Evaluating Recent Policies to Accelerate Generic Drug Entry

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Abstract

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Generic drugs can bring more competition to the market and help to reduce drug costs. Governmental pharmaceutical regulations operate to balance innovation, access, and cost. Encouraging more generic entries is one mechanism to provide more competition.

In this dissertation, we examined several recent policies that aim at accelerating generic drug entry. In Chapter 1, we presented a brief introduction about the background and rationale for the research. In Chapter 2, we evaluated whether the enactment of the Generic Drug User Fee Amendments (GDUFA) has already led to an increase in the speed of entry for different orders of entrants. In Chapter 3, we utilized both existing literature and nationally representative survey data to deepen our understanding of the changes in drug price and volume associated with more

generic competition. In Chapter 4, we seek to estimate the potential economic impact from future policy to encourage faster generic entry, combining evidence of market dynamic changes from Chapter 3 as well as hazard of entry modeled in Chapter 2.

Through the policy analysis in Chapter 2, we found that in markets where the first generic entered with patent challenge, GDFUA slowed the time-to-entry for the second entrant, but its impact was not significant for subsequent entries. GDUFA had null impact on the time-to-entry for the first generics that entered without patent challenge but significantly slowed down time to some of the subsequent generic entries. Our results suggest that GDUFA may have decelerated generic entries in the market beyond the first entry. Therefore, the overall price impact of this policy remains unclear. Future evaluation should combine the joint effect of GDUFA with future policies that specifically aim to accelerate subsequent generic entries. In Chapter 3, through meta-analysis, we found that more generic drug competition is associated with decreasing generic drug price, but not branded drug price, a finding known as the generic competition paradox. The Bayesian linear regression analysis found price reduction post-generic entry exists for both generic and branded drugs. It also revealed that generic market share and overall drug volume increase with respect to more generic competition. Lastly, in Chapter 4, we quantified the potential benefit from accelerating the approval of the first three generic entrants. Increased competition has minimum impact on drug expenditure reduction. This indicates that a general policy to expediate the review for the first three generics may not be as useful for expenditure reduction, as the total number of generic entrants is not affected.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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I am also grateful to my committee members Beth Devine and Gary Chan. Beth has been a great mentor to me throughout my graduate study, guiding me to build a curriculum that has helped develop a well-rounded skillset, providing me with great research ideas, and introducing me to precious resources to help me move forward and collaborate with more experts in the fields. Gary has also provided solid guidance in the methods for my research especially in survival analysis. I really appreciate his patience working with students outside his own department, as well as his sharp eyes to spot issues in my research.

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At last, I would also like to thank my parents Liang Chen and Yajun Zhu, and my fiancé Benjamin Thomas for their understanding, encouragement and support.

Chapter 1. INTRODUCTION

1.1 BACKGROUND

Generic drugs can bring more competition to the market and help to reduce drug costs. Governmental pharmaceutical regulations operate to balance innovation, access, and cost. Encouraging more generic entries is one mechanism to provide more competition. In the background section, we provided an overview of the policy landscape related to generic drug competition, as well as a summary of existing evidence on how drug prices and utilization change in response to generic competition.

1.1.1 *Policy Landscape*

The Drug Price Competition and Patent Term Restoration Act (The Hatch-Waxman Act) amended the Federal Food, Drug, and Cosmetic Act (FD&CA) in 1984 to encourage generic entry by lowering the requirement from conducting trials to simply showing the generic drugs are "bioequivalent" to the branded drugs, and introducing the 180-day exclusivity for the first-to-challenge Abbreviated New Drug Application (ANDA) applicant as an incentive for generic manufacturers to enter the market before patent expiry [1]. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) further amended the FD&CA by modifying the 180-day exclusivity eligibility (from patent-based to branded drug-based) and trigger for faster generic entry [2].

To continue encouraging and accelerating generic competition, several policies have been created in recent years. In 2012, a five-year program, the Generic Drug User Fee Amendments (GDUFA) was enacted [3]. Before October 2012, only firms submitting new drug applications

(NDAs) were subject to the user fee, but since then it also applies to generic applications. By charging ANDA applicants a user fee, GDUFA is intended to speed access to safe and effective generic drugs for the public by increasing resources at the FDA, and reducing costs. In 2017, Congress reauthorized GDUFA (GDUFA II) through 2022 [4]. Moreover, in June 2017, the Food and Drug Administration (FDA) announced the launch of the Drug Competition Action Plan (DCAP) [5], aiming to resolve regulatory obstacles to generic access, increase the efficiency and predictability of the FDA's review process, and reduce gaming by branded companies that can delay generic drug entry. Early steps the FDA took included: (a) introducing "Priority Review" instead of Office of Generic Drugs' (OGD) previous "first-in, first-reviewed" approach for eligible ANDA applicants, (b) prioritizing review of generic drug applications until there are three generics approved for a brand product, and (c) expediting subsequent drug approval once the 180-day exclusivity is triggered[6].

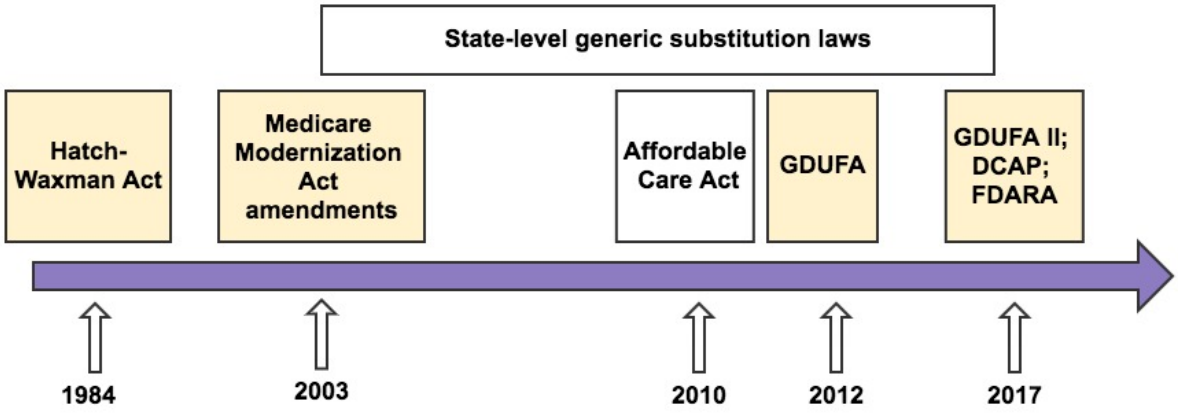


Figure 1.1 Timeline for key policies related to generic competition

Notes: Policies highlighted in yellow are direct policies that may affect generic entry. Policies in white are indirect policies.

Furthermore, the FDA Reauthorization Act of 2017 (FDARA) was signed into law in August 2017 to amend the Federal Food, Drug, and Cosmetic Act (FD&C Act) [7]. A Competitive Generic Therapy (CGT) designation was created to increase generic drug's incentive to enter. When there is inadequate competition (defined as only one drug listed in the Orange Book (OB), no matter branded or generic), the next eligible entrant can enjoy a 180-day exclusivity.

There are also several indirect policies that promotes generic use which may encourage generic drugs to enter. The first is the Affordable Care Act (ACA, 2010) that increased rebate of generics in Medicaid, coverage of generics in Medicare, as well as commercial insurance access for non-Medicare eligible people [8] [9, 10]. Increase in rebate was transformed into higher cost outside Medicaid, while increase in generic coverage effectively lead to increase in generic use and cost-savings. State-level registration changes in generic substitution consents have also shown to increase generic drug use [11].

In addition, a few policies and plans have been proposed to further encourage generic entry. The FDA has planned to harmonize the generic drug standard overseas to promote international generic drugs to enter, as well as build a Knowledge-aided Assessment & Structured Application (KASA) platform to increase efficiency of ANDA reviews by partial automated analysis instead of manual review [12, 13]. Senators have also introduced registrations to promote generic entry by removing barriers, such as the requirement for branded drug companies to provide bioequivalence samples for generic development, and more collaboration with the Federal Trade Commission (FTC) to stop reverse payment to delay generic entry [14].

1.1.2 *Generic Competition's Impact on the Market Dynamics*

After reviewing recent policies that may affect generic drug entry, in this section, we examined our second interest, which is how generic competition affects market dynamics including drug pricing and utilization. This would help us to better quantify the policy impacts in the evaluation. Existing literature has fairly consistent findings regarding how drug prices respond to generic drug competition in the US setting. After generic drug entry, the generic drug prices usually decrease over time, while branded drug price may rise slightly in response (such as Caves et al. (1991), Saha et al. (2006), Berndt et al. (2011), Dafny et al. (2017), Dave et al. (2017), Aitken et al. (2018)) [15-20]. Reiffen and Ward (2005) also found that generic drug price remains above the marginal-cost after more than 8 entrants on the market [21]. The decrease in generic drug price is related to increased competition in the market. The increase in branded drug price is the so-called "generic competition paradox", where the incumbent drug remains a high price to attract price-insensitive customers and those with brand loyalty. Similar directions of price changes were also found in markets outside the US by Vandoros and Kanavos (2013), who evaluated six European drug markets [22].

Generic competition not only affects drug price, but also the market structures such as the share of branded vs. generic drugs, and the overall volume of drug consumption. For market share, studies found branded drugs' market share decreases over time post generic entry, but there are big variations across therapeutic area and drugs (such as Aronsson et al. (2001), Saha et al. (2006), Grabowski et al. (2007), Huckfeldt and Knittel (2011), Aitken et al. (2018)) [16, 20, 23-25]. Lakdawalla et al. (2017) examined the long-term market share changes, and found that generics take 74% and 77% of the market 5 and 10 years after any generic entry [26].

For overall volume (generic and branded drug combined), literature showed mixed results. Caves et al. (1991) and Conti et al. (2016) found increased utilization after generic entry, while Berndt et al. (2003) and Huckfeldt and Knittel (2011) observed a decrease in volume [15, 25, 27, 28]. Reasons for decreased utilization include the reformulation of branded drugs, decreased marketing efforts, or competition from newer drugs.

Given the uncertainty in how drug utilization and branded drug price change with respect to more generic competition, the Congressional Budget Office (CBO) concluded that the major impact of generic competition on drug spending is from generic substitution (due to the price reduction) [29]. Sack et al. (2018) estimated that substituting branded drug consumption in Medicare in 2016 would bring an estimated reduction of $925 million on drug spending of 1500 medications with the highest total spending [30].

As summarized above, many studies examined the impact of different numbers of generic competitors on drug price, market structure and expenditures. However, there is only one literature review that systematically examined the impact on price change, and it did not consider the number of generic drugs [31]. To deepen our understanding in this domain, we have decided to conduct our own evidence synthesis and analysis.

1.2 RESEARCH OBJECTIVES

We would like to evaluate the efficiency of GDUFA as well as to quantify the potential reduction in drug expenditure from the more recent policy, DCAP. The Prescription Drug User Fee Act (PDUFA) for branded drug applicants (NDAs) is a policy similar to GDUFA that was created by Congress in 1992, and has been renewed every 5 years [32]. By charging each branded drug

applicant a one-time user fee, it helps to expedite the branded drug approval process. Economic analyses have been conducted to study PDUFA's efficacy and its impact on increased consumer welfare [33]. However, since GDUFA I-II and DCAP are fairly recent policies, few studies have been conducted to evaluate their efficacy and impact.

On the one hand, for GDUFA, assessment by the FDA regarding initial successes and areas of improvement was conducted using internal application data, but only data in years 3 and 4 of GDUFA was reviewed, not capturing the whole picture of GDUFA's impact [34]. GDUFA also increased FDA-supported research of generic drugs [35]. Economic analyses of GDUFA mainly focus on the comparison of fee structures with other similar policies [36], as well as with GDUFA II [37]. Concerns have been raised regarding adequate incentives for generic manufacturers, especially smaller ones. Dong et al. (2017) compares the fee structure of GDUFA I with other human drug user fee acts (prescription drug, biosimilar, and medical device), and concludes that GDUFA has a relatively regressive fee structure, penalizing small companies and new generic entrants. Berndt et al. (2018) also points out that compared to GDUFA I, the additional annual fee from GDUFA II may lessen such incentives. Therefore, we would like to examine whether GDUFA I already speeds up generic entry, and impacts different orders of generic entry differently.

On the other hand, all these policies are targeting at promotion of more generic competition and therefore a more rapid decline in drug prices for the respective drug classes. The average price reduction from the first generic entrants is approximately 40%, while this reduction further increases to 55% and 70% after the second and third generic entries, respectively [38]. Therefore, compared to GDUFA, expanding the scope to accelerate the speed of entry for the second and third entrants in DCAP will likely lead to quicker price declines, lower medical

expenditures, and greater incentives for generic competitors (especially after the first generic entry) to enter the market. However, since DCAP and GDUFA II were initiated around the end of 2017, no study has evaluated their impacts due to inadequate empirical evidence. Here we propose to estimate the extra economic savings that DCAP will bring via simulation.

As illustrated in Figure 1.2, the focus of this study is to evaluate whether the enactment of GDUFA has already led to an increase in the speed of entry for different orders of entrants (in Chapter 2), and to understand the change in price and quantity consumed as well as overall drug spending, affected by the uptake of generic entrants with different levels of generic competition (in Chapter 3). The next step is to estimate the potential economic impact from DCAP, using evidence of market dynamic changes from Chapter 3 as well as hazard of entry modeled in Chapter 2. Background, methods, results and conclusion for each chapter will be discussed in detail in the following chapters.

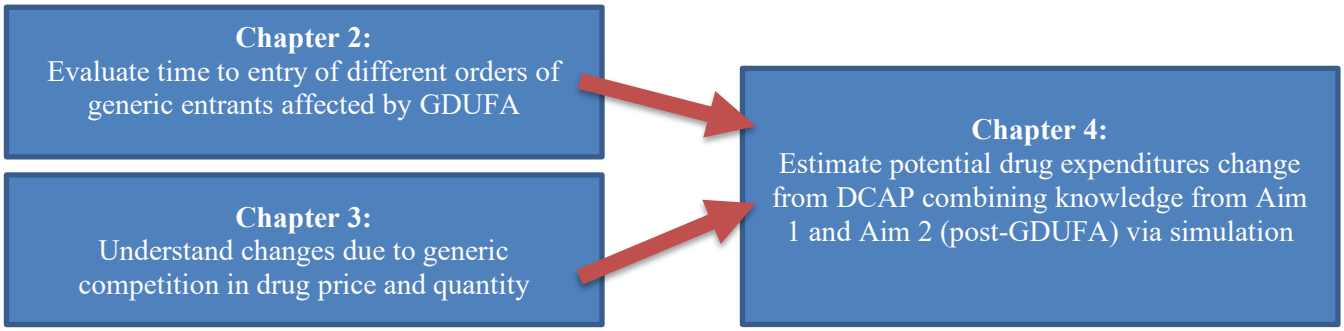


Figure 1.2 Conceptual Framework

Chapter 2. EVALUATING THE POLICY IMPACT ON TIME TO GENERIC DRUG ENTRY

2.1 INTRODUCTION

In 2012, the Generic Drug User Fee Amendments (GDUFA) was enacted to speed access to generic drugs and promote price competition in the pharmaceutical market. Since appreciable price competition is only triggered after multiple generic entries in a market, we evaluated the impact of GDUFA with a focus on the time-to-entry for different orders of generic entrants. We identified the order of generic entry for each branded drug using drug approval and exclusivity information from the Orange Book database between 2007 and 2017. Recurrent event survival analysis was applied to study the time-to-entry for generic drugs impacted by GDUFA, taking into account differentiating different orders of event.

2.2 BACKGROUND

Generic drugs can bring more competition to the market and help to reduce drug costs. Governmental pharmaceutical regulations operate to balance innovation, access, and cost. Encouraging more generic entries is one mechanism to provide more competition.

The Drug Price Competition and Patent Term Restoration Act (The Hatch-Waxman Act) amended the Federal Food, Drug, and Cosmetic Act (FD&CA) in 1984 to encourage generic entries into a market by lowering the requirement of conducting clinical trials to simply showing that the generic version of a drug is “bioequivalent” to the brand-name drug and introducing a 180-day exclusivity period for the first Abbreviated New Drug Application (ANDA) applicant that successfully challenges the patent, as an incentive for generic manufacturers to enter the

market before patent expiration [1]. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) further amended the FD&CA by modifying the 180-day exclusivity eligibility (from patent-based to branded drug-based[1]) and trigger for faster generic entry [2].

Several policies have been enacted in recent years to continue encouraging and accelerating generic competition. In 2012, a five-year program, the Generic Drug User Fee Amendments (GDUFA), was enacted [3]. Before October 2012, only firms submitting new drug applications (NDAs) were subject to the user fee under the Prescription Drug User Fee Act (PDUFA, enacted in 1992), but since GDUFA was enacted, the user fee has also been applied to generic applications. This fee is intended to increase the US Food and Drug Administration's (FDA) resources, which can be used to accelerate the public's access to safe and effective generic drugs and to reduce healthcare costs by promoting price competition. In 2017, the US Congress reauthorized GDUFA (GDUFA II) through 2022 [4].

GDUFA proposes reaching a 10-month review cycle for 90% of the ANDAs, with a target revenue of approximately $299 million. New ANDAs submitted on or after October 1, 2012, are subject to a one-time new-ANDA filing fee [4]. If the ANDA is not approved or is withdrawn, then 75% of the ANDA filing fee will be refunded. Moreover, any finished dosage form (FDF) or active pharmaceutical ingredient (API) facility with at least one pending or approved generic drug submission is subject to an annual facility fee, with a higher foreign levy for foreign facilities.

[1] One branded drug may hold multiple patents.

Economic analyses have been conducted to study PDUFA's impact on increased consumer welfare [33]. However, since GDUFA is a fairly recent policy, few studies have been conducted to evaluate its efficiency and impact. The FDA claims that it has met GDUFA's expectation of shortening the review cycle and eliminating backlogged applications [13]. The total number of ANDAs and the proportion of first-cycle approvals have both increased [34]. However, Dong et al. compared the fee structure of GDUFA with other human drug user-fee acts (for prescription drugs, biosimilars, and medical devices) and concluded that GDUFA has a relatively regressive fee structure (e.g., no first-time or small business exemptions), penalizing small companies, foreign manufacturers and new generic entrants [36]. Using regression analysis, Berndt et al. found an increase in the drug market's exit rate post-GDUFA, indicating an increased market concentration [10]. Additionally, no study has examined how GDUFA has affected the time-to-entry for generic drugs.

We examined whether GDUFA sped up generic entry and whether the policy has differentially impacted the time-to-entry for different orders of generic entrants. This examination is important, especially because the average price reduction from the first generic entrants is approximately 40%, while this reduction further increases to 55% and 70% after the second and third generic entries, respectively [38]. Therefore, understanding the timing of subsequent orders of generic entry is important for understanding the effect of policy on generics-driven price competition.

2.3 METHODS

2.3.1 *Data*

The main dataset is from the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (OB) online database [39], which includes information regarding drug names,

ingredients, strengths, routes, application numbers, product numbers, approval dates, and manufacturer names and whether the drugs are brand-name or generic. We excluded discontinued and over-the-counter drugs and linked brand-name drugs to therapeutic equivalent generic competitors using data on ingredients, route, and strength. Drugs with the same ingredient-route-strength form were categorized in the same cluster and viewed as "therapeutic equivalents" [40]. The order of generic entry for each brand-name drug can be constructed using the time of approval. To identify patent challenges as well as when brand-name drugs were at risk of generic competition, historical patent expiration dates and exclusivity expiration dates were obtained by filing Freedom of Information Act (FOIA) requests with the FDA [41].

We also controlled for therapeutic class in the Anatomical Therapeutic Chemical (ATC) level 1 classification, competition from authorized generics launched or authorized by brand-name drug companies, and brand-name drug Elements to Assure Safe Use (ETASU) status requiring monitoring, as well as the availability of product-specific guidance for generic drug development, which will likely affect the speed of generic entry (see Appendix A.1) [42].

