N | Y | Y |
| Time fixed effect | Y | Y | Y |
| N | 1,582 | 1,409 | 1,561 |
| Adjusted $R^2$ | 0.425 | 0.902 | 0.862 |
| First stage F-statistic | 41.69 | 60.91 | 652.71 |
| Hansen J-statistic | 0.674 | 1.030 | 0.101 |
| Hansen J p-value | 0.412 | 0.310 | 0.751 |
| **Marginal effects:**<br>**Relabel * U.S.** | **-0.343** | **-0.104** | **-0.158** |

Table A.12: Effects of Relabeling on Demand across Market Size and Concentration
Dependent variable is the natural logarithm of sales, ln(*Sales*). Models 1-2 split the sample across the bottom and top quartile of sales within a 4-digit ATC market. Models 3-4 split the sample across the bottom and top quartile of market concentration or HHI within a 4-digit ATC market. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands,* and *Number of generics*. The models are log-linear, as such the marginal effects are calculated using the equation exp($\beta$-1) where $\beta$ is the respective coefficient on our variable of interest, (*Relabel*U.S.*). Marginal effects for our variables of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

| | Model 1 | Model 2 | Model 3 | Model 4 |
|---|---|---|---|---|
| | Bottom Quartile | Top Quartile | Bottom Quartile | Top Quartile |
| DV = ln(Sales) | Sales | | HHI | |
| Relabel | 0.055** | 0.058 | 0.151* | 0.175*** |
| | (0.027) | (0.070) | (0.085) | (0.054) |
| U.S. | 0.204*** | 1.116*** | -0.029 | 0.890*** |
| | (0.024) | (0.061) | (0.059) | (0.049) |
| Relabel * U.S. | -0.100*** | -0.221*** | -0.259*** | -0.240*** |
| | (0.025) | (0.055) | (0.063) | (0.043) |
| ln(Price) | -0.221*** | -1.280*** | 0.173 | -0.681*** |
| | (0.036) | (0.125) | (0.119) | (0.046) |
| ln(Lagged promotion stock) | 0.459*** | 0.721*** | 1.057*** | 0.685*** |
| | (0.031) | (0.026) | (0.047) | (0.036) |
| Controls | Y | Y | Y | Y |
| Drug fixed effect | Y | Y | Y | Y |
| Market fixed effect | N | N | N | N |
| Time fixed effect | Y | Y | Y | Y |
| N | 1,369 | 1,972 | 1,300 | 1,930 |
| Adjusted $R^2$ | 0.241 | 0.504 | 0.332 | 0.431 |
| First stage F-statistic | 21.26 | 54.41 | 26.57 | 113.48 |
| Hansen J-statistic | 1.927 | 4.276 | 0.054 | 0.002 |
| Hansen J p-value | 0.165 | 0.233 | 0.817 | 0.961 |
| **Marginal effects: Relabel * U.S.** | **-0.095** | **-0.198** | **-0.228** | **-0.213** |

Table A.13: Effects of Relabeling on Market ATC-N

Dependent variable is the natural logarithm of sales, ln(*Sales*). The sample includes only those drugs within the 1-digit ATC market N or nervous system. The unit of analysis in Model 1 is the focal drug level, Model 2 is the 4-digit ATC market (ATC4) level and Model 3 is the 3-digit ATC market (ATC3) level. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands*, and *Number of generics*. The models are log-linear, as such the marginal effects are calculated using the equation exp($\beta$-1) where $\beta$ is the respective coefficient on our variable of interest, (*Relabel*U.S.*). Marginal effects for our variables of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * p $<$ 0.10, ** p $<$ 0.05, *** p $<$ 0.01.

| DV = ln (Sales) | Model 1<br>Focal Drug | Model 2<br>ATC4 market | Model 3<br>ATC3 market |
|---|---|---|---|
| Relabel | 0.100 | 0.017 | -0.010 |
| | (0.092) | (0.040) | (0.042) |
| U.S. | 0.289*** | 1.117*** | 1.026*** |
| | (0.109) | (0.067) | (0.057) |
| Relabel * U.S. | -0.241*** | -0.022 | 0.039 |
| | (0.074) | (0.053) | (0.054) |
| ln(Price) | -0.236 | 1.744*** | 1.372*** |
| | (0.311) | (0.148) | (0.155) |
| ln(Lagged promotion stock) | 0.961*** | 0.170*** | 0.188*** |
| | (0.032) | (0.014) | (0.010) |
| Controls | Y | Y | Y |
| Drug fixed effect | Y | N | N |
| Market fixed effect | N | Y | Y |
| Time fixed effect | Y | Y | Y |
| N | 1,148 | 1,027 | 949 |
| Adjusted $R^2$ | 0.602 | 0.852 | 0.859 |
| First stage F-statistic | 92.95 | 243.58 | 156.74 |
| Hansen J-statistic | 0.342 | 0.286 | 0.839 |
| Hansen J p-value | 0.559 | 0.593 | 0.360 |
| **Marginal effects:**<br>**Relabel * U.S.** | **-0.214** | | |

Table A.14: Effects of Relabeling on Market ATC-J

Dependent variable is the natural logarithm of sales, ln(*Sales*). The sample includes only those drugs within the 1-digit ATC market J or anti-infectives. The unit of analysis in Model 1 is the focal drug level, Model 2 is the 4-digit ATC market (ATC4) level and Model 3 is the 3-digit ATC market (ATC3) level. Price is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands*, and *Number of generics*. The models are log-linear, as such the marginal effects are calculated using the equation exp($\beta$-1) where $\beta$ is the respective coefficient on our variable of interest, (*Relabel*U.S.*). Marginal effects for our variables of interest are reported in the lower panel. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * p $<$ 0.10, ** p $<$ 0.05, *** p $<$ 0.01.

| DV = ln(Sales) | Model 1<br>Focal Drug | Model 2<br>ATC4 market | Model 3<br>ATC3 market |
|---|---|---|---|
| Relabel | 0.174 | 0.292*** | 0.187*** |
| | (0.128) | (0.076) | (0.040) |
| U.S. | 1.549*** | 1.557*** | 1.888*** |
| | (0.128) | (0.167) | (0.153) |
| Relabel * U.S. | -0.277*** | -0.149** | -0.145*** |
| | (0.103) | (0.072) | (0.044) |
| ln(Price) | -3.225*** | -0.159 | -1.216*** |
| | (0.513) | (0.126) | (0.260) |
| ln(Lagged promotion stock) | 0.541*** | 0.241*** | 0.137*** |
| | (0.064) | (0.031) | (0.027) |
| Controls | Y | Y | Y |
| Drug fixed effect | Y | N | N |
| Market fixed effect | N | Y | Y |
| Time fixed effect | Y | Y | Y |
| N | 1,126 | 1,108 | 1,022 |
| Adjusted $R^2$ | -0.107 | 0.781 | 0.882 |
| First stage F-statistic | 15.86 | 240.35 | 20.23 |
| Hansen J-statistic | 3.808 | 1.779 | 0.457 |
| Hansen J p-value | 0.149 | 0.182 | 0.499 |
| **Marginal effects:**<br>**Relabel * U.S.** | **-0.242** | **-0.138** | **-0.135** |