2.3.2 *Recurrent Event Survival Analysis*

2.3.2.1 Main Analysis

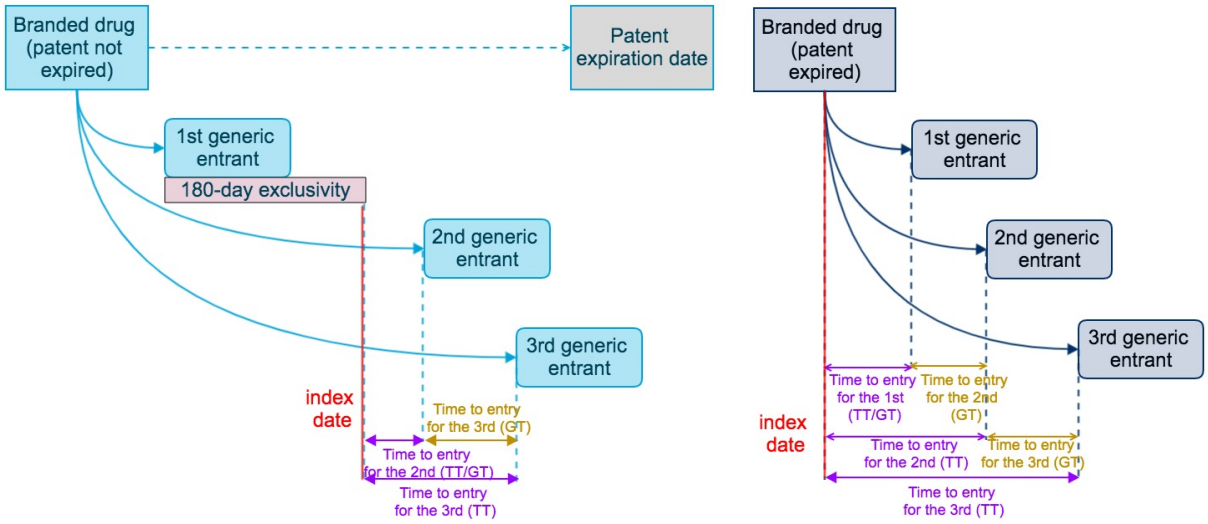
Generic competitors for each brand-name drug are viewed as "therapeutic equivalents" to or perfect substitutes for the brand-name version, and natural clustering exists. Therefore, we viewed their entries as recurrent events. Compared to the traditional Cox proportional hazard model, recurrent event survival analysis not only analyzes the first occurring event but also utilizes information beyond the first event [43, 44].

We identified the order of generic entry for each brand-name drug between October 1st, 2007, and September 30th, 2017 (5 years before and after the enactment of GDUFA), using drug approval and exclusivity information. We distinguished between generic entry with and without a patent challenge (PC) for the first entrants and created indicators for different orders of generic entry based on their approval dates. The reason for separating "With PC" and "Without PC" cases is that, with a successful PC, the first generic competitor could enter the market before patent expiration with a 180-day exclusivity period where no other generic competitors could enter (other than authorized generics from the brand-name drug manufacturer). Therefore, as listed in Figure 2.1, the index date for time-to-entry is defined differently in these two scenarios.

In the "With PC" scenario, since the first generic entrant challenges the patent and obtains approval before the patent expiration date, we defined the index date as the end of its 180-day exclusivity period, when subsequent generic entries can happen. We considered both total time (TT) and gap time (GT). TT measures the time between the index date and the subsequent generic drug approval date, while GT measures the time between the last generic entry date and the subsequent approval date.

In the "Without PC" scenario, the index date is the brand-name drug's patent expiration date. In this scenario, it is challenging to define the index date (patent expiration date), as each brand-name drug may be associated with more than one patent. Regarding which patent to use to identify the patent expiration date, the studies vary in their methods, including the use of the latest patent [45], the earliest and key patent [46], or contacting companies directly [15]. The latest-expiring patent may not be the ideal choice, as some generic entries occurred at a much earlier date [46]. Therefore, in our main analysis, we used the earliest-expiring patent (plus 6-

month exclusivity if applicable) as the index date. We also changed the index date to the latest patent expiration date as a robustness check for strategic secondary patents [47].



a: With patent challenge (With PC) b: Without patent challenge (Without PC)

Figure 2.1 Time-to-entry with and without Patent Challenge (PC)

Source: Authors' own plots.

Notes: Left (a): With patent challenge; right (b): Without patent challenge. TT: total-time, time between the index date and drug entry date; GT: gap-time, time between previous entry date and current drug entry date. The index date for the "With PC" scenario is the end of the 180-day exclusivity, while for the "Without PC" scenario the index date is patent expiry date.

Moreover, for the entry date, we used the approval date instead of the marketing date, as generic drug companies have less control over the approval date compared to the date of marketing. From a policy perspective, the approval date is also a better indicator of GDUFA's impact on how fast the FDA will approve generic drugs so the companies can start marketing.

We defined the time-to-entry of generic entrants for each brand-name drug as an indicator of the speed of generic entry. The predictor of interest is the impact of GDUFA, i.e., the policy shock that occurred after October 1st, 2012. Every ANDA applicant in the database whose application had not been approved or who had not submitted the application by this day was assigned a value of 1 for this variable. Since GDUFA was renewed in 2017, we excluded all cases after this renewal date to avoid changes in time-to-entry affected by GDUFA II. We also applied administrative censoring to pre-GDUFA observations to preserve the consistency in the length of the censoring window (see Appendix A.2) [48].

Based on the order of entry, each event was assigned to a different stratum, and a stratum-specific (i.e., order-specific) hazard ratio (HR) can be estimated to examine whether there were differentiated effects of GDUFA on different orders of entry. The conditional model, also called the Prentice, Williams and Peterson (PWP) model, was used in the main analysis, where a brand-name drug is only at risk of the k^{th} generic entry, conditional on the occurrence of the k-1^{th} entry [49]. We focused on the conditional GT model, which evaluates the effect of GDUFA since the previous entry event(s) occurred. We also applied the conditional TT model in the sensitivity analysis, which studies the policy's impact on time-to-generic-entry using the date when any generic entry is possible. These conditional models have a potential selection bias, as the risk set for the k^{th} event is a selected subset where the k-1^{th} entry occurred. Therefore, we further addressed this potential bias by modeling in a marginal model, allowing each brand-name drug to be at risk of the k^{th} generic entry even if the k-1^{th} entry has not occurred.

The data structure for the analysis is also provided in the Appendix A.3 [48]. For each model, the coefficient of interest is the policy indicator GDUFA for each order of entry. Due to our interest in the first several entries, we limited our scope to no more than five competitors upon market

entry. We adjusted for confounders including route, therapeutic class, year of index time (linear, centered around year 2012), competition from authorized generics, ETASU status for brand-name drug, and the availability of guidance to help prepare ANDAs [42].

2.3.2.2 Sensitivity Analysis

Since the conditional models do not control for unmeasured confounding, such as market size or other drug-specific characteristics that will affect the speed of entry, we also applied a random effect (conditional frailty; see Appendix A.3 [48]) model that considers heterogeneity across drugs as well as event dependency across events, with an additional random effect that is shared across all generic competitors for each brand-name drug [50].

Furthermore, as mentioned previously, in the main analysis for the "Without PC" group, we used the earliest patent expiration dates as the index dates instead of the latest expiration dates. In the sensitivity analysis, we examined whether using the latest patent expiration dates or the first entrants' entry dates as the index dates would change the conclusion. Moreover, we also controlled for the impact of the Affordable Care Act (ACA) in the sensitivity analysis, as its promotion of the use of generics may encourage generic drug entry [9].

2.3.3 *Descriptive Analysis*

In addition to survival analysis, we conducted a descriptive analysis to illustrate the number of generic entries over time. A falsification test was also conducted to explore whether GDUFA had an impact on the number of brand-name drug entrants [51]. Unadjusted Kaplan-Meier (K-M) curves to compare the hazards of the first, second, and third generic entries pre- and post-GDUFA were also plotted.

Software R (version 3.6.0) was used for data analyses in this chapter as well as the next two.

2.4 RESULTS

2.4.1 *Descriptive analysis*

Figure 2.2 (top) illustrates the overall number of newly approved generic drugs over time, which increased dramatically post-GDUFA, while the number of brand-name drugs during this period only increased moderately, as expected, and was not affected by GDUFA. The trend of an increase in generic drug entries after GDUFA is consistent with other literature [37, 52].

Next, in Figure 2.2 (bottom), we examine the trend in brand-name drug patent expiration dates over time among those that were subjected to a PC. The dates for both the earliest-expiring patent and the latest-expiring patent for an ingredient-route-strength unit were included, which may be different for any brand-name drug with multiple patents. Irrespective of using the earliest versus latest patent expiration dates, there was a steady decline in the number of patent expirations post-GDUFA. Figure 2 suggests that the spike in generic entries observed post-GDUFA may be partially explained by the peak of patent expirations pre-GDUFA (the so-called "patent cliff") [53].

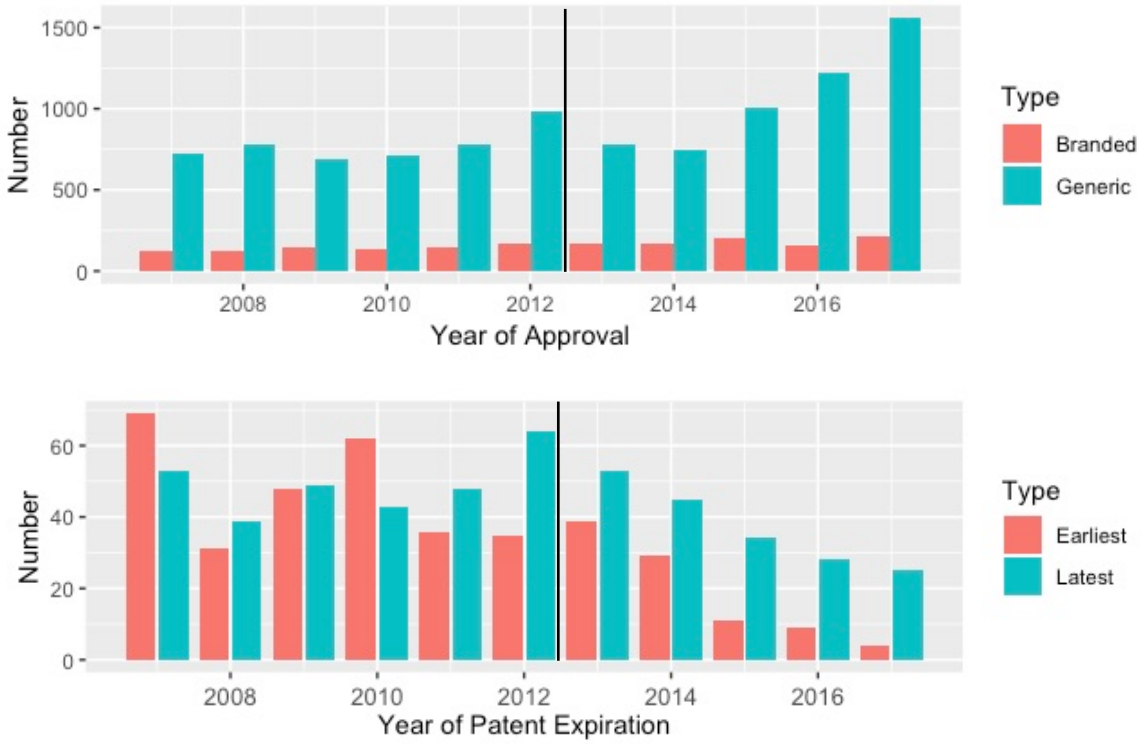


Figure 2.2 Trends in the Number of Drug Entries and Patent Expirations over Time

Source: Authors' calculation from Orange Book database and Orange Book Historical List of Patents, 2007-2017.

Notes: Top: Number of branded and generic entry by year; bottom: Number of branded drug patents expired by year. Black vertical line: enactment of GDUFA. A branded drug may have multiple patents that have a different expiration date; here we used the earliest and latest expiring dates for each branded drug.

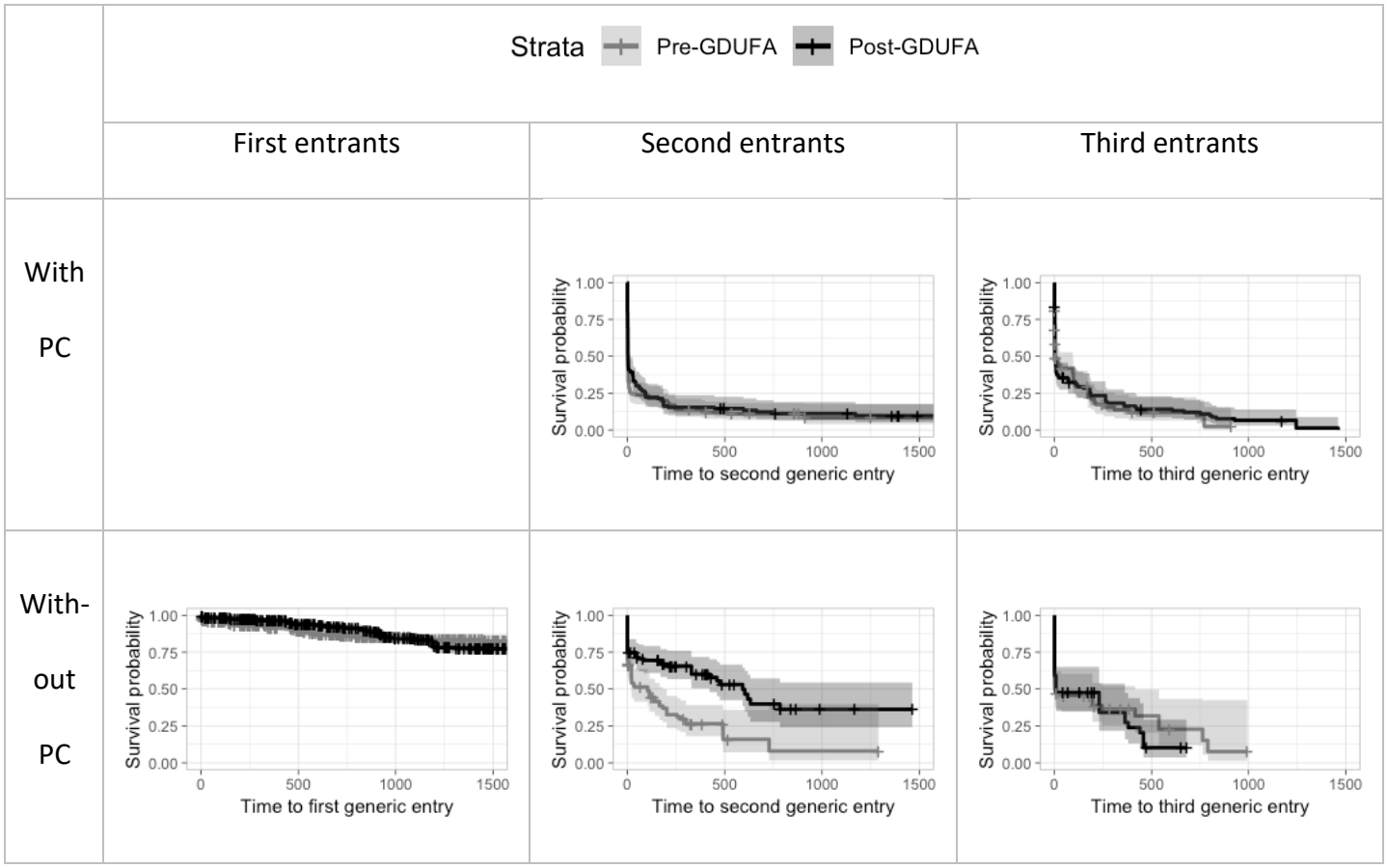


Figure 2.3 K-M Curves for First Three Entrants, With and Without Patent Challenge (PC)

Source: Authors' calculation using data sources explained in Methods.

Notes: x-axis: Time-to-entry since last generic entry for the same branded drug happened. Crosses indicate censored cases. We did not study first entrants that challenged the patent - therefore the upper-left case has no K-M curve.

Figure 2.3 plots the unadjusted K-M curves for the first, second, and third generic entries pre- and post-GDUFA. In the "With PC" markets, since our index date is the end of the first entrants' exclusivity period, we do not have a K-M curve for the first entrants. A steeper K-M curve suggests a larger hazard and therefore quicker generic entry. For generics entering markets after the first entrant has entered with a PC, pre- and post-GDUFA survival rates are similar, indicating similar time-to-entry. In markets without PCs, the time-to-entry for the first generic

also appears to be similar pre- and post-GDUFA. However, the time from the first generic entry to the second generic entry appears to be longer post-GDUFA compared to pre-GDUFA.

2.4.2 *Recurrent Event Survival Analysis*

Table 2.1 reports the Conditional-GT model results for both the "With PC" and "Without PC" scenarios.

For the "With PC" group that consists of 897 generic entrants that entered 223 ingredient-route-strength-specific drug markets where a PC occurred, the results (Model 1 in Table 2.1) suggest that the adjusted hazard ratio (HR) of GDUFA for the entrance of the second generic competitor is 0.44 (95% CI 0.31- 0.63), indicating a longer time to entry from the end of the exclusivity period post-GDUFA. Accelerating effects of GDUFA on time to the subsequent entrants (3^{rd}, 4^{th}, 5^{th} and 6^{th}) are observed, but the effects are not statistically significant.

In Model 1, we also found that the presence of authorized generics deters subsequent generic entries, which is consistent with the motivations of brand-name drug companies to launch authorized generics during the 180-day exclusivity period. We did not adjust for ETASU status, as only a low proportion of drugs have this status. Additionally, we found that there was a significant trend toward faster entry of generic products with PCs over time, which makes the delaying effect of GDUFA even starker.

Table 2.1 Conditional Gap-Time Model Results

Variables	**With PC (n=897, entry = 763)**	**Without PC (n=1252, entry = 403)**
	Model 1: Conditional GT Time to generic entry from PC exclusivity expiration date	**Model 2: Conditional GT** Time to generic entry from branded drugs' earliest patent expiration date
Effect of GDUFA on each stratum (# of generic competitors upon entry)		
0	-	0.97 (0.49, 1.92)
1	0.44** (0.31, 0.63)	0.37** (0.20, 0.65)
2	1.43 (1.05, 1.96)	0.80 (0.44, 1.44)
3	1.12 (0.77, 1.61)	0.41* (0.18, 0.89)
4	1.21 (0.85, 1.74)	0.47 (0.17, 1.33)
5	1.28 (0.85, 1.93)	0.71 (0.24, 2.09)
Route (vs. oral)		
Injection	1.18 (0.78, 1.77)	1.46 (0.70, 3.05)
Other	0.64* (0.44, 0.93)	0.44* (0.23, 0.84)
Authorized generics	0.77** (0.65, 0.91)	0.85 (0.62, 1.16)
ETASU status	-	0.06** (0.01, 0.43)
Guidance for generic application	1.09 (0.91, 1.31)	1.99** (1.49, 2.67)
Index year	1.16** (1.09, 1.23)	1.04 (0.92, 1.19)
ATC-1	A(+), B(+), C (+), H (+), M (+), N (+), and P (-) are significant	A (-), B (-) and G (-) are significant

*: p value less than 0.05

**: p-value less than 0.01

For the "Without PC" group (Model 2 in Table 2.1), there are 1,252 generic drugs that entered 390 ingredient-route-strength-specific markets where patent naturally expired. For the first generic entrants, the conditional GT model shows that GDUFA was associated with a null effect on the time-to-entry after patent expirations, namely, an HR of 0.97 (95% CI 0.49-1.92). However, GDUFA significantly increased the time-to-entry of the second generic from the first entry (HR 0.37, 95% CI 0.20-0.65). Regarding the subsequent entrants, GDUFA decelerated the time-to-entry of the fourth generic drug and had an insignificant impact on the other orders of entry.

In the "Without PC" group, ETASU status for brand-name drugs deters the generics' entry, while the accessibility of drug-specific FDA guidance for generic applications enables generic drugs to enter faster. We did not find a significant negative impact from authorized generics since their competition is unlikely to have as large of an impact in this scenario as during the 180-day exclusivity period for the "With PC" drugs.

2.4.3 *Sensitivity Analysis*

In sensitivity analyses, we examined additional models that could affect the model conclusions, including 1) the application of the conditional TT, conditional frailty, and marginal models; 2) the use of the latest patent expiration dates and the first generic entry dates rather than the earliest patent expiration dates as the index dates for the "Without PC" group; and 3) an adjustment for the impact of the ACA. The adjusted model results are listed in Appendix A.5 and A.6. The results remain consistent for the "With PC" group, in which there was a similar or even longer time-to-entry for the second entrants but not the subsequent entrants post-GDUFA. For the "Without PC" group, there were insignificant changes or even slower speeds of entry for different generic entrants.

2.5 CONCLUSION

The aim of GDUFA is to speed up generic entry, and faster generic entry is one way to lower generic prices. Since it is not obvious that one can look at the number of generic drug approvals to evaluate GDUFA's full impact, we extended our scope to study the impact of GDUFA on the time-to-entry of generic drugs. As speed of entry is a time-to-event variable, survival analysis is applicable in this setting. This approach is different from the approaches in the existing literature that define time-to-entry as a brand-name drug's market exclusivity period and only study the speed of the first generic entry using descriptive analysis or linear regression analysis [24, 54]. Recurrent event survival analysis was applied to study the correlated time-to-entry of subsequent generic drugs for the same ingredient-route-strength combination. We selected this combination as patents were tied to it, which enabled us to evaluate whether GDUFA's overall aim for faster generic entry has been effective. Moreover, we analyzed whether there is a differential effect of GDUFA on different orders of entry and located the potential areas for policy improvements.

We examined two scenarios: when the generic drug challenged the brand-name drug's patent and when no generic entry occurred before the brand-name drug's patent expired. In both cases, we analyzed the impact of GDUFA on time-to-entry from the last generic entry date using a conditional GT model.

For entries "With PC", the results suggest a slowdown in time-to-entry for the second entrants and no significant effect of GDUFA on subsequent entrants. In the "Without PC" scenario, GDUFA also slowed the second entrants. Moreover, we did not find evidence that GDUFA sped up generic entries.

Our results remained mostly consistent across a variety of sensitivity analyses that dealt with alternative model specifications, selection issues in the risk set, the ambiguity of patent expiration dates, and adjustments for other national policies during this time. In the "With PC" case, we found consistent results in the sensitivity analyses, while in the "Without PC" case, although the results were consistent in most scenarios, the negative impact of GDUFA on second entrants disappeared in the frailty models.

One reason for slowed second generic in the conditional GT models may be the fact that GDUFA might have been responsible for bringing some of the first generics to the market for new drugs where generic entry might not have happened without GDUFA. Indeed, as observed in the descriptive analysis results and reported by several studies, a larger number of generics entered post-GDUFA [37, 52]. However, this issue of selection of drugs where first entry happens is not present in our marginal model, which examined the universe of drugs for the time-to-entry for all future generic entries and found similar results to the conditional models. This evidence suggests that GDUFA may have had a larger impact on the extensive margin (the number of first entrants) than on the intensive margin (the number of entrants for a single product). Given the FDA's limited resources, it is also plausible that prioritizing the first entrants may have had a negative impact on the review of subsequent entrants.

Another possible explanation for the insufficient evidence of accelerated entry is the priority to clear out backlogged applications. However, to ensure a consistent censoring window pre- and post-GDUFA, all backlogged applications that were pending pre-GDUFA were censored on the last day before GDUFA took effect. These backlogged cases did not contribute to the post-GDUFA observations, but their review may have slowed the review of newly submitted applications post-GDUFA.

It is interesting to note that the insignificant or negative effects of GDUFA on generic entrants were different from those of PDUFA, which was enacted in 1992 as the first user fee act of the FDA for patented drugs. Many studies have found evidence of PDUFA's positive impacts on the speed of approval, research and development (R&D) spending, innovation return, and societal welfare [33, 55, 56].

In general, the incentives and financial burdens introduced by GDUFA should be different than those introduced by PDUFA. For brand-name drugs, there is a high sunk cost in R&D spending, and drug approval means a longer period of market exclusivity (monopoly) before the fixed patent expiration date. Thus, faster approval is rewarding. However, for generic manufacturers, there is usually no R&D spending or market exclusivity involved. Thus, such a strong incentive from PDUFA will not be present. Even for first entrants that challenge patents and enjoy market exclusivity, the exclusivity period is fixed (180 days, which is not affected by quicker entry).

Furthermore, for smaller companies, the introduction of the user fee means an extra burden of sunk costs and annual costs from facility fees. Compared to PDUFA, GDUFA does not offer a small-business first-time fee waiver. This extra fixed cost may affect some small companies' entry decisions, especially when market prices are already approaching the marginal costs. Thus, more incentives are needed in future policies to encourage generic competition.

In June 2017, the FDA announced the launch of the Drug Competition Action Plan (DCAP) [5], aiming to resolve regulatory obstacles to generic access, to increase the efficiency and predictability of the FDA's review process and to reduce gaming by brand-name companies that can delay generic drug entry. Early steps the FDA has taken include prioritizing the review of generic drug applications until there are three generics approved for a brand product [6].

Our conclusion regarding the effectiveness of GDUFA in accelerating access to generic drugs suggests the necessity of the DCAP. Since the literature shows that more than one generic entry is needed for appreciable price effects, given the observed impacts on the first three entrants from GDUFA, expanding the scope in the DCAP to accelerate the speed of entry for more entrants will likely lead to quicker price declines, lower medical expenditures, and greater incentives for generic competitors, especially after the first generic enters the market.

There are a few limitations to this study. First, the direct indicator for the efficiency of GDUFA is the time between the date of an ANDA submission and approval. A FOIA was submitted to the FDA for ANDA submission dates, but those dates were only available for a subset of approved generic drugs. Thus, due to the incompleteness of the data, we instead used the patent/exclusivity expiration date and date of approval for each generic entrant to calculate time-to-entry. Nevertheless, the rate of entry is a meaningful outcome to examine, as faster entry will directly introduce more competition and cost reduction to the market. Moreover, time-to-entry may capture not only FDA's efficiency in the ANDA review process but also generic companies' reactions to policies in market entry decisions.

Furthermore, the FDA may have sped up its review process after receiving funds from the collected user fees, but there might be a lag in effect (e.g., recruiting and training take time), which cannot be fully captured by our pre-post policy analysis. By examining the time-to-entry by year post-GDUFA, we did see some increase in the speed over time (Appendix A.7). However, given the limited data points, a longer follow-up time is needed to fully test this hypothesis.

On the other hand, the market size for brand-name drugs is a key driver for faster generic entry, but no sales or revenue data were available. The adjustments using therapeutic class and added frailty may not have fully adjusted for such endogeneity, which is a key limitation of our study.

Last, since there is no control group or state-level variation for GDUFA, it is difficult to draw any causal conclusions. Falsification tests using brand-name drugs were considered, but it is challenging to define the appropriate time-to-entry [51]. Instead, we could only show that the number of brand-name drugs is not affected by GDUFA.

There may be other policies that were in effect during GDUFA I that also influenced the time-to-entry for generic drugs and other aspects of generic competition, such as ACA and state-level generic substitution laws [10, 11]. Therefore, the observed outcomes may not be solely affected by GDUFA. However, controlling for ACA did not change our conclusions. Our study's analyses on time-to-entry still reveals the trend comparing 2013-2017 to 2007-2012, and areas where more policy improvement is needed.

Our results suggest that GDUFA may have decelerated generic entries into the market, beyond the first entry, with the most negative effect on second entrants. The reasons may be due to the FDA's prioritization of backlogged and the first-to-submit post-GDUFA applicants, lag between fee income and utilization to increase processing scale, and fees decrease incentives for generics to challenge patents or compete to be the first to enter the market. Since faster successive entries lead to a faster price reduction, it would be helpful to prioritize the review of more entrants and maintain sufficient incentives for generic drug manufacturers.

Chapter 3. UNDERSTANDING THE MARKET DYNAMICS WITH RESPECT TO MORE GENERIC COMPETITTION

3.1 INTRODUCTION

Generic competition breaks branded drug company's monopoly power protected by patent and leads to reduction in drug expenditure with lower prices. One estimate suggests that substituting branded drug consumption in Medicare in 2016 would bring an estimated reduction of $925 million on drug spending of 1500 medications with the highest total spending [30]. Most recent literature focuses on price and quantity changes with respect to time since generic drug entry rather than the number of generic drugs [17, 21, 57]. However, given the FDA's expanded focus of priority review from first generic entrant to the first three entrants, we would like to examine whether the number of firms in the market affects price, quantity and overall drug spending differently, in order to inform policy decisions.

Luo et al. (2016) studied branded drug usage and the price change of branded and generic drug before any generic competition, during the 180-day exclusivity period and after subsequent generic entries, using commercial claims data with a focus on atorvastatin [58]. They observed delays in generic uptake and high levels of out-of-pocket (OOP) spending during the exclusivity period. The interesting market dynamics from monopoly to oligopoly and then monopolistic competition with the related price, drug usage and expenditures change are worth further exploration.

In this chapter, we examined how generic drug entry would affect generic and branded drug prices and quantities. In specific, we would like to understand how different numbers of generic

entrants affect drug prices as well as quantities consumed. We first conducted a systematic literature review followed by a Bayesian meta-analysis (BMA) to synthetize existing evidence. Then, using the information from BMA as prior information, we further utilized the longitudinal Medical Expenditure Panel Survey (MEPS) prescription medication data, a nationally representative data source, to obtain estimates of these market structure changes in a Bayesian framework.

3.2 BACKGROUND

As discussed in Chapter 1, many studies examined the impact of generic competitors on drug price, market share, overall utilization and drug expenditures. However, there is only one systematic review that examined price change, and it did not consider the number of generic drugs [31]. Some studies only reported the aggregated change in price or utilization, but did not properly model the impact. Among studies that included models, the literature is also divided into two main groups: many used the time since loss of exclusivity to evaluate the corresponding market structure change over time, while the others were more interested in modeling impact from different generic counts, which is our focus for the evidence synthesis. Furthermore, within the limited amount of studies, many are not up-to-date, and have heterogeneity in study design and data use (e.g. therapeutic area of focus, time period, etc.). These pose challenges in synthesis and generalization of the effect size.

On the other hand, the majority of the literature in this field utilizes data from IMS Health (Now IQVIA), where subscription is needed [59]. Nevertheless, researchers such as Huckfeldt and Knittel (2011) and Lakdawalla et al. (2017) used publicly available MEPS data to study drug prices and volume. However, as a survey data that sampled patients and relied on one representative household member to report everyone's drug use, MEPS leads to under-

documentation of the number of different drugs, thus cannot capture the complete drug use and sales information like IMS Health data do [60].

As illustrated in Figure 3.1, both existing literature and MEPS data have their advantages and shortcomings. The Bayesian framework enables us to combine these two imperfect pieces together which allows compensation of one for the other. Specifically, evidence from the literature can be viewed as prior information, when we use MEPS data for the analysis. Combing prior and data, we can obtain the posterior, which reflects our updated belief in generic competition's impact on market dynamics.

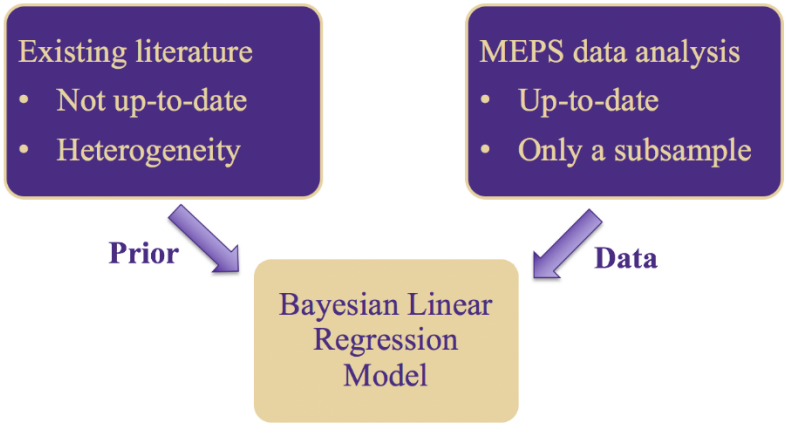


Figure 3.1 Conceptual Framework for Chapter 3

The next three sections focus on three main components of this chapter, namely the systematic literature review, the BMA, and the Bayesian linear regression model using MEPS data. For each section, we discuss the methods as well as the results. Then, we conclude with a discussion summarizing all three components.

3.3 SYSTEMATIC LITERATURE REVIEW

3.3.1 *Methods*

3.3.1.1 Data

A structured literature search was conducted in selected electronic databases to identify related literature on drug price and quantity change with respect to generic drug entry. Six databases were selected based on systematic literature review studies in related areas (drug pricing and utilization), including PubMed, EMBASE, EconLit, Business Source Complete, the National Bureau of Economic Research (NBER) bibliographic databases, and Google Scholar [61-63][2].

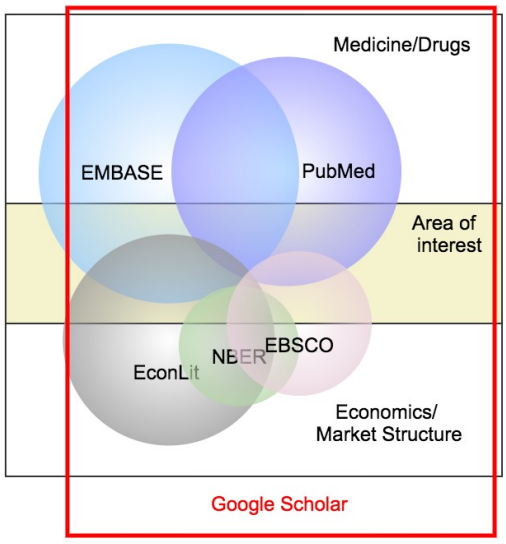


Figure 3.2 Databases used and their focuses

Note: The sizes of the circles are not proportional to the size of the databases

As illustrated in Figure 3.2, PubMed and EMBASE have a focus on health science (medical/drugs), while the rest are focused on economics, business and market structure.

[2] A UW health science librarian (Diana Louden) was consulted regarding the databases and search strategy.

Because our target is literature that studied the market structure changes with respect to generic drugs, what we targeted is the overlap between these two different areas (the yellow shaded area). A bigger emphasis was placed on the economic literature, since we are interested in whether regression models have been applied, the model structure as well as the covariates used. EconLit consists of articles, books, dissertations and working papers on economics, while Business Source Complete includes magazines, newspapers, and journals with a broader focus on both economics and business [64]. NBER is a smaller database with working papers, that covers topics in health care and health economics. As illustrated, we included NBER in case there are working papers that the other two economics databases did not capture, unlike another dataset RePEc (Research Papers in Economics) that is fully included by EconLit [65]. Since NBER's search engine does not yield a finite number of results, we included the top 100 records. For more drug-related search, PubMed is handy and quick, updated daily (faster than Google Scholar) [66]. EMBASE is similar to PubMed, but has the advantage of excluding overlaps with PubMed to increase efficiency. For Google Scholar, there is a potential concern in data quality, as the order of results is listed based on time of visits, but not on quality of publication [66]. Nevertheless, based on recommendation from literature and its uniqueness as a search engine of the whole internet, we included the top 100 relevant references from it [67, 68].

3.3.1.2 Search Criteria

The specific question for the search is: In the US, how does the number of generic drugs that enter after patent expiration affect drug price (relative and absolute), market share, and drug utilization? Search terms were defined accordingly (see Appendix B.1 for more detailed

regarding the detailed search term used, for different databases). We also added requirements for English language only, and publications after 1984 (after The Hatch-Waxman Act).

For eligible studies, we identified those that modeled the association between the number of generics (as the predictor of interest, X) and the outcomes of interest (Y) including generic drug price, branded drug price, generic drug market share, and overall drug utilization. Other inclusion criteria include 1) having the consideration of patent expiry, and 2) conducted in the US setting. We excluded studies that focus on countries other than US, only examine a certain drug or a limited number of drugs for a certain therapeutic class (e.g. case study), as well as studies that do not use a formal statistical model to examine the association between the number of generic competitors and drug price, market share, or utilization (such as table or graph only). A detailed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was included to document the different phases of the systematic review [69].

Since we are the most interested in how previous studies modeled the impact of the number of generic competitors on drug price and quantity, we documented the model used as well as covariates included in each eligible study. If most studies used a certain regression model (e.g. linear with no log transformation) for a specific outcome, we adopted the model format for the ease of updating coefficients values, so the posteriors from the meta-analysis can be directly used as prior for the Bayesian regression using MEPS data.

3.3.2 *Results*

Literature searches and screening were conducted between September 2019 and November 2019. A systematic review online tool, Covidence, was used to streamline the screening process [70]. The PRISMA flow diagram can be found in Figure 3.3. Our search yielded 449 records, among which 16 were eligible based on the search criteria we defined.

Table 3.1 provides a summary of these 16 studies regarding data source, sample, unit of analysis, time frame, outcome(s) of interest and their forms (e.g whether log transformed), predictor of interest and its forms, model used, and assumption about endogeneity. There are big variations in the time frame, form of variables, and other model designs. Specifically, the number of generic drugs (X) has been modeled both as a continuous variable and as a categorical variable. A log-transformation of X was also used in several studies. Similarly, for the outcome(s) of interest, both Y and log-transformed Y were used in different studies.

For generic drug price, the most common model form is to regress log(Y) on X, which was present in 5 studies (Dafny et al., 2017; Frank and Salkever, 1997; Grabowski et al., 2007; Helland and Seabury, 2016; Regan, 2008) [18, 24, 71-73]. Therefore, these 5 studies were included in the BMA. Other studies that regressed Y on X, Y on log(X), and log(Y) on log(X) were excluded. For branded drug price, 3 studies with similar model structures (regress log(Y) on X) were included for BMA (Dafny et al., 2017; Frank and Salkever, 1997; Regan, 2008) [18, 71, 73]. For drug utilization, only three studies examined it with inconsistent model structure, thus we did not have enough power to conduct a BMA.

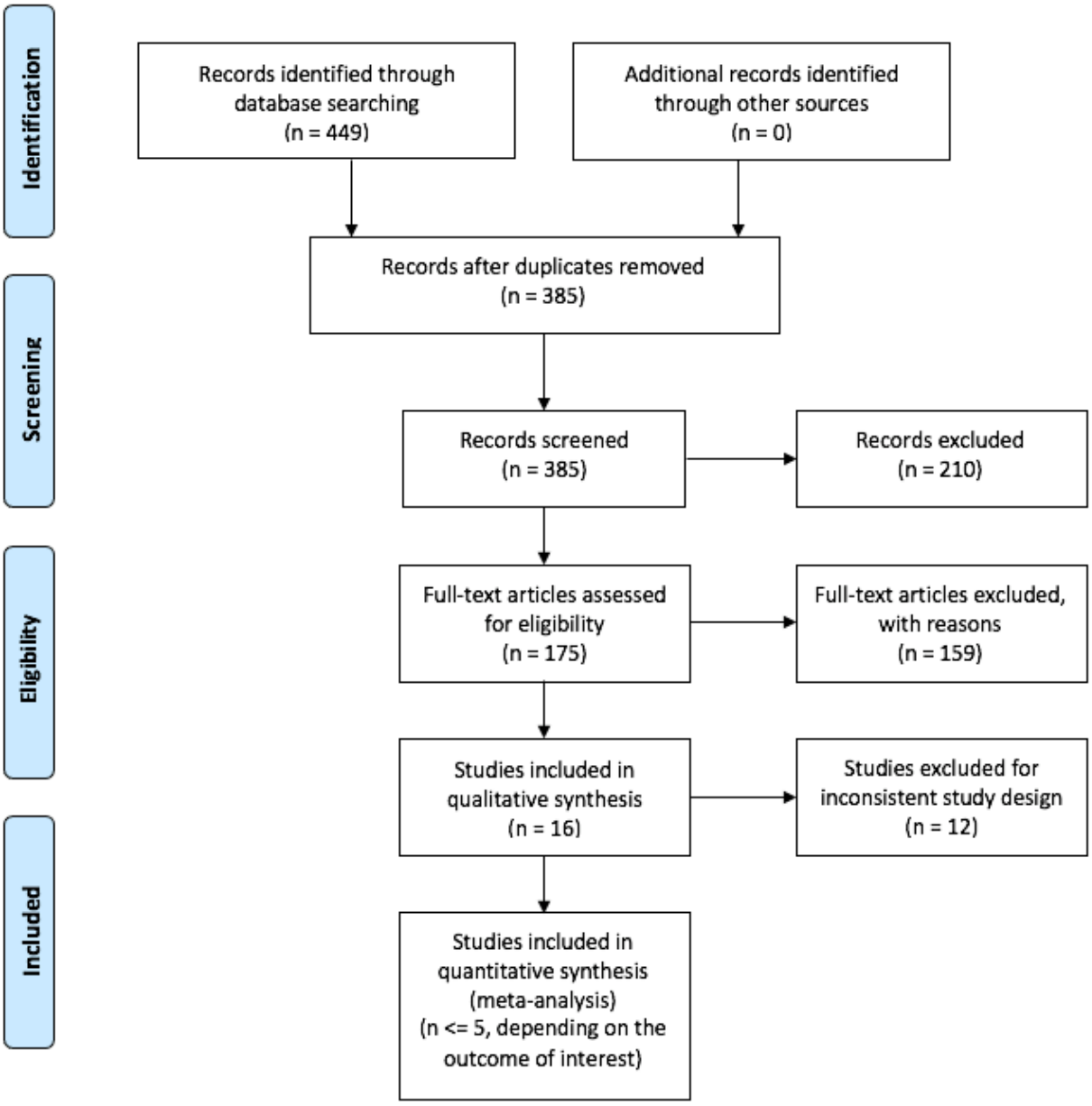


Figure 3.3 PRISMA Flow Diagram

Table 3.1 Summary of Studies Included in the Qualitative Review

	Study	Data	Sample	Unit	Time scale	Outcome (Y)	Main predictor (X)	Model	Assumption
1	Berndt 2017 [10]	IMS	General	molecule-route-strength	2004-2016	ln(generic price)	ln(N); ln(HHI)	OLS	N exogenous
2	Caves 1991 [15]	IMS	General	most popular dose for each molecule	1976-1987	change in ln(price)	change in N	GLS	N endogenous
3	Conti 2016 [27]	IMS	Specialty	molecule-route/molecule-route-strength	2001-2007	ln(generic price); ln(branded price); volume	ln(N), ln(N2)	OLS	N exogenous
4	Dafny 2017 [18]	IMS	General	molecule-route-strength	2007-2010	ln(generic price); total quantity	N, time since LOE	OLS; FE	N exogenous
5	Frank 1997 [71]	IMS	General	molecule level	1984-1987	ln(generic price); ln(branded price)	N, ln(branded price)	FE; 2SLS	N exogenous/endogenous
6	Grabowski 2007 [24]	IMS	General	molecule level	1992-1998	ln(generic to branded price)	N	OLS	N exogenous
7	Helland 2016 [72]	Ingenix-Touchstone database	General	molecule level	1998-2008	ln(average price of both branded and generic); ln(total quantity)	N	OLS; 2SLS	N exogenous/endogenous
8	Morton 1997 [74]	IMS	Cardiovascular	molecule-route-strength-package	1989-1991	ln(generic price); ln(branded price)	N*policy dummy	OLS	N exogenous
9	Olson 2018 [75]	IMS	General	molecule-route-strength	2003-2010	price	categorical N, time since LOE	OLS	N exogenous
10	Regan 2008 [73]	NDC Health	General	molecule level	1998-2002	ln(generic price); ln(branded price)	N, N of other in class	FE; RE	N endogenous
11	Reiffen 2005 [21]	IMS	General	best selling type	1980-1990	average generic price; first generic price	categorical N	RE	N endogenous
12	Saha 2006 [16]	IMS	General	molecule level	1992-1998	ln(generic to branded price); ln(branded price)	N, predicted market share	OLS; GLS	N endogenous
13	Suh 2000 [76]	IMS	General	molecule level	1984-1987	generic price; branded price; price difference	N, HHI	OLS	N exogenous
14	Wiggins 2004 [77]	IMS	Antiinfectives	NA	1984-1990	price	N; 1/(N+1)	Weighted OLS	N exogenous
15	Tenn 2014 [78]	IMS	General	molecule-route-strength	2003-2008	ln(generic price)	categorical N	OLS	N exogenous
16	Yu 2014 [79]	IMS	General	molecule level	1992-2000	ln(generic price)	N*ln(time), ln(time), order of entry	OLS	N exogenous

3.4 Bayesian Meta-Analysis

3.4.1 *Methods*

As the next step in the systematic literature review, we conducted a Bayesian random-effects meta-analysis to quantitatively synthetize the evidence from literature.

First of all, the evidence to synthetize is the association between the number of generics (X) and drug price or quantity (Y), reported from a regression model. In other words, we would like to synthetize the standardized regression (beta) coefficient. However, meta-analysis is not typically used in this setting. If different multivariate regression models adjusted for different independent variables (Z), then the association between X and Y is not independent [80]. Without individual-level data (which is not usually reported in the studies), the correlation coefficients are unknown. Nevertheless, other researchers found that the correlation coefficient is highly correlated with the coefficient of interest, and argued that the standardized regression coefficient can and should be meta-analyzed [81, 82].

Moreover, we adopted a random-effects meta-analysis model, as most of the studies vary in their time frame, data used etc., it is more practical to assume the true effect varies across studies (rather than a fixed-effects model, where a universal true effect is assumed) [83].

Lastly, we chose the Bayesian framework, since we would like to combine the information from both the literature and current data we have. The Bayesian setting enabled us to update the belief once information from the meta-analysis is available. For future updating, the framework (model) needs to be established first. Therefore, the main objective of the BMA is to decide the selection of covariates and model form, rather than obtaining very accurate posterior distribution (which is left for the next part of Chapter 2 to achieve). However, the use of strong priors may affect the estimated posterior distributions (heavily influenced by priors), or even lead to a bias.

By using non-informative priors, we could explore how the data will update such belief without bringing in additional information from literature [84].

3.4.1.1 Base Model

Our base case Bayesian random-effects meta-analysis model only includes studies with a consistent model design (e.g. same transformation of the variables if present, such as treating the dependent variable as continuous rather than categorical, or log transformation of the drug price). The model setup is discussed below.

Denote each study as j. From each study, we obtained the beta coefficient of interest $\beta_{1,j}$, as well as its standard error $s_{1,j}$. The random-effects model has a hierarchical structure, where we assume all the studies are exchangeable but not necessarily identical [85]. Beta coefficients $\beta_{1,j}$ are drawn from a normal distribution with hyperparameters (γ_1, τ_1), which presents the population distribution (see equation 3.1). What we would like to estimate is the true effect γ_1, the mean effect size of the population distribution. Under-script "*1*" denotes that this is only the first coefficient (the number of generic competitors) among a list of covariates included in the model, when estimating drug price. Since we assume the true effect varies across study, the heterogeneity τ_1 captures the between-study variance. Figure 3.4 illustrates the model structure in the base case.

The first stage of the hierarchical normal model is listed in equation 3.1. The second stage is the prior distribution, expressed in two hyperparameters, mean γ_1 and standard deviation τ_1 (see equation 3.2). Lastly, hyperprior distributions are assigned to the hyperparameters (equations 3.3 and 3.4).

<u>From each study j:</u>

$\beta_{1,j} \mid \gamma_{1,j},\ s_{1,j} \sim N\left(\gamma_{1,j},\ {s_{1,j}}^2\right)$ for study 1, 2, …, j, …, J

(3.1)

Priors:

$\gamma_{1,j} \mid \gamma_1,\ \tau_1 \sim N(\gamma_1,\ {\tau_1}^2)$ for study 1, 2, …, j, …, J

(3.2)

Hyperpriors:

$\gamma_1 \sim N(0,\ 100)$

(3.3)

$\tau_1 \sim HalfCauchy(scale = 0.005)$

(3.4)

As discussed previously, without existing information, a non-informative prior is usually preferred, as no additional information is brought in. Nevertheless, when data are sparse (e.g. fewer than 5 studies can be found, which was the case in Section 3.3.2), the estimate for the between-study heterogeneity, τ_1, will affect the interval estimation of the covariates of interest. Random-effect meta-analysis tends to produce wider confidence intervals, as unmeasured between-study difference is added to the sampling error, increasing the level of uncertainty [83]. This issue will become larger when the sample size is small, or few studies are found. Therefore, the choice of prior is very important especially given a small number of studies available and relatively small sample sizes. Lambert et al. (2005) suggested that when studies provide sparse data, using vague prior such as inverse-gamma may affect precision, and therefore coverage intervals and corresponding inference [86]. Spiegelhalter et al. (2003) also pointed out that although being a proper prior, inverse gamma shows strong preference to lower τ [87]. Friede et al. (2016) and Olga et al. (2013) recommended the use of (weakly) informative priors such as half-normal distributions, so that most of the probability mass is used to measure small to large

between-study heterogeneity, limiting the unreasonably large between-study variability [88, 89]. Results from Friede and others further showed a relatively narrower standard error. Therefore, we replaced the non-informative prior for τ_i with half Cauchy distributions. By assigning a more informative prior, the precision could be improved. The scale value choice was based on Gelman et. al (2013), a value slightly higher than the expected standard deviation (which we used the pooled standard deviation from the studies), so the prior is only weakly informative [85].

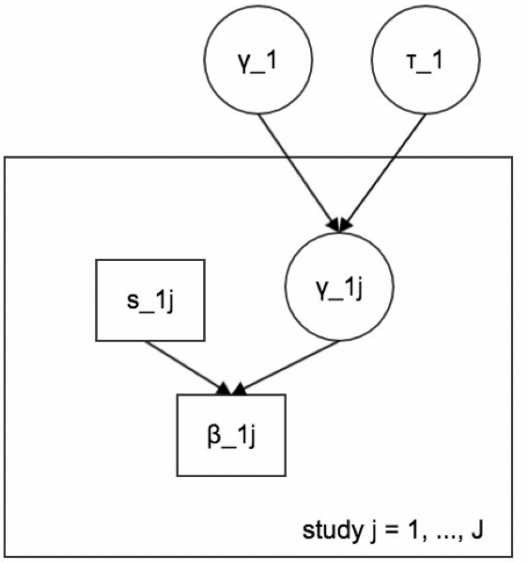


Figure 3.4 Base Case BMA (random-effects) Model

rstan, the R interface to Stan was used for modeling [90]. Each time, 4 chains were run each with 5000 Markov chain Monte Carlo (MCMC) draws in the post burn-in phase. For the ease of sampling in Stan (to increase the effective sample size), non-centered reparameterization was used [91, 92]. To ensure model convergence and no autocorrelation is present, model diagnostics plots such as the trace plot and auto correlation function (ACF) plot of key variables were

created [93]. Forest plots summarizing the same coefficient from different studies, along with the overall meta-analyzed results were also created to illustrate the results for the base model.

3.4.1.2 Model Extensions

The base model has several limitations. Firstly, as mentioned earlier, studies may have adjusted for different covariates Z or have slightly different study designs, which makes the beta coefficient for X incomparable. For example, not all models adjusted for different therapeutic class. In addition, some studies assumed the number of generics is exogenous, while other studies used instrumental variable (IV) to address the endogeneity from the number of generics. To address this, we modified the model to correct the biases from these differences in study design. Secondly, one study may use multiple models, such as both ordinary least square (OLS) and 2-stage least square (2SLS), to answer the same research question. Inclusion of only one model per study limited the evidence to synthetize. Thus, we also extended the model to enable the inclusion of multiple models per literature. Lastly, the number of models included is limited by the model structure. For example, if more studies modeled the number of generics as a continuous variable rather than a categorical variable, in order to keep a consistent model structure, we would lose information from the categorical models. Therefore, we also proposed an extension to combine these different model forms together.

3.4.1.2.1 Extension I: Bias correction

To adjust for different study designs such as covariates included, or different assumptions on endogeneity, we extended the model by assuming an additive sum of the biases alongside the true effect γ_1. Equation 3.5 is similar to equation 3.1, but $\theta_{1,j}$ now consists of both $\gamma_{1,j}$ and the sum of biases multiplied by an indicator, $I_{k,\,j}$, for each bias k. Figure 3.5 also illustrates this extension. For instance, one bias is “not adjusting for branded drug price”, when the outcome of

interest is generic drug price. Thus, for any study that failed to adjust for this covariate, an additional bias term was included. Other biases we considered were 1) "not considering endogeneity", and 2) "not using molecule-route-strength level as the unit of analysis". For each bias, a non-informative prior was assigned (equation 3.8).

From each study j:

$$\beta_{1,j} \mid \theta_{1,j},\ s_{1,j} \sim N\left(\theta_{1,j},\ {s_{1,j}}^2\right) \quad \text{for study 1, 2, …, j, …, J} \tag{3.5}$$

$$\theta_{1,j} = \gamma_{1,j} + \sum_k I_{k,j}\, Bias_k \quad \text{for study 1, 2, …, j, …, J; bias 1, 2, …, k, …, K} \tag{3.6}$$

Priors:

$$\gamma_{1,j} \mid \gamma_1,\ \tau_1 \sim N(\gamma_1,\ {\tau_1}^2) \quad \text{for study 1, 2, …, j, …, J} \tag{3.7}$$

$$Bias_k \sim N(0,\ 100) \quad \text{for bias 1, 2, …, k, …, K} \tag{3.8}$$

Hyperpriors:

$$\gamma_1 \sim N(0,\ 100) \tag{3.9}$$

$$\tau_1 \sim HalfCauchy(scale = 0.005) \tag{3.10}$$

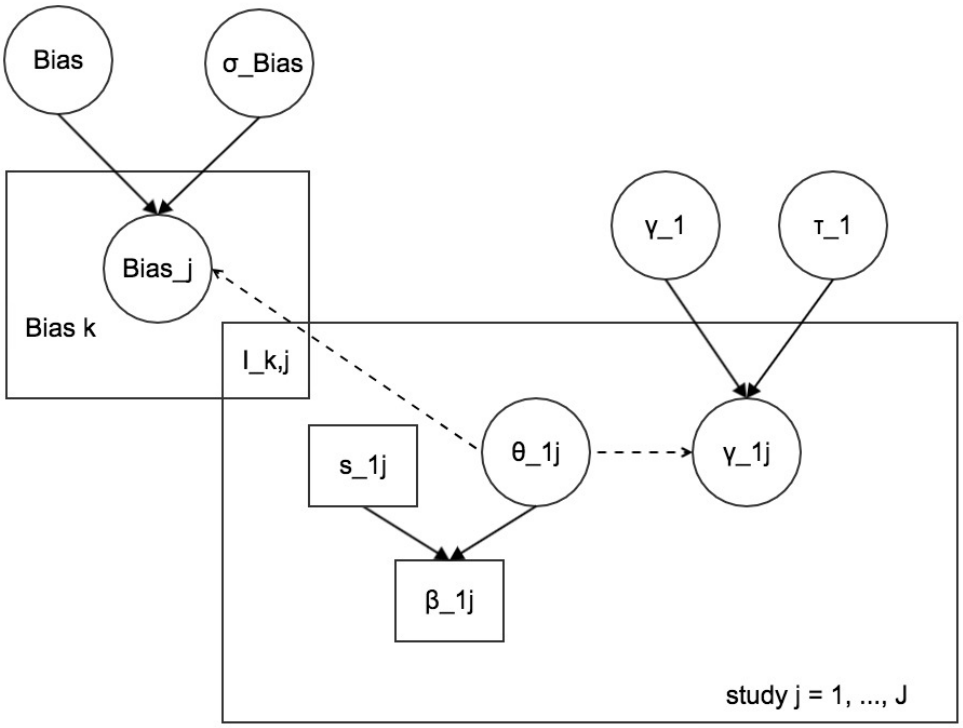


Figure 3.5 BMA Model with Bias Correction

3.4.1.2.2 Extension II: Use multiple models per literature

The second extension enabled us to use multiple models from one study, if multiple study designs were used to answer the same question. For example, Frank and Salkever (1997), Helland and Seabury (2016) and Regan (2008) all considered both OLS and 2SLS when examining the relationship between the number of generics and drug price [71-73]. Since multiple models used by the same study are correlated (e.g. same dataset used), an additional level was built into the hierarchical structure to allow for correlation. Both model-level (Q) and study-level (J) were considered. Equation 3.11 and Figure 3.6 illustrate this extension from the base model.

$\beta_{1,q,j} \mid \gamma_{1,j},\ s_{1,q,j} \sim N\left(\gamma_{1,j},\ {s_{1,q,j}}^2\right)$ for model 1, 2, …, q, …, Q; study 1, 2, …, j, …, J

(3.11)

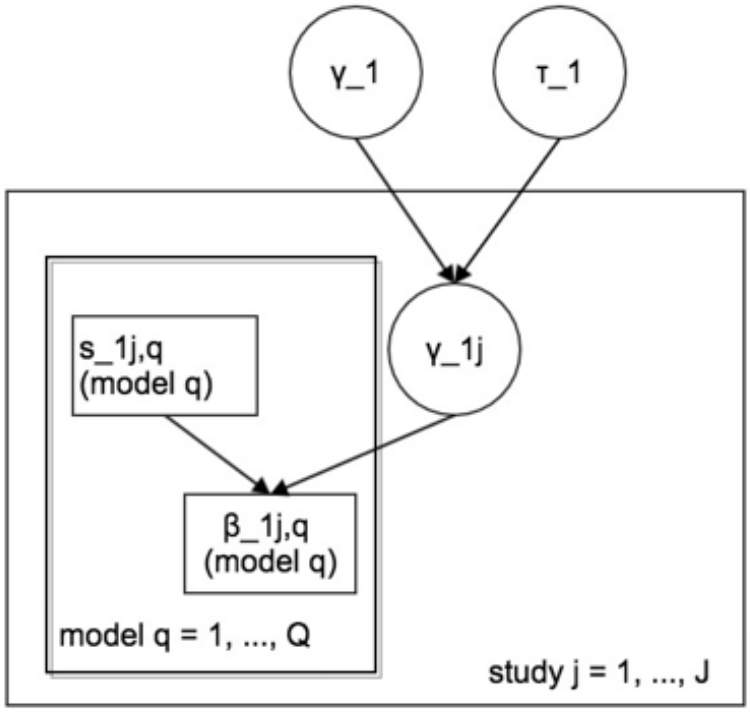


Figure 3.6 BMA with Model- and Study-Specific Effects

Furthermore, extension I and II can be easily combined. One of the biases we considered in extension I is "not considering endogeneity". Therefore, if one study has both OLS and 2SLS models included, the bias indicator $I_{k,\,q,j}$ (see equation 3.12-13) would capture this difference in model design ($I_{k,\,q=1,j} = 1$ for the OLS model, and $I_{k,\,q=2,j} = 0$ for the 2SLS model).

$\beta_{1,q,j} \mid \gamma_{1,j},\ s_{1,q,j} \sim N\left(\theta_{1,q,j},\ {s_{1,q,j}}^2\right)$ for model 1, 2, …, q, …, Q; study 1, 2, …, j, …, J

(3.12)

$\theta_{1,q,j} = \gamma_{1,j} + \sum_k I_{k,q,j} Bias_k$ for model 1, 2, …, q, …, Q; study 1, 2, …, j, …, J; bias 1, 2, …, k, …, K

(3.13)

3.4.1.2.3 Extension III: Combine different model forms

Apart from the inconsistency in the transformation of variables (whether log-transformed or not), studies may also have different assumptions about whether the impact from the predictor (number of generics) is linear. The majority of the studies treated the number of generics as linear/continuous, while several studies modeled it as a categorical variable instead. Limiting to the continuous form reduces the number of studies we could meta-analyze. Furthermore, historical data from the FDA indicated that the average price reduction became steeper only after the second and third generics entered the market [38]. With more generic entrants in the market and the price approaching marginal cost, the speed of reduction in drug prices would also slow down. In this sense, simply modeling the predictor as a continuous variable may not capture the full market dynamics.

Thus, in this extension, we sought to utilize both models with the continuous or categorical version of the predictor, by transforming the linear coefficient into weighted categorical coefficients. Since we would like to capture both the steep price drop from the first few entrants as well as the flattened change for later entrants, we assume a categorical change up until three entrants in the market, and a linear trend for the successive entrants. In the sensitivity analysis, we also varied this assumption by modeling the linear change for the 5th entrants and above, as well as the 6th entrants and above.

The key assumption is that the linear beta coefficient is a weighted average of the categorical coefficients, based on the proportion of each subgroup. The notation used in this extension is

slightly different from the previous models. For a model that models the number of generics as a continuous variable (equation 3.14), N denotes this continuous value for each drug. β_L denotes its beta coefficient. β_0 represents the intercept, and x_k (for k = 2, …, K) denotes other variables included in the regression, such as therapeutic class or time since the loss of exclusivity, which may vary by study. While for a study that models the number of generics as a categorical variable (equation 3.15), there are three generic-count-related variables: $\boldsymbol{I}(2^{nd})$ and $\boldsymbol{I}(3^{rd})$ that indicates whether the entrant is second or third in order, and $\boldsymbol{I}(4^{+}) * N$ that models a continuous relationship beyond the 3rd entry. The corresponding beta coefficients are namely β_C_1, β_C_2, and β_C_3.

Linear model: $y = \beta_0 + \beta_L * N + \beta_2 x_2 + \cdots + \beta_k x_k + \epsilon$

(3.14)

Categorical model: $y = \beta_0 + \ \beta\_C_1 * \boldsymbol{I}(2^{nd}) + \beta\_C_2 * \boldsymbol{I}(3^{rd}) + \beta\_C_3 * \boldsymbol{I}(4^{+}) * N + \beta_2 x_2 + \cdots + \beta_k x_k + \epsilon$

(3.15)

Notations for the extended meta-analysis are discussed next. In equation 3.16, β_L_j denotes the linear coefficient for the number of generics, from study j that modeled the number of generics as continuous. Similarly, s_L_j represents its corresponding standard error, and γ_L_j is the mean of the study-specific linear effect. Among M studies that modeled the number of generics as a categorical variable, $\beta\_C_{1,m}$ and $s\_C_{1,m}$ denote the beta coefficient and corresponding standard error of the price effect of the second entrant in comparison to the first entrant from study m; $\beta\_C_{2,m}$ and $s\_C_{2,m}$ denote the beta coefficient and corresponding standard error of the price

effect of the third entrant in comparison to the first entrant from study m; and $\beta\_C_{3,m}$ denotes the linear price effect of the fourth and beyond entrants in comparison to the first entrant from study m. p_1, p_2 and p_3 denotes the proportion of the 1st, 2nd and 3rd generic entrants in each study's dataset. $1 - \sum_1^3 p_i$ represents the proportion of any entrants beyond the 3rd.

For J studies that modeled N as a continuous variable, equation 3.16 is similar to the base model (equation 3.1). Equation 3.17 transforms γ_L_j, the mean of the study-specific linear effect, into a weighted sum of the categorical effects. For M studies that modeled N as a categorical variable, equation 3.18 and 3.19 are again similar to equation 3.1. Equation 3.20 is slightly different, since some studies may model more categorical groups beyond the fourth entry. For example, instead of modeling a linear relationship for 4+ entrants as we proposed, Tenn and Wendling (2014) modeled the 4th entrant vs. the 1st, the 5th entrant vs. the 1st, etc [78]. Therefore, equation 3.20 converts those estimates into a linear effect by dividing the corresponding order of entry.

For the weighted sum, the weights come from the proportion of different order of entrants in the dataset. For studies without the proportion of each entrant reported, we used a negative binomial (NB) distribution to sample the proportion for each entrant. N_{mean_j}, the average number of generic entrants, is reported in each study j. Prior for the scale parameter ν was set after examining the distribution of different entrants from OB (see the Appendix B.4 for more details). The other priors and hyperpriors are similar to the base case.

<u>Among J studies that modeled a continuous N</u>

$$\beta\_L_j \mid \gamma\_L_j,\ s\_L_j \sim N\left(\gamma\_L_j,\ {s\_L_j}^2\right) \qquad \text{for study 1, 2, …, j, …, J}$$

(3.16)

$\gamma\_L_j = \frac{(p_2 * \gamma\_C_{1,j} + p_3 * \gamma\_C_{2,j} + (1 - \sum_1^3 p_i)\gamma\_C_{3,j})}{(1-p_1)}$ for study 1, 2, …, j, …, J; entrants 4, 5, …, k, …,9, 10

(3.17)

Among M studies that modeled categorical N

$\beta\_C_{1,m} \sim N(\gamma\_C_{1,m}, s\_C_{1,m}{}^2)$ for study 1, 2, …, m, …, M

(3.18)

$\beta\_C_{2,n} \sim N(\gamma\_C_{2,m}, s\_C_{2,m}{}^2)$ for study 1, 2, …, m, …, M

(3.19)

$\beta\_C_{3,k,m} \sim N(\gamma\_C_{3,m}, s\_C_{3,k,m}{}^2)$ for study 1, 2, …, m, …, M; entrants 4, 5, …, k, …,9, 10

Where $\beta\_C_{3,k,m} = \frac{\beta\_C_{k,m}}{k}, s\_C_{3,k,m} = \frac{s\_C_{k,m}}{k}$

(3.20)

With % of different entrants not available from the study, we use NB to simulate:

$p_{k,j} \sim NegativeBinomial(\mu_j, \nu) = \frac{e^{-\mu_j \nu}(\mu_j \nu)^k}{k!}$ for study 1, 2, …, j_mis, …, J_mis; k = 0, 1, …, 10

(3.21)

Where $\mu = N_{mean_j}$

Priors

$\gamma\_C_{1,j} \sim N(\gamma\_C_1, \tau_1{}^2)$ for study 1, 2, …, j, …, J; 1, 2, …, m, …, M

$\gamma\_C_{2,j} \sim N(\gamma\_C_2, \tau_2{}^2)$ for study 1, 2, …, j, …, J; 1, 2, …, m, …, M

$\gamma\_C_{3,j} \sim N(\gamma\_C_3, \tau_3{}^2)$ for study 1, 2, …, j, …, J; 1, 2, …, m, …, M

(3.22)

$$\nu \sim N(0.6, 0.01)$$

(3.23)

Hyperpriors

$$\gamma\_C_1 \sim N(0, 100)$$

$$\tau_1 \sim HN(scale = 0.005)$$

$$\gamma\_C_2 \sim N(0, 100)$$

$$\tau_2 \sim HN(scale = 0.005)$$

$$\gamma\_C_3 \sim N(0, 100)$$

$$\tau_3 \sim HN(scale = 0.005)$$

(3.24)

3.4.2 *Results*

3.4.2.1 Base Model

As mentioned in the previous section, we identified 5 studies that regressed log-transformed generic drug price on the number of generics (continuous), and 3 studies on branded drug price (see Appendix B.2 and B.3 for details about the model format and regression coefficient results) [18, 24, 71-73]. In the base model, we meta-analyzed the beta coefficient by using one model from each study. Regan (2008) discovered that generic drug entry leads to insignificant decrease or even an increase in generic drug price, which is counterintuitive[3]. Thus, we decided to include their generic drug price model as a sensitivity analysis rather than in the main analysis.

[3] Even the author was not convinced by the results, who later used a binary indicator for generic entry to get a more robust model.

Figure 3.7 shows the forest plot for the beta coefficient that examines the association between the number of generics and log-transformed generic drug price. Although with slightly different study designs such as covariates controlled and assumptions on endogeneity, 4 studies had very close results. Translating the log-transformed relationship into relative price changes, the BMA base model revealed that one extra generic entrant is associated with a generic drug price decrease of about 7.69%[4] (95% Credible Interval (CI): [5.45%, 10.00%]).

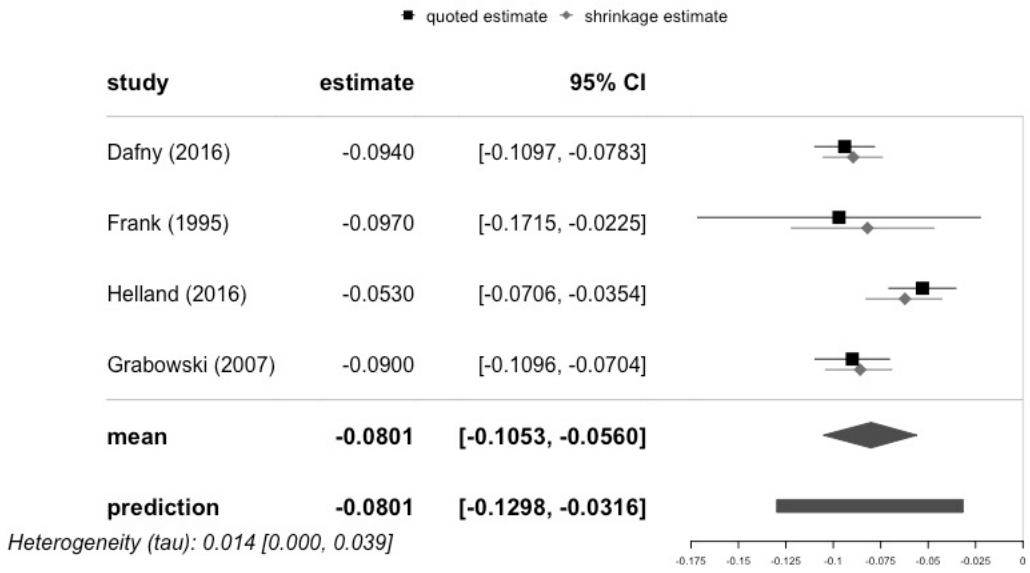


Figure 3.7 Forest Plot for Generic Drug Price

For branded drug price, forest plot (Figure 3.8) illustrates that one extra generic entrant is associated with a branded drug price increase of about 0.97%[5] (95% CI: [0.49%, 1.43%]).

[4] exp(-0.0801) - 1 = -0.0769
[5] exp(0.0097) - 1 = 0.0097

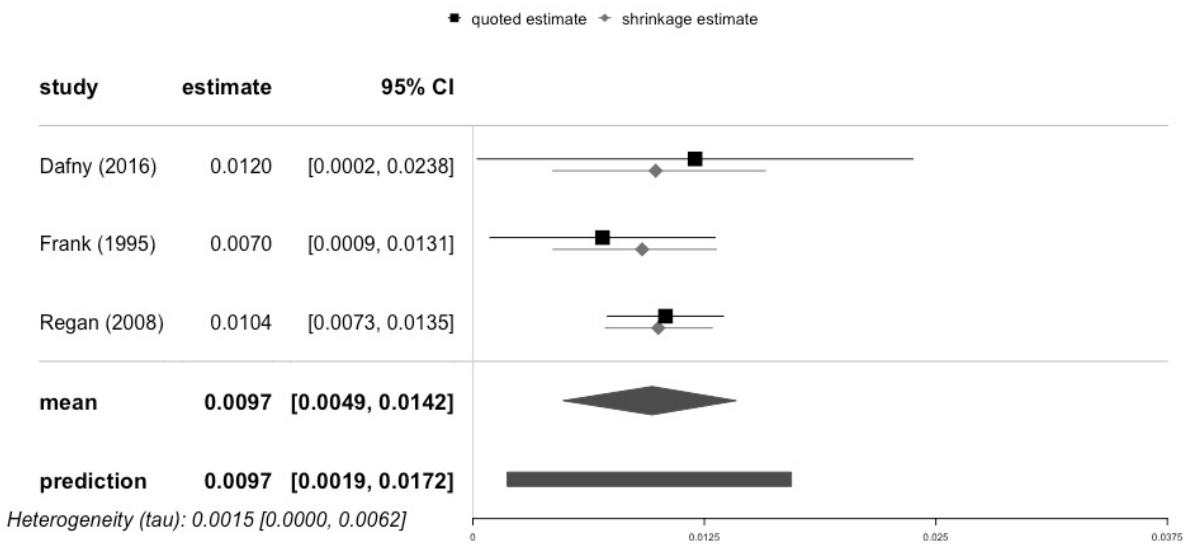


Figure 3.8 Forest Plot for Branded Drug Price

3.4.2.2 Model Extensions

3.4.2.2.1 Extension I: Bias correction

For generic drug price changes, we considered three biases, 1) "not considering endogeneity", 2) "not using molecule-route-strength level as the unit of analysis", and 3) "not adjusting for branded drug price". The posterior mean for beta coefficient is -0.075, with 95% CI [-0.171, 0.036] (see Table 3.2). In other words, after the bias correction, we found that one extra generic entrant is associated with a generic drug price decrease of 7.31% (CI: decrease of [-3.38%, 15.50%]). Compared to the base model, more uncertainty of the price impact is present.

For branded drug price changes, we only included the first two biases, 1) "not considering endogeneity" and 2) "not using molecule-route-strength level as the unit of analysis". The posterior mean for beta coefficient is 0.007, with 95% CI [-0.009, 0.010], translating to a branded price increase of 0.70% (CI: [-8.30%, 10.28%]) per generic entry after the bias correction.

3.4.2.2.2 Extension II: Use multiple models per literature

For generic drug price, Helland and Seabury (2016) as well as Regan (2008) investigated both OLS and 2SLS models [72, 73]. For branded drug price, Frank and Salkever (1997) also used both [71]. We included bias correction in this extension as well, since the "not considering endogeneity" bias would account for differences in the endogeneity assumption within each study. The Appendix listed details about different models as well as the beta coefficient results and their standard errors for each study.

The posterior mean for beta coefficient on generic drug price is -0.111, with 95% CI [-0.184, -0.020] (see Table 3.2). Compared to the base case, after accounting for bias in not adjusting for endogeneity and including multiple models per study, the price reduction is bigger, with the effect remaining statistically significant. The posterior mean for beta coefficient on branded drug price is 0.020, with 95% CI [-0.003, 0.064].

3.4.2.2.3 Extension III: Combine different model forms

For this extension, we included one additional study that modeled the relationship between log-transformed generic price and the number of generics as a categorical variable (Tenn and Wendling (2014)) [78]. Similar price impact was found for both the second and third entrants, and the slope of price reduction is less steep for the later entrants.

We did not find any study that modeled the association between log-transformed branded price and categorical N.

Table 3.2 BMA Results (Beta Coefficient) for Base Case and Extensions

	Generic drug price	**Branded drug price**
Base model	-0.080 [-0.105, -0.056]	0.010 [0.005, 0.014]
Extension I: Bias correction	-0.075 [-0.171, 0.036]	0.007 [-0.009, 0.107]
Extension I + II: Bias correction + multiple models per literature	-0.111 [-0.184, -0.020]	0.020 [-0.003, 0.064]
Extension III: Combine different model forms	2nd vs. 1st: -0.092 [-0.118, -0.067] 3rd vs. 1st: -0.091 [-0.132, -0.051] 4+ vs. 1st: -0.050 [-0.063, -0.038]	NA

3.4.2.3 Sensitivity Analyses

The inclusion of Regan (2008)'s study on generic drug price change did not change the main results (see Table 3.3, in comparison to Table 3.2). However, due to the limited studies we examined and the insignificant association this study found, in all scenarios, we see a smaller beta-coefficient estimate with a wider CI.

We also varied the model form in extension III to have different numbers of categorical groups (see Table 3.3). A slightly bigger price drop is observed for the 4th and 5th entrants. Similarly, the successive entrants lead to a flatter price change compared to the previous entrants.

Table 3.3 Sensitivity Analyses Results (Beta Coefficient)

	Generic drug price
Base case + Regan (2008)	-0.060 [-0.102, -0.021]
Extension I + Regan (2008)	-0.035 [-0.135, 0.064]
Extension II + Regan (2008)	-0.072 [-0.157, 0.029]
Extension III: Four categories	2^{nd} vs. 1^{st}: -0.087 [-0.115, -0.058] 3^{rd} vs. 1^{st}: -0.078 [-0.123, -0.033] 4^{th} vs. 1^{st}: -0.094 [-0.119, -0.064] 5+ vs. 1^{st}: -0.050 [-0.063, -0.045]
Extension III: Five categories	2^{nd} vs. 1^{st}: -0.087 [-0.118, -0.077] 3^{rd} vs. 1^{st}: -0.079 [-0.128, -0.032] 4^{th} vs. 1^{st}: -0.110 [-0.144, -0.075] 5^{th} vs. 1^{st}: -0.221 [-0.288, -0.154] 6+ vs. 1^{st}: -0.051 [-0.066, -0.046]

3.4.3 *Conclusion*

We found that more generic drug competition is associated with decreasing generic drug price, but not branded drug price, a finding known as the generic competition paradox [22]. Simply adding bias correction helps to meta-analyze evidence on similar parameters despite differences in studies, but adds to the posterior uncertainty of the estimates. Studies that examined both OLS and 2SLS on the same dataset found that OLS underestimates generic competition's impact on both the generic drug price reduction and branded drug price increase. This is consistent with our

meta-analyzed results when both bias correction and multiple studies per model were considered, as the beta coefficient estimates are bigger compared to the base model.

Nevertheless, a linear relationship may not fully capture how generic competition affects drug price. The model extension to combine categorical and linear effects from different models revealed similar results, with a slightly bigger generic price reduction after second generic entries, and a smaller price reduction scale for 4th entrants and beyond.

3.5 Bayesian Linear Regression Analysis

3.5.1 *Methods*

3.5.1.1 Data

The BMA provided informatively prior information about how generic and branded price are associated with the number of generic entrants. Next, we used this information as the prior and conducted a more up-to-date analysis using MEPS prescribed medicines data.

In specific, the annual MEPS prescribed medicines data from 2007 to 2017 were used for data analysis [94]. Each drug was identified by its National Drug Code (NDC). Along with drug name and NDC code, drug price was also reported, which is the sum of out-of-pocket payment, payment by Medicare/Medicaid and other payers. Prices charged from these different components were also reported.

Moreover, in order to determine the level of competition each branded drug face over time, we used the FDA's Orange Book (OB) online database [39] that we utilized in Chapter 2, which includes information regarding drug name, ingredients, strength, route, application number, product number, approval date, manufacturer name, and whether the drug is branded or generic. We linked branded drugs to their bioequivalent generic competitors using data on ingredients,

strength and route, and obtain the rank of generic entry. Since NDC code is not available in OB, FDA's NDC database was also used to map drug ingredients, strength and route to NDC code, providing a crosswalk between OB and MEPS [95]. MEPS data provides the 11-digit code, while FDA provides the 10-digit code. We converted the FDA NDC code to 11-digit to link MEPS data with FDA NDC and OB (see the Appendix B.5 for more details) [96]. In order to combine information on drug price and utilization from MEPS and information on generic drug competition from OB, we only kept the subset where MEPS NDC code can be linked to OB, so information regarding generic drug entries can be obtained. A flow chart illustrating these different steps and the changes in sample size is provided in the Appendix B.7.

One limitation of the FDA NDC data is that not all listed drugs have their NDC reported. In specific, due to drug listing requirements under section 510 of the FD&C Act, 21 USC 360, starting from July 2009, the FDA moved to electronic submission of drug registration and listing information [95]. As a result, marketed drugs for which listing information was not submitted electronically were excluded, along with other excluded list drugs, such as "drugs manufactured exclusively for a private label distributor", or "drugs that are marketed solely as part of a kit or combination product or inner layer of a multi-level packaged product not marketed individually". Therefore, historically used NDCs that are no longer in use are likely not captured in the current dataset, which would lead to mismatch between NDC with MEPS.

Researchers have used other private NDC databases or NBER's public use NDC data archive to address this issue [26, 97]. We filed a FOIA to the FDA to request historical NDCs between 2007 and 2017[6], and also followed Lin (2019) to construct a "NDC universe" using 10 archived

[6] We requested historical NDC data between 2007 and 2017. Staff from the FDA's Regulatory Counsel shared a dataset that reflects spreadsheet reflecting historical NDC data from 2009 to 2018 instead, which we used as the "historical NDC" dataset.

NDC datasets between 2007 and 2012 from NBER [97, 98]. The quality of matching increased after these two data sources were included.

For the analysis, we aggregated this subset of the MEPS data by year, and reported in each year, for each drug (molecule-route-strength), the average inflation-adjusted branded and generic drug total price, total utilization for generic and branded drug after applying the survey weights, the number of generic competitors, the number of years since the branded drug lost exclusivity, and the total branded drug utilization, as well as price a year prior to any generic entry.

3.5.1.2 Model

As mentioned in Section 3.4, we utilized information from the BMA as prior information for our MEPS data analysis. However, what prior distribution should we use? There have been discussions regarding whether to use the mean distribution of the effect size from a meta-analysis (marginal distribution), or a predictive distribution that represents the posterior belief about a "future" observation [85, 99]. Since our interest is in understanding the general distribution rather than judging heterogeneity or designing new studies, we have decided to use the marginal distributions.

We built a Bayesian hierarchical linear regression model for how log-transformed generic and branded price are affected by the number of generics drugs, which was the most common model used by existing literature. The hierarchical structure was included since we usually have multiple observations of the drug price for different years, when the total number of generics varies over time. Thus, we assumed that observations for each drug across different years are correlated. i indicates each observation, and j indicates different drugs (molecule-route-strength). Multiple observations of the same drug across several years would have different i but clustered in the same drug group j. Without the hierarchical structure, the regression model can be

expressed as in equation 3.25. y_i is the log-transformed generic or branded drug price from MEPS. $X_i\boldsymbol{\beta}$ is a vectorized expression of the k predictors included in the model, including the intercept (so the first column of X_i, x_{0_i}, is constant 1, see equation 3.26). β_1 is the beta coefficient for the number of generic competitors (assuming continuous, x_{1_i}), which is our focus of interest.

$$y_i \sim N(X_i\boldsymbol{\beta}, {\sigma_y}^2)$$

(3.25)

$$X_i\boldsymbol{\beta} = \beta_0 + \beta_1 x_{1_i} + \beta_2 x_{2_i} + \cdots + \beta_k x_{k_i}$$

(3.26)

Next, we extended the model to allow for varying-intercept and varying-slope. Following Gelman and Hill (2006), we adopted the terms "vary-intercept" and "varying-slope" rather than "fixed-" , "random-" and "mixed-effect" which are not very easy to interpret by their names, and to avoid confusion when compared to "random-" and "fixed-effects" models in the meta-analysis [100].

We first assumed a varying-intercept model (equation 3.27), where the only coefficient that varies by drug j is the constant term (the intercept). $\beta_{0_{j[i]}}$, the intercept, now includes drug-level variations.

$$y_i \sim N(X_i\boldsymbol{\beta}, {\sigma_y}^2)$$

$$X_i\boldsymbol{\beta} = \beta_{0_{j[i]}} + \beta_1 x_{1_i} + \beta_2 x_{2_i} + \cdots + \beta_k x_{k_i}$$

(3.27)

Without any prior belief, we would assign noninformative priors to all the coefficients, their standard deviations and correlations between coefficients. Nevertheless, from the BMA, we have

obtained some belief on how generic and branded drug prices are affected by the number of entrants. Therefore, informative or weakly informative priors obtained in the BMA (reported in Table 3.2, from the base case and the extended model with bias-corrected, multiple models per literature) were also used as the varying intercept model with variation.

We further extended the model by allowing variation of the beta coefficients (slopes) by drug. Equation 3.28 shows the first modification when only the coefficient for the number of generics (β_1) varies by drug. This can be further extended if the other coefficients (β_2, …, β_k) also vary by drug (equation 3.29, or 3.30 in the matrix notation).

$$y_i \sim N(\beta_{0\,j[i]} + \beta_{1\,j[i]} x_{1_i} + \beta_2\, x_{2_i} + \cdots + \beta_k\, x_{k_i}, {\sigma_y}^2) \quad (3.28)$$

$$y_i \sim N(\beta_{0\,j[i]} + \beta_{1\,j[i]} x_{1_i} + \beta_{2\,j[i]} x_{2_i} + \cdots + \beta_{k\,j[i]} x_{k_i}, {\sigma_y}^2) \quad (3.29)$$

$$y_i \sim N(X_i \boldsymbol{B}_{j[i]}, {\sigma_y}^2) \quad (3.30)$$

Thus, for each four different outcomes of interest (generic drug price, branded drug price, generic drug market share, and total utilization of generic and branded drugs combined), we fit three models that: 1) have a varying intercept, 2) have a varying intercept and one varying slope (for N), and 3) have a varying intercept and all varying slopes. For outcomes where we have some prior information (generic and branded drug, using the posterior from the BMA), models with different priors were fitted.

Apart from the number of generics, based on literature, we controlled for time since the loss of exclusivity for the branded drug, as well as the log-transformed branded drug price prior to any

generic competition. In the sensitivity analysis, we added drug route (oral/injection/other), drug therapeutic class (ATC level 1), whether there's competition from authorized generics (AG), and whether the first generic entered by challenging the patent. We also varied the unit of analysis (grouping variable) to be molecule rather than molecule-route-strength in the main analysis, since drug pricing for the same molecule may also be correlated.

3.5.1.3 Validation

In order to evaluate model performance, we split the data into training and test data sets. Given the large number of drug groups and relatively small group size, for drugs with only one observation available, we kept them in the training set. If multiple observations are available, we randomly split the data by half, and dropped any test set where no observation for the same drug is assigned to the training set. The percentage of each test set outcome being covered by the 95% CI of the predicted test data outcome was reported as the coverage probability. A higher coverage probability is desired.

3.5.2 *Results*

3.5.2.1 Validity of MEPS NDC data

First of all, sample size shrinkage occurred when we matched NDC code to link MEPS data to OB for information regarding generic competition (see Appendix B.7).

We first linked the OB to FDA NDC. Since the NDC dataset does not provide product number (the identifier for different route/strength for drugs with the same ANDA number), while there is a great inconsistency in how drug strength was coded between two datasets, we have 81.0% (799/986) of the unique drugs left. We denote this subset the OB-NDC dataset.

Next, we linked NDC code in MEPS with OB-NDC. A bigger sample size reduction occurred due to failure to match NDC codes. Only 45.6% (364/799) of the unique drugs in OB-NDC can be matched to NDC in MEPS, even after adding historical FDA NDC codes, excluded NDC codes, and the "NDC universe" constructed from NBER data archive [95]. We did expect some data loss, as MEPS prescribed medicines data relies on self-report. Given the sampled MEPS population and the underreport of drugs taken, some drugs in OB with a small drug volume may not be captured in MEPS [60]. However, the high missingness also raised a question about NDC data quality in MEPS.

As illustrated in Figure 3.9, using the FDA current NDC data alone, about 35-50% of the MEPS unique drugs can be matched via NDC code (the red line). The proportion of drugs in MEPS that can be matched has increased over time, which reflects the incompleteness in historical NDC data for earlier years. Adding historical FDA NDC data leads to a small improvement (the green line). Adding the "NDC universe" improved matching on a bigger scale (the blue line, 50-65%). Similar patterns can be seen in Figure 3.10, where the proportion of unique NDC and total drug prescription records that can be matched were plotted over time. Even after the inclusion of additional datasets, only 75-85% of the NDC codes documented in MEPS can be matched to the list of NDC codes from the FDA. Since some of MEPS' NDC code were imputed, we also examined the match for imputed and original groups. Nevertheless, we did not find a significant difference, indicating imputation is not the reason for the low quality in NDC code matching [101]. Therefore, caution need to be taken when using NDC codes documented in MEPS for data analysis.

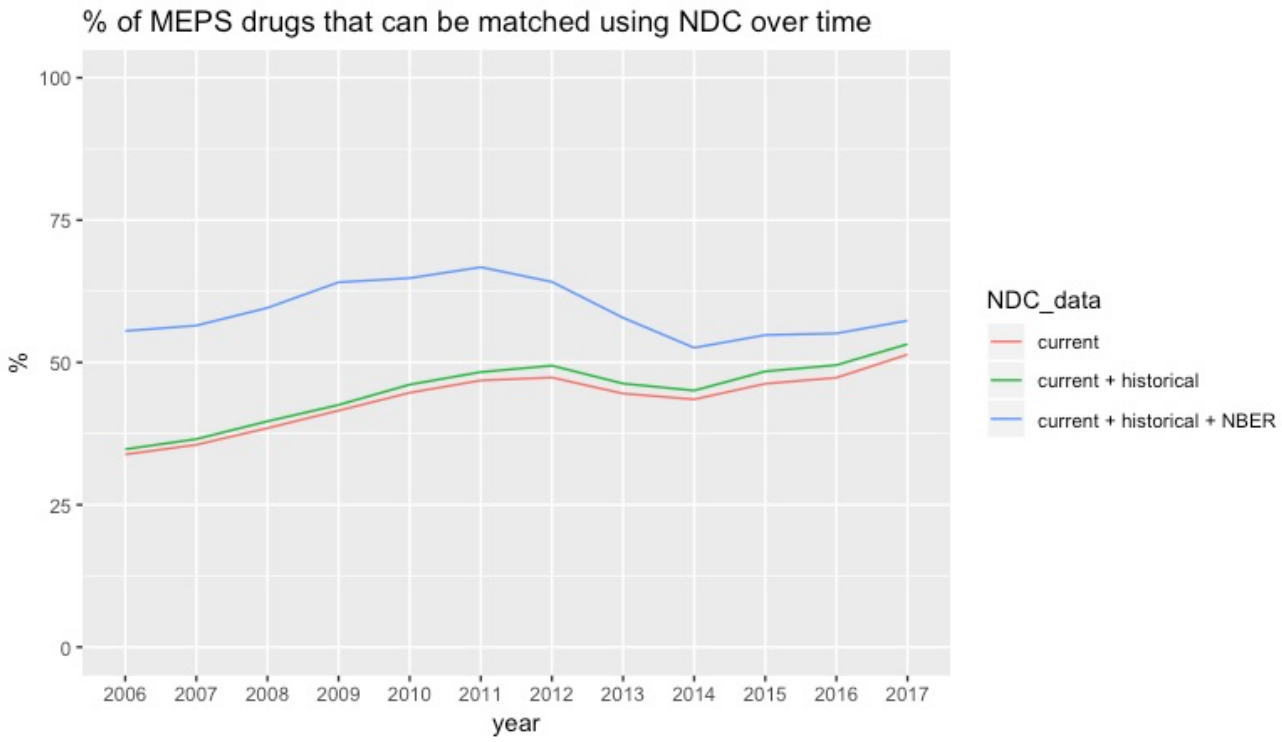


Figure 3.9 The proportion of unique drugs in MEPS that can be matched, by NDC data source

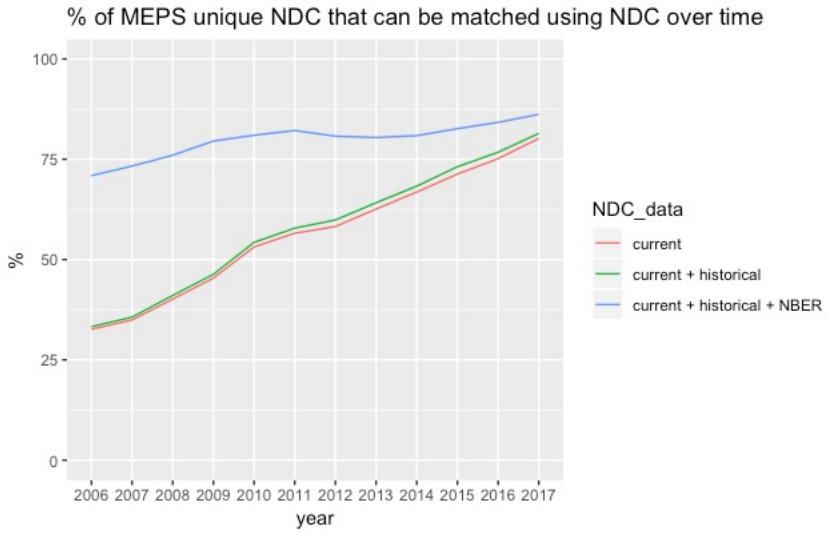


Figure 3.10 The proportion of unique NDC in MEPS that can be matched, by NDC data source

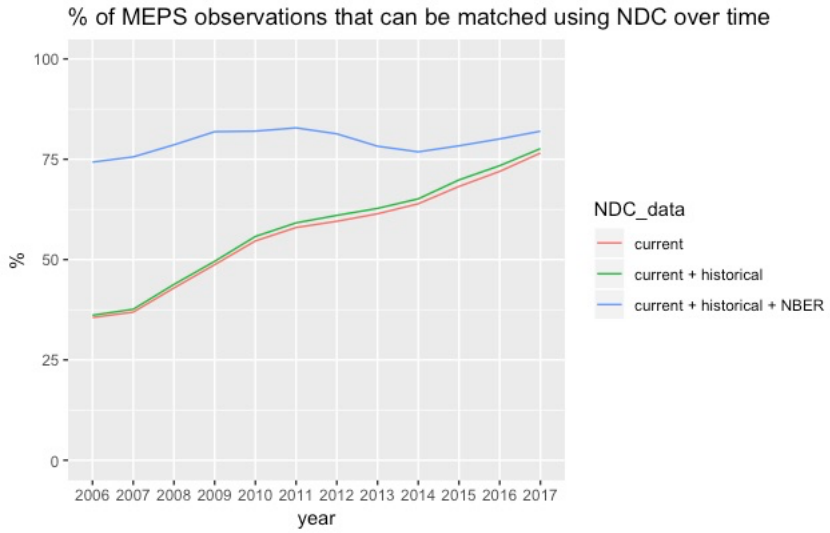


Figure 3.11 The proportion of prescription records in MEPS that can be matched, by NDC data source

3.5.2.2 Regression Results

As presented in Table 3.4, using the varying intercept models, for generic drug price change, our results are very similar to findings in the BMA. One additional generic competitor is associated with about 6.4% price reduction[7]. Using a more informative prior from the BMA slightly improved the coverage probability.

For branded drugs, surprisingly, when using noninformative priors, we see a reduction in drug price with respect to more generic entry, with the result being statistically significant. However, the price effect is smaller on branded drug than generic drug, with one additional entry associated with a 4.3% decrease in branded drug price[8]. When informative priors for the number of generics from the BMA (base case) were used, the effect on branded price became slightly positive, although insignificant (one additional entry associated with an increase of 0.1%[9]).

[7] exp(-0.0665) - 1 = -0.064
[8] exp(-0.0438) – 1 = -0.043
[9] exp(0.00099) – 1 = 0.00099

These two scenarios are the extreme cases, when non-informative and strongly informative priors were used. In the third scenario, we used a weakly informative prior from the BMA (bias-corrected, and multiple models per literature). An additional generic entry is associated with a milder branded price reduction of 2.8%, with the effect being statistically significant[10]. The coverage probabilities are similar with informative or noninformative priors.

Moreover, we found a generic drug's market share increases by 3.4 percentage point with one additional generic drug entry. For overall utilization, we found one additional generic entry is associated with an increase in overall volume of 6.9%[11], which is consistent with the direction of change found in some existing literature (e.g. Caves et al. (1991) and Conti et al. (2016))[15, 27]. Varying slope models showed similar results (see Appendix B.8 and B.9). We also conducted sensitivity analyses by controlling for drug routes, ATC, AG, patent challenge status, and used molecule-level rather than molecule-route-strength level as the unit of analysis. The estimates for the price impact were similar in all the scenarios we examined, yet the coverage probabilities were not as good as in the main analysis (see Appendix B.10). Our results remained robust.

[10] exp(-0.02877) – 1 = -0.0283
[11] exp(0.0664) – 1 = 0.069

Table 3.4 Varying-intercept Regression Model Results

Model	**Prior for the number of generics (N)**	**Beta-coefficient in Training**	**% of test data covered by 95% CI**
Generic drug price, log-transformed (659 observations in training, 594 in test; 261 unique drugs)	Non-informative *N(0, 10)*	-0.0664 [-0.08614, -0.04634]	93.0%
	From BMA (base) *N(-0.08, 0.02)*	-0.06921 [-0.08711, -0.05136]	93.6%
	From BMA (bias corrected) *N(-0.11, 0.07)*	-0.06715 [-0.08671, -0.04738]	93.4%
Branded drug price, log-transformed (621 observations in training, 539 in test; 283 unique drugs)	Non-informative *N(0, 10)*	-0.04381 [-0.06588, -0.02207]	93.1%
	From BMA (base) *N(0.01, 0.005)*	0.00099 [-0.00793, 0.01001]	92.9%
	From BMA (bias corrected) *N(0.02, 0.02)*	-0.02877 [-0.04766, -0.00989]	93.1%
Generic drug market share (441 observations in training, 362 in test; 220 unique drugs)	Non-informative *N(0, 10)*	0.03422 [0.02735, 0.04131]	97.8%
Total utilization (generic + branded), log-transformed (441 observations in training, 362 in test; 220 unique drugs)	Non-informative *N(0, 10)*	0.06641 [0.03361, 0.09827]	93.9%

3.6 DISCUSSION

Our systematic literature review and meta-analysis revealed the heterogeneity in how generic competition affects drug price is modeled. Inconsistency in modeling (e.g. whether examining absolute or relative price change, whether using net or list price, whether modeling the number of generics as a continuous or categorical variable, whether considering endogeneity, and what other variables to include) can lead to very different conclusions and implications. Thus, although many studies applied statistical models on this topic (16 that qualified for the qualitative review), it is hard to utilize all to generalize the conclusion. The majority of the studies also viewed the number of generics as a continuous variable, which assumes a linear relationship that may not be practical. Moreover, few studies examined how market structure like drug total utilization and market share changes are associated with more generic competition, which is worth future investigation.

Among the studies we meta-analyzed, we found more generic competition is associated with generic price reduction and a slightly increase in branded drug price. Furthermore, our estimated posterior distribution of the effects can be used as informative priors for future studies, which we discussed in more detail in Section 3.5.

Through the Bayesian linear regression analysis in Section 3.5, we found price reduction for both generic and branded drugs. Generic drug price faces a sharper decrease compared to branded drugs, and the scale of change is similar to our conclusion in the BMA. However, for branded drug price, although in the BMA we found the “generic competition paradox” where branded drug price remains sticky or increased slightly post generic entry, using MEPS data, we found a small price reduction over time. This may be due to that our analysis has a longer time period (10 years) compared to a short time period used in literature which ranges from two to three years.

Over a longer time span, the dynamic of branded drug pricing may be different, where branded drug price is less sticky. We also found small increases in generic drugs' market share as well as overall drug volume in association with increased generic competition. Therefore, faster entry would lead to cost savings. We estimated the scale of savings in the next Chapter.

There are several limitations in the BMA. First of all, our meta-analysis was limited by an inconsistent model format, thus a small number of studies were included for the evidence synthesis. In the base case, we assumed the beta coefficient is highly correlated with the effect size, regardless of many differences in model designs. Although this was addressed when we added the extension with bias correction, our assumption of additive biases and our selection of the biases might not capture all the model differences and correlations.

The Bayesian linear regression analysis also has several limitations. The biggest issue is the loss of data due to incomplete NDC data, which caused the downstream analysis to lack power and generalizability. We improved data quality by constructing an "NDC universe" using historical NDC codes provided in NBER data(public use data archive) [98]. In addition, we also plan to use the SSR Health's dataset for branded drug price to validate drug price data in MEPS [102]. In this dataset, around 1,000 branded drugs' prices for each quarter are documented between 2007 and 2018, which we could use as an alternative source for the estimation of branded drug's price change. Furthermore, for generic and branded drug prices, the model format is limited by the most frequent one found in literature (log-transformed price in a linear model), which may not be as practical as using a generalized linear regression with a log link. We also did not control for competition from other branded drugs and their generic substitutes for the same drug indication, which would also affect the drug markets we are examining. Lastly, our model did not account for endogeneity, as we do not have data on some widely used IVs such as drug

revenue prior to generic entry. If desired, we could use drug sales (drug price multiplied by its volume) as a proxy for drug revenue as a robustness check.

Chapter 4. ESTIMATING THE POTENTIAL POLICY IMPACT ON DRUG EXPENDITURE REDUCTION

4.1 INTRODUCTION

In Chapter 2, we showed that GDUFA may not necessarily accelerate all successive generic entries, especially after the first and second generic entrants. Potentially, some other policy targeted at accelerating more generic entries may help, such as DCAP that proposes to grant priority review status to applicants until there are three generic competitors in the market. Thus, in this chapter, we quantified the potential impact on health expenditures by shortening the time to entry for the first three entrants, via simulation of the entry time. In specific, quicker generic drug entry brings the drug price down faster. From Chapter 3, we obtained a better understanding of how drug price is affected by the number of generic drug entrants. Therefore, using knowledge from Chapter 3 regarding drug price change, and time to entry data from Chapter 2 for each drug, we estimated the change in drug expenditure if more generic entries happen quicker.

4.2 BACKGROUND

In June 2017, the Food and Drug Administration (FDA) announced the launch of the Drug Competition Action Plan (DCAP) [5], aiming to resolve regulatory obstacles to generic access, increase the efficiency and predictability of the FDA's review process, and reduce gaming by

branded companies that can delay generic drug entry. Early steps the FDA took included: (a) introducing “Priority Review” instead of Office of Generic Drugs’ (OGD) previous “first-in, first-reviewed” approach for eligible ANDA applicants, (b) prioritizing review of generic drug applications until there are three generics approved for a brand product, and (c) expediting subsequent drug approval once the 180-day exclusivity is triggered[6]. Given the expedited review time for drugs with less generic competition, it is promising to further reduce time to generic drug entry and therefore drug expenditures.

Ching (2010) estimated how generic demand changes in response to a hypothetical policy that increases the likelihood of approved generic entry [103]. For the policy experiment, a hypothetical policy shock was included as the intercept term in the fitted logistic regression model. Similarly, given the proposal of DCAP to accelerate review for the first three generic entrants, we could estimate its impact by modifying the survival model (and therefore expediated time to entry) with the added policy shock.

On the other hand, from Chapter 3, through existing literature and updated analysis using MEPS data, we have obtained a better understanding of how market structures change in response to increased levels of generic competition. Therefore, with simulated time to entry being shortened, we expect more generic competition that happens earlier. Therefore, it is possible to quantify the corresponding price and utilization changes associated with the “simulated” increase in generic competition, and furthermore provide an estimate for the scale of reduction in drug expenditures.

4.3 METHODS

4.3.1 *Data*

We used model estimates of drug price and quantity changes obtained and real drug prices and quantities from MEPS in Chapter 3, as well as the OB data and estimated hazard of entry for generics in Chapter 2 for the policy experiment. Due to high missingness in MEPS data, we interpolated the data for years in between non-missing prices and quantities, assuming a linear change over time. Drugs were dropped if no branded or generic drug price is available between 2013 and 2017.

4.3.2 *Policy Experiment*

4.3.2.1 Accelerated gap time to entry

Since DCAP was launched in late 2017, given the short time duration, it is hard to quantify its impact using currently available data. Instead, we used simulation to estimate the potential change in speed of entry for the first three generic competitors and the subsequent reduction in drug expenditures. We focused our attention on branded drugs that faced generic entry between 2012 and 2017 (5-years during GDUFA I) and have been included in Chapter 2 and 3 for the analysis. For the first three generic entrants corresponding to each branded drug without PC, we shortened the gap time by increasing the hazard of entry to different scales. If the first entered with PC, we increased the hazard of entry for second and third entrants only.

The Conditional-GT model from Chapter 2 was used to simulate the new time to entry after increase in hazard, but with a slightly different model form. Since only drugs facing generic competition post-GDUFA were included in this aim, we exclude the interaction between GDUFA and stratums for the number of prior events.

The survival function for a proportional hazard model is listed in equation 4.1, where the cumulative baseline hazard function is expressed in equation 4.2, with stratum-specific hazard functions using the notation j [104]. The cumulative distribution function is $1 - S(t|X)$, listed in equation 4.3. $\hat{\beta}$ represents the fitted coefficients from the post-GDUFA Conditional-GT model.

$$S(t|X) = \exp\{-H_0(t) * exp(X\hat{\beta})\} \quad (4.1)$$

$$H_0(t) = \int_0^{t-t_{j-1}} h_{0j}(u)du \quad (4.2)$$

$$F(t|X) = 1 - \exp\{-H_0(t) * exp(X\hat{\beta})\}. \quad (4.3)$$

Assuming $F(\cdot)$ is the cumulative distribution for a random variable y, then $U = F(y) \sim Unif[0,1]$, so as $1 - U$. Thus, let T denote the gap time, then we have:

$$U = \exp\{-H_0(T) * exp(X\hat{\beta})\} \sim Unif[0,1]. \quad (4.4)$$

We could further obtain gap time T as the inverse of baseline cumulative hazard expressed in equation 4.5, without knowing the exact inverse function ${H_0}^{-1}(\cdot)$.

$$T = {H_0}^{-1}\{-log(U) * exp(-X\hat{\beta})\}. \quad (4.5)$$

Similar to Ching (2010), we added a policy shock $\log(k)$ to the intercept in the equation to get simulated gap time under the policy experiment (see equation 4.6) [103]. $k = 1$ indicates no policy impact.

$$T = H_0^{-1}\{-log(U) * exp\left(-X\hat{\beta} - \log(k)\right)\}.$$

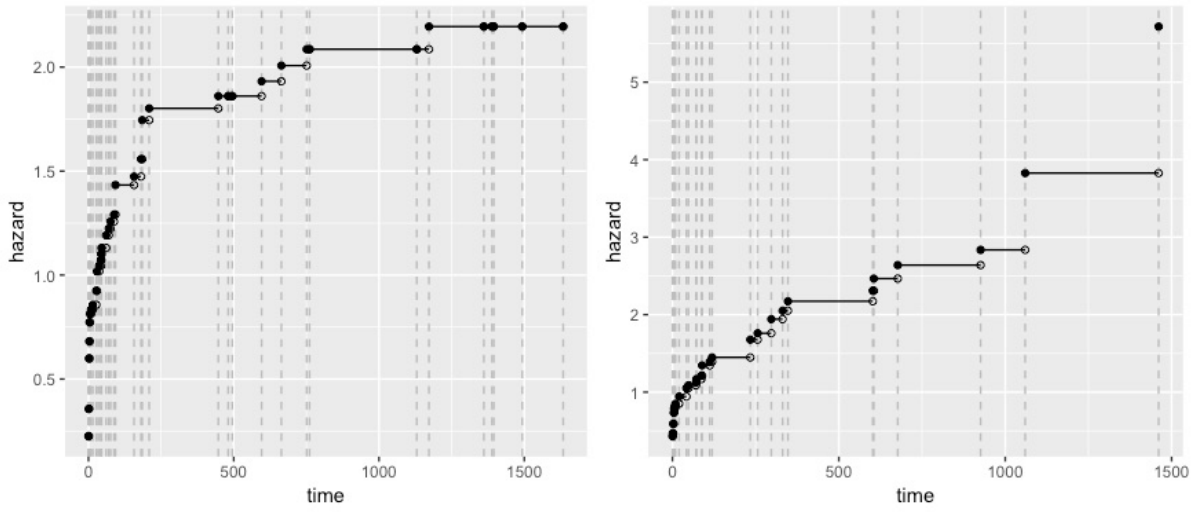
(4.6)

In the base case, we used H_0 from the Conditional-GT model to get T. Nevertheless, as an extension to the Cox proportional hazard model, H_0 from the Conditional-GT model is time-dependent and non-parametric. To overcome this, we used the empirical H_0 distribution obtained after fitting the Conditional-GT model using the *basehaz* package in R. Since the current event model put different orders of entry in different strata with a different hazard function, we denote H_{0j} to be the hazard function for the jth entrants. Thus, equation 4.6 becomes:

$$T_j = H_{0j}^{-1}\{-log(U) * exp\left(-X\hat{\beta} - \log(k)\right)\}.$$

(4.7)

To get $H_{0j}^{-1}(\cdot)$, as illustrated in Figure 4.1, based on simulated hazard on the y-axis, the corresponding gap time can be obtained by finding the corresponding value on the x-axis. Since the empirical cumulative hazard is a step function, we first checked whether the calculated value $-log(U) * exp\left(-X\hat{\beta} - \log(k)\right)$ can be matched to the baseline hazard. If so, the corresponding time was assigned. If not, we matched it with the closest baseline that is bigger than the calculated value. However, for each order of entry, we have many drugs entered on the same day as the previous entrants, thus they have tied gap time of 0 days (see Figure 2.3, where the survival probabilities dropped sharply around gap time = 0). For these drugs with same day entry, the policy will not likely affect their time-to-entry. Therefore, drugs with gap time to entry equals 0 were excluded from the simulation. For the simulated cumulative hazard that corresponds to a gap time of 0, we also replace the value with the smallest positive gap time.



Left: Second entrants Right: Third Entrants

Figure 4.1 Cumulative Hazard for Second and Third Entrants, with PC (Conditional-GT)

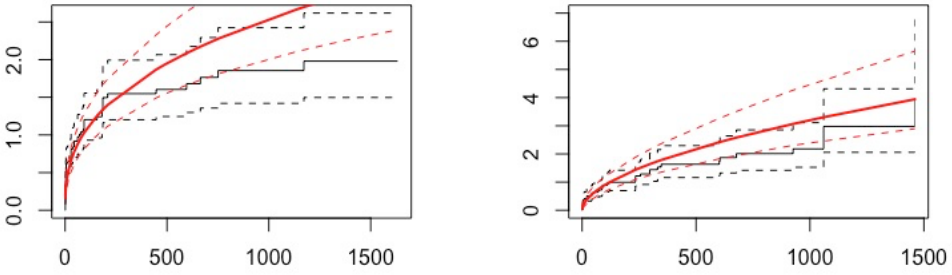
Many ties and estimation using the empirical step function may also lead to biases in simulation. In specific, our application of the Breslow estimator to deal with ties may perform poorly given the large number of ties we have [105]. In addition, the step function with big jumps in value may lead to an overestimation of the gap time, if simulated hazard cannot match with empirical hazard. We also considered to fit a Weibull model for those with positive gap times, as its parametric form enables a one-to-one mapping of ${H_{0j}}^{-1}(\cdot)$. Compared to the Cox model where ${H_{0j}}^{-1}(\cdot)$ is non-parametric, the Weibull distribution with scale parameter λ and shape parameter ν has a parametric form (equation 4.8). The simulated gap time is listed in equation 4.9 [104]. As illustrated in Figure 4.2, compared to Figure 4.1, the cumulative hazard function is continuous and smooth. However, as the Weibull model cannot capture recurrent events, we also posed a stronger assumption of conditional independence between different orders of entrants for the same drug, unlike in Conditional-GT.

$$H_0{}^{-1}(t) = (\lambda^{-1}t)^{\frac{1}{\nu}}$$

(4.8)

$$T = \{\lambda^{-1} * -log(U) * exp\big(-X\hat{\beta} - \log(k)\big)\}^{\frac{1}{\nu}} = \lambda^{-1}\left(\frac{-\log(U)}{\exp(X\hat{\beta}+\log(k))}\right)^{\frac{1}{\nu}}$$

(4.9)



Left: Second entrants Right: Third Entrants

Figure 4.2 Cumulative Hazard for Second and Third Entrants, with PC (Weibull)

4.3.2.2 Estimation of price, quantity and expenditure changes

However, estimating the change in time to entry from the policy is not the end goal. We wanted to further estimate the potential drug expenditure changes from faster generic entries. For each drug, the overall expenditure is calculated by summing up the expenditure of generic and branded drug consumption (see equation 4.10). Even if gap time is only shortened for the first three entrants, the successive entrants will also be affected by having earlier simulated approval dates. Therefore, for a given time, the price of generic and branded drugs would be affected.

In specific, for each year between 2013 and 2017, we re-calculated the simulated number of generics entered for each drug by aggregating and counting the simulated approval dates by year (Table 4.1, column 4).

Moreover, from Chapter 3, we found evidence that one additional generic entry is associated with a generic price reduction of 6.4%, and a branded drug price reduction of 4.3%. These can then be used to estimate branded and generic drug price, by taking into account the difference between simulated and real number of generics by year (Table 4.1, column 5-7). We also examined how the results would change if we use the posterior distributions from the BMA instead (a generic price reduction of 8.0%, and a branded drug price increase of 0.97%).

Table 4.1 Sample Table to Illustrate the Simulation of Price, Quantity and Expenditure

Drug	**Year**	**# of generic entrants N**	**Simulated # of generic entrants N^***	**Difference in # of generics ΔN**	**Predicted branded drug price** $p_B^* = p_B * (1 - 4.3\% * \Delta N)$	**Predicted generic drug price** $p_G^* = p_G * (1 - 6.4\% * \Delta N)$	**Predicted generic drug utilization** $Q_G^* = Q_G(1 + \varepsilon \frac{p_G * - p_G}{p_G})$	**Expenditures Overall expenditures** $E^* = p_B^*(Q - Q_G^*) + p_G^* Q_G^*$,
A	2013	0	0	0	$p_{B,2013}$	$p_{G,2013}$	$Q_{G,2013}$	E_{2013}^*
A	2014	1	2	1	$p_{B,2014}^*$	$p_{G,2014}^*$	$Q_{G,2014}^*$	E_{2014}^*
A	2015	2	3	1	$p_{B,2015}^*$	$p_{G,2015}^*$	$Q_{G,2015}^*$	E_{2015}^*
A	2016	2	3	1	$p_{B,2016}^*$	$p_{G,2016}^*$	$Q_{G,2016}^*$	E_{2016}^*
A	2017	3	3	0	$p_{B,2017}^*$	$p_{G,2017}^*$	$Q_{G,2017}^*$	E_{2017}^*

On the other hand, from Chapter 3, we found mixed results from the literature regarding the overall utilization change, and our MEPS data analysis also found a nonsignificant change in overall volume in response to more generic competition. Therefore, we assume that the overall utilization Q $(= Q_B + Q_G)$ is fixed. Then, we modeled the change in Q_G through generic price change and the price elasticity of demand. Denote the price elasticity as ε, it measures the relative change in quantity divided by the relative change in price (equation 4.11). Following the

results from Yeung et al. (2018), we viewed $\varepsilon = -0.16$ [106]. By rearranging equation 4.11, we got $Q_G{}^*$, the new generic drug volume, as a function of original volume from MEPS (Q_G), price elasticity ε, and relative price change (ΔP_G). We could further obtain the new estimated drug expenditure, in equation 4.13.

$$E = p_B Q_B + p_G Q_G$$

(4.10)

$$\varepsilon = \frac{\Delta Q}{\Delta P} = \frac{Q^* - Q}{Q} \frac{P}{P^* - P}$$

(4.11)

$$Q_G{}^* = Q_G + Q_G \varepsilon \, \Delta P_G$$

(4.12)

$$E^* = p_B{}^* Q_B{}^* + p_G{}^* Q_G{}^* = p_B{}^* (Q - Q_G{}^*) + p_G{}^* Q_G{}^*,$$

Where $Q = Q_B + Q_G$, $Q_G{}^* = Q_G(1 + \varepsilon \, \Delta P_G)$

(4.13)

In the next section, we describe the detailed steps for the policy experiment to get simulated drug expenditure changes.

4.3.2.3 Steps

1. We kept MEPS data when generic entry happens post GDUFA (2013-2017). For each drug (molecule-route-strength combination), the number of generic competitors per year was reported (implemented in Chapter 3).
2. We re-ran the gap-time survival model, to get the cumulative baseline hazard for different orders of entrants (2nd and 3rd entrants for "with PC"; 1st, 2nd and 3rd entrants for "without

PC"). For a semi-parametric Conditional-GT model, the empirical cumulative hazard function was obtained. While for a parametric Weibull model, fitted scale parameter λ and shape parameter ν were estimated to construct ${H_{0j}}^{-1}(\cdot)$.

3. We set a hypothetical policy shock that equals k. We sampled from a uniform distribution 500 times, each time got simulated (gap) time to entry, using equation 4.7 (or equation 4.9 for the Weibull model), among drugs with at least one positive gap time for the first three entrants.
    a. Each time, we calculated the simulated approval time for all entrants (with simulated gap time for (1st,) 2nd and 3rd entrants, and the actual gap time for the successive entrants). Since time to entry for the first few entrants are shortened, the successive entrants will also be affected and have earlier simulated approval dates.
    b. We re-calculated the simulated total number of entrants per year, for 2013-2017.
    c. Then, we calculated the difference in the number of entrants per year, and applied the price changes accordingly. Taken from Chapter 3, for each drug, we drew from a normal distribution with mean equals -6.4% multiplied by ΔN, and -4.3% multiplied by ΔN.
    d. Next, we calculated the simulated generic volume and overall expenditure, as described in Table 4.1.
    e. Lastly, we summarized across the 500 simulations to get the average change in over expenditure, for assumed policy shock k.
4. We varied the baseline hazard scale change (from 0.1 to 5, each time with a 0.2 unit of the incremental change), and repeated step 3 each time.

4.4 RESULTS

4.4.1 *Data Size*

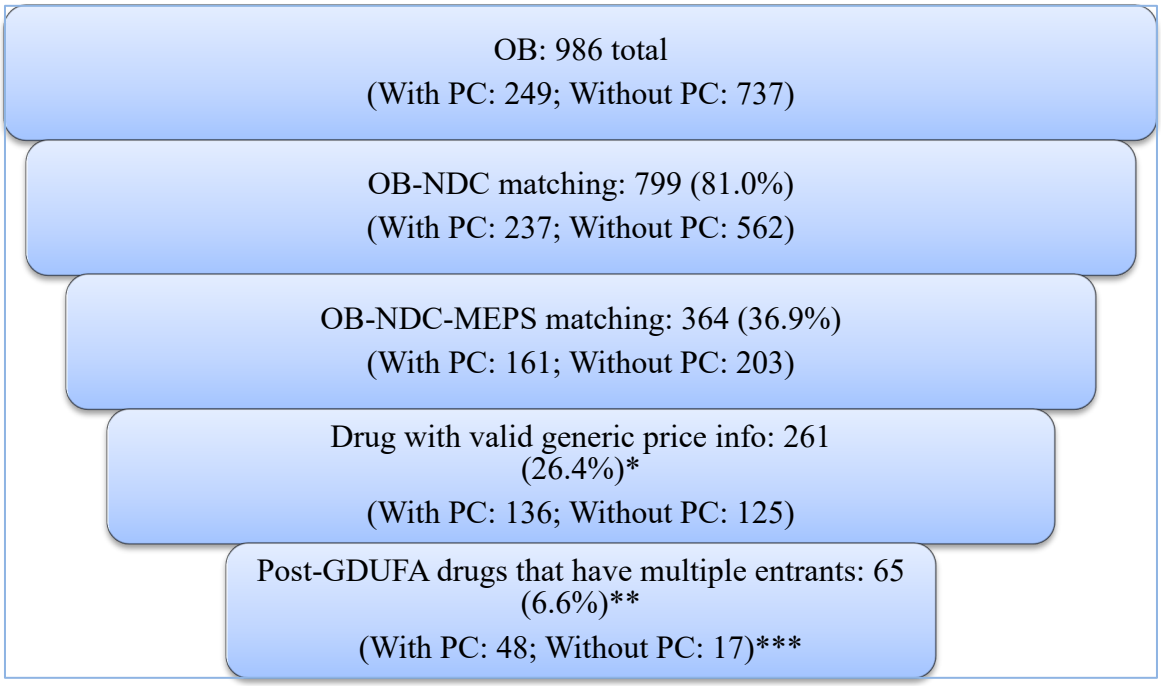


Figure 4.3 Flow Diagram of Sample Size Change in Different Steps

Note:

*Compared to the regression, for model fitting in Chapter 3, this count further decreased if we miss branded drug price prior to loss of exclusivity, or assigned all observations to the test set (thus the drug would be excluded)

** For "With PC" group, have at least two generic entrants; For "Without PC" group, have at least one generic entrant.

***Further lose drugs if for the same order of entry, there are ties (the gap time equals 0)

Figure 4.3 is an extension of Appendix B.7, where we showed further changes in the data size, after we applied further restriction regarding time frame and positive gap time. Again, the data

loss in the upper stream is mainly due to the incompleteness of the FDA NDC code that affects the sample size severely in the downstream, and makes the conclusion harder to generalize.

4.4.2 *Accelerated gap time*

Table 4.2 presented the actual and simulated gap time for the "with PC" group, for second and third entrants in MEPS where we can link to OB with positive gap times. The sample size is very small. We expected when k=1, the simulated gap time to be close to the actual distribution. Nevertheless, especially for the 3rd entrants (only 8 observations), the simulated time was off, for both Conditional-GT and Weibull models.

Table 4.2 Actual and Simulated Gap Times, for with PC

		Median gap time	**Mean gap time**
Actual	Second (n=32)	2	47.3
	Third (n=8)	69.5	404
Conditional-GT model, simulated 100 times (using equation 4.7)			
Simulated, k = 1 (no impact)	second	1	101
	third	2	168
Simulated, k = 2	second	1	14
	third	1	34.9
Simulated, k = 5	second	1	1.1
	third	1	3.93
Weibull model, simulated 100 times (using equation 4.9)			
Simulated, k = 1	second	8.15	175
	third	6.34	26.3
Simulated, k = 2	second	1.40	27.2

	third	1.58	6.22
Simulated, k = 5	second	0.13	2.29
	third	0.35	1.31

For the "Without PC" group (Table 4.3), the simulated time in Conditional-GT assuming no impact is closer to the actual gap time, yet the Weibull model greatly over-estimated the gap time.

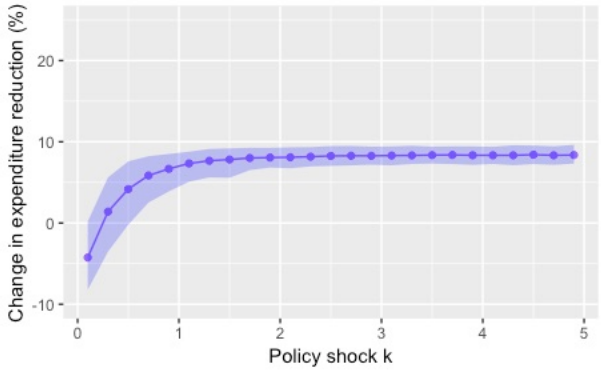
Table 4.3 Actual and Simulated Gap Times, for without PC

		Median gap time	**Mean gap time**
Actual	First (n=10)	668	523.6
	Second (n=8)	516.5	554.9
	Third (n=3)	1	250.3
Conditional-GT model, simulated 100 times (using equation 4.7)			
Simulated, k = 1 (no impact)	First	1	158
	Second	395	618
	Third	77	227
Simulated, k = 2	First	1	37.1
	Second	80	301
	Third	278	87
Simulated, k = 5	First	1	2.1
	Second	2	77.7
	Third	1	14.4
Weibull model, simulated 100 times (using equation 4.9)			
Simulated, k = 1	First	702631	2677300
	Second	390	752
	Third	120	241
Simulated, k = 2	First	1776949	498298

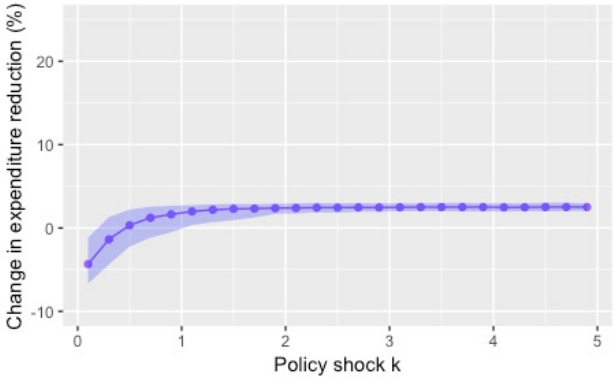
	Second	183	340
	Third	53.9	100
Simulated, k = 5	First	1050735	252188
	Second	67.6	127
	Third	30.3	13.7

4.4.3 *Estimation of the Drug Expenditure Reduction*

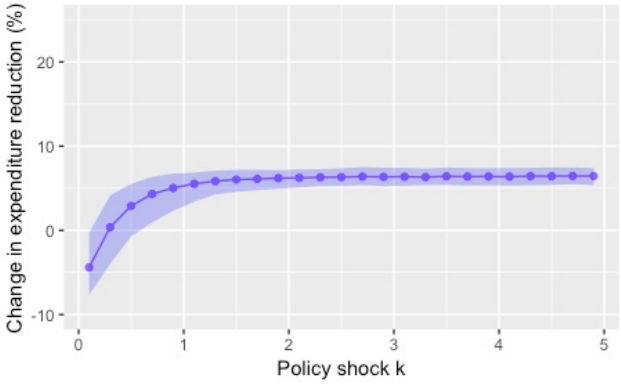
Although lacking power, we still proceeded to show the estimated drug expenditure change, for the Conditional-GT simulated results. The Weibull model was not used as it did not reproduce a close estimate to the empirical gap time. Varying the policy shock from 0.1 to 5, if we use the price change estimates results in Chapter 3 using the noninformative priors from BMA, the average change in relative drug expenditure was plotted in Figure 4.4 (a). As expected, with an increase in the value of k, there is an increase in the scale of drug expenditures reduction. The upper bound for drug expenditure reduction is around 8.3% (95% CI: [7.2%, 9.5%]). Although there is a neutral impact from the policy experiment when k = 1 (equivalent to the policy shock equals 0, when no policy impact is posed to the intercept of the model), we did see a reduction in overall expenditures. Reasons for this include an underestimation of the gap time from simulation, as reported in Table 4.2 and 4.3. Furthermore, we are estimating the effect aggregated by year, therefore most of the impact would come from several entries early in the year (e.g. approval date in early 2014 becomes late 2013 after a small reduction in the gap time, will lead to more generic counts in the previous year). The small sample size also made it hard to capture the real changes.



(a) Using price estimates with noninformative priors



(b) Using price estimates with informative priors from the BMA (base case)



(c) Using price estimates with weakly informative priors from the BMA (bias-corrected)

Figure 4.4 Overall Drug Expenditure Changes with Respect to Change in k, using different price change estimates from Chapter 3

We also ran the same policy experiment using price change estimates from the BMA with informative priors (base case), where more generic competition leads to a small increase in branded drug price. As illustrated in Figure 4.4 (b), the average change in relative drug expenditure becomes smaller (upper bound 2.5%, with 95% CI [2.0%, 3.0%]). This suggests that the long-term branded drug price reduction is a key driver to cost reduction in our simulation, especially when market share and total utilization remain stable[12]. If we use price change estimates from the BMA with the bias-corrected, weakly informative priors (see Figure 4.4 (c)), the upper bound of the drug expenditures reduction becomes 6.4% (95%CI [5.4%, 7.4%]).

[12] We fixed total utilization, but allowed variation in generic vs. branded volumes. Generic consumption was impacted by generic price change. Since generic price change was minimal, we did not see a big impact in market share changes.

4.5 DISCUSSION

Our policy experiment showed that to only prioritize the first three entrants for each drug would not bring a considerable amount of benefit, especially if branded drug price remains sticky post generic competition. This indicates that a general policy to expediate the review for the first three generics may not be as useful for expenditure reduction, since the total number of generic entrants is not affected. Moreover, DCAP will not likely impact many drugs that face fierce generic competition and same day entry of multiple drugs (since the gap time cannot be further shortened). Designing future policies that increase the total amount of competition, or create regulations to lower branded drug prices may be more helpful in controlling drug spending. There are several limitations in this analysis. First, similar to Chapter 3, the incomplete NDC code for matching caused a big data loss, which limited the sample we could use for simulation in this Chapter. Second, instead of simulating drug price as well as market share and drug utilization, we assumed a fixed total utilization, with the demand for generic drug estimated through one universal price elasticity. However, as mentioned by Ching (2010), the price elasticity may be different for a heterogenous population, where price insensitive consumers went for the branded drug, and price sensitive consumers purchased the generic version) [103, 107]. Therefore, modeling the quantity change in generic and branded drugs separately using different price elasticities may yield more accurate estimations. Furthermore, the value for the policy shock, k, is an arbitrary number and lacks real policy meaning.

Chapter 5. CONCLUSION

In Chapter 2, survival analysis was applied to study the correlated time to entry of generic drugs for the same molecule, and the impact from GDUFA I over time. Since speed of entry (time to each generic drug entry) is a time-to-event variable, it is natural to use survival analysis in this setting. This is different from existing literature that defines time to entry as a branded drug's market exclusive period, where only speed of the first generic entry is studied using linear regression [57]. By looking at time to each generic drug entry, we were able to evaluate whether GDUFA's aim for faster entry is effective. By separating the impact of GDUFA on different orders of entry, we could analyze whether there is a differentiated effect, and locate the potential areas for policy improvements.

Our results suggest that GDUFA may have decelerated generic entries into the market, beyond the first entry, with the most negative effect on second entrants. The reasons may be due to the FDA's prioritization of backlogged and the first-to-submit post-GDUFA applicants, lag between fee income and utilization to increase processing scale, and fees decrease incentives for generics to challenge patents or compete to be the first to enter the market. Since faster successive entries lead to a faster price reduction, it would be helpful to prioritize the review of more entrants and maintain sufficient incentives for generic drug manufacturers, especially given that the extra economic burden in GDUFA II (annual fee based on the number of ANDAs per manufacturer) may discourage generic entry especially for small companies.

Analyses from Chapter 3 helped us to better understand and quantify the drug price changes from generic entry. The evidence synthesis provided a systematic review of evidence in these

areas, which has not yet been established in existing literature. However, most studies that analyzed the relationship between drug price and number of generic competitors were not up-to-date [108, 109]. One recent study is available using MarketScan data from 2008 to 2014, which is a private insurance claim database that may not be nationally representative [19]. Therefore, it is important to use newer and nationally presentative information to estimate the effect of generic entries on drug prices and utilization, and further infer the impact on reduction in drug spending. Thus, by setting up a Bayesian framework, we were able to update our beliefs regarding the impact of different levels of generic competition on drug price changes, combining evidence collected from literature and new evidence gathered from data. Specifically, we utilized the information from a nationally representative database, MEPS, for the inference. For literature with heterogeneity in the data source, method and sample size, the Bayesian meta-analysis also enabled us to summarize the information in a systematic way that could be used as prior information for our model to increase generalizability.

Through the Bayesian linear regression analysis using MEPS data, we found price reduction for both generic and branded drugs. Generic drug price faces a sharper decrease compared to branded drugs, and the scale of change is similar to our conclusion in the BMA (about 6.4% reduction in generic price associated with one additional generic entry). However, for branded drug price, although in the BMA we found the “generic competition paradox” where branded drug price remains sticky or increased slightly post generic entry, using MEPS data, we found a small price reduction over time (about 2.8% reduction in branded drug price associated with one additional generic entry). This may be due to that our analysis has a longer time period (10 years) compared to a short time period used in the literature, which ranges from two to three years. We

also found increased generic competition is associated with small increases in generic drugs' market share as well as overall drug volume.

The findings from Chapter 4 link the information collected in Chapter 2 and 3 together, and further deepened the understanding of the economic impact from accelerated generic entry. We found a very small, potential reduction in overall drug expenditures based on DCAP to only accelerate the review until there are three generics in the market. Therefore, our study also calls for researchers and policymakers in designing future policies to encourage more generic entrants into the market, have better control over branded drug price, as well as target drug markets that already face a higher level of competition shortly post the loss of exclusivity.

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APPENDIX A

A.1. Details of the adjusted variables in the model

To control for therapeutic classes, the NDC database from the FDA has been used. As the NDC database no longer provides information regarding therapeutic classes, RxNorm mapping algorithm that maps NDC codes to Anatomical Therapeutic Chemical (ATC) classes have been applied [110]. We then merge the ATC information into OB using application number, which is both available in the OB and NDC datasets. The ATC level 1 classification has been used with 14 different categories [111]. Each drug can be classified as multiple ATC level 1 categories. Competition from authorized generics (AG) launched or authorized by branded drug companies may also affect generic entry, and information of AG is available from the FDA [112]. Also, whether branded drug has approved Risk Evaluation and Mitigation Strategy (REMS) and whether Product-Specific Guidance for Generic Drug Development is available will likely affect the speed of generic drug entry, so data from the FDA are used to adjust for their impacts [42, 113, 114].

A.2. Details regarding dataset construction

Two datasets have been created, based on whether the first generic drug entered with PC. In the "Without PC" dataset, for branded drugs with no generic competition, there will be only one row of observation, with the start time as index time, and stop time as the time difference between index date and end of follow-up (2017-09-30). The indicator for generic entry (0 or 1) will be 0, so as the number of prior generic entry event(s). For drugs with at least one generic entry, there will be at least one row with the indicator for generic entry equals 1, while the number of prior generic entry event(s) increases accordingly. To account for censoring, we have also included an extra row for the time period between last observed entry and end of follow-up, with the indicator for generic entry equals 0. Construction of the "With PC" dataset is similar, except for that drugs with only one generic competitor is now viewed as being censored for second entry, and the number of prior generic entry event(s) has a starting value of 1 instead of 0, due to the difference in the definition of index times.

To prevent the left truncation and length bias, we restrict the samples as below, especially focusing on restricting the administrative censoring window for pre-GDUFA events:

- For pre-GDUFA: only include patent expiry dates after Oct 1 2007 and the events happened before Oct 1 2012 (i.e. censor everyone at Sept 30 2012);
- For post-GDUFA: only include patent expiry dates after Oct 1 2012 (and censor everyone at Sept 30 2017);
- Add censored cases for last generic entry with entry status equals 0 and the number of competitors increased by 1; furthermore, depends on whether index date is pre- or post-GDUFA, we use different cutoff times accordingly
- Apply administrative censoring to branded drugs without generic entry (without PC)/first entrants without second entrants (with PC); depends on whether index date is pre- or post-GDUFA, we use different cutoff times accordingly
- Apply administrative censoring to branded drug (without PC)/first entrant (with PC) with index date pre-GDUFA, but had the next generic entry post-GDUFA; used 2012-09-30 as cutoff time

For drugs with multiple entries at the same time (same approval date), we assigned them different ranks, with a 0.001-day difference in their entry time. For the "With PC" dataset, if multiple drugs challenged the patent, we only considered the subsequent entries after 180-day exclusivity expired. In our survival analysis, we use the earliest patent expiration date as the index date for the "Without PC" group. For first entrants in this group, none of them entered before the corresponding earliest patent expiration date. 25.1 percent of them entered before the latest patent expiration date. For the "With PC" group, 45.6 percent of the first entrants entered before expiration of the earliest patent, suggesting that they have succeeded in challenging the earliest expiring patent. 100 percent of these first entrants entered before the expiration of the last expiring patent. Our observations are consistent with the grouping, as first entrants in the "With PC" group all entered before patent expiration, while all first entrants in the "Without PC" group entered after patent expiration.

A.3 Technical details of the models

The equations for each of these models are listed below. Conditional frailty models are referenced from Box-Steffensmeier and De Boef (2006).

- Conditional-TT: $\boldsymbol{h(t) = Y_{ij}(t)h_{0j}(t)exp(X_i(t)\beta_j)}$
- Conditional-GT: $\boldsymbol{h(t) = Y_{ij}(t)h_{0j}(t - t_{j-1})exp(X_i(t)\beta_j)}$
- Conditional frailty-TT: $\boldsymbol{h(t) = Y_{ij}(t)h_{0j}(t)exp(X_i(t)\beta_j + \omega_i)}$
- Conditional frailty-GT: $\boldsymbol{h(t) = Y_{ij}(t)h_{0j}(t - t_{j-1})exp(X_i(t)\beta_j + \omega_i)}$
- Marginal (TT): $\boldsymbol{h(t) = Y_{ij}(t)h_{0j}(t)exp(X_i(t)\beta_j)}$

On the left-hand side of each equation, $\boldsymbol{h(t)}$ indicates the hazard at time t. On the right-hand side, the equations are slightly different across models. All four models assume that a branded drug cannot be at risk of the second generic entry until the first generic entry happens. Each event is assigned to a separate stratum, where the stratum-specific coefficient ($\boldsymbol{\beta_j}$) can be estimated. This allows different baseline hazard $\boldsymbol{h_{0j}}$ for different order of entrants. $\boldsymbol{Y_{ij}(t)}$ remains to be 0, and becomes 1 until the j-1 entrant entered. The difference for two models lies in the estimated hazard: TT estimates the hazard since the index date ($\boldsymbol{t - 0}$), while GT estimates the hazard since previous event ($\boldsymbol{t - t_{j-1}}$). Since different ordered events will be placed in different stratum, there won't be any reference group, and $\boldsymbol{\beta_j}$ for GDUFA estimates the HR post- and pre-GDUFA among the j^{th} entrants. For higher order events (such as the 25th entrants), there may only be one or two observations in the sample, making the stratum size extremely small, leading to low power in estimation. Therefore, we pre-specified the event order k to be six and only limit the analysis to up to the 6^{th} entrants. However, the PWP model does not control for unmeasured confounding, such as market size or other drug-specific characteristics that will

affect the speed of entry. Therefore, we also applied a random effect (frailty) model that considers heterogeneity across drugs as well as event dependency across events, with an additional term $\boldsymbol{\omega_i}$ that is shared across all generic competitors for each branded drug [50].

The equations for the conditional frailty models are very similar to the Conditional (PWP) models, with an additional term $\boldsymbol{\omega_i}$. Interpretations of the covariates $\boldsymbol{\beta_j}$ The random effect $\boldsymbol{\omega_i}$ is across branded drug (each cluster) shared by all orders of entry, but is assumed to be constant over time. Different distribution assumptions are available including gamma, Gaussian and t-distribution, and we adapted the commonly used gamma frailty like in Box-Steensmeier and Boef (2006) [50]. The shared frailty model assumes that given the frailty, all failure times are conditionally independent [115]. Therefore, although controlled for heterogeneity, such assumption might be too strict.

The marginal model (also called the Wei, Lin, and Weissfeld (WLW) model) has very similar expression as the Conditional-TT model. As mentioned in Chapter 2, the main difference is how the risk set is defined. Since the marginal model assumes that the branded drug is at risk of any future generic entries, for each index, all possible events (in our analysis up to the 6th entry) are listed as one observation. If no generic entry ever happened, all 6 events (for the 1st up till the 6th entry) are viewed as being censored.

The sample data structure for both the conditional and marginal models are listed below.

Sample data structure

Table A.1: Sample data structure for the conditional model

Index	Drug name	Index date	Time of approval	Generic entry	Start time	Stop time	Gap time	Order of entry	# of competitors	GUDFA	Other variables
1	ACETAMINOPHEN	2013-11-02	2016-03-22	1	0	871	871	1	0	1	
1	ACETAMINOPHEN	2013-11-02	2016-06-13	1	871	954	83	2	1	1	
1	ACETAMINOPHEN	2013-11-02	-	0	954	1428	474	3	2	1	
2	APREPITANT	2008-03-26	2012-09-24	1	0	1643	1643	1	0	0	
2	APREPITANT	2008-03-26	-	0	1643	1469*	6	2	1	0	
3	TRIUMEQ	2016-09-28	-	0	0	366	366	1	0	1	

*: Administrative censoring (pre-GDUFA) with cutoff time as 2012-09-30 applied.

Table A.2: Sample data structure for the marginal model (6 events for each index)

Index	Drug name	Index date	Time of approval	Generic entry	Start time	Stop time	Gap time	Order of entry	# of competitors	GUDFA	Other variables
1	ACETAMINOPHEN	2013-11-02	2016-03-22	1	0	871	871	1	0	1	
1	ACETAMINOPHEN	2013-11-02	2016-06-13	1	871	954	83	2	1	1	
1	ACETAMINOPHEN	2013-11-02	-	0	954	1428	474	3	2	1	
1	ACETAMINOPHEN	2013-11-02	-	0	954	1428	474	4	3	1	
1	ACETAMINOPHEN	2013-11-02	-	0	954	1428	474	5	4	1	
1	ACETAMINOPHEN	2013-11-02	-	0	954	1428	474	6	5	1	

2	APREPITANT	2008-03-26	2012-09-24	1	0	1643	1643	1	0	0	
2	APREPITANT	2008-03-26	-	0	1643	1469*	6	2	1	0	
2	APREPITANT	2008-03-26	-	0	1643	1469*	6	3	2	0	
2	APREPITANT	2008-03-26	-	0	1643	1469*	6	4	3	0	
2	APREPITANT	2008-03-26	-	0	1643	1469*	6	5	4	0	
2	APREPITANT	2008-03-26	-	0	1643	1469*	6	6	5	0	
3	TRIUMEQ	2016-09-28	-	0	0	366	366	1	0	1	
3	TRIUMEQ	2016-09-28	-	0	0	366	366	2	1	1	
3	TRIUMEQ	2016-09-28	-	0	0	366	366	3	2	1	
3	TRIUMEQ	2016-09-28	-	0	0	366	366	4	3	1	
3	TRIUMEQ	2016-09-28	-	0	0	366	366	5	4	1	
3	TRIUMEQ	2016-09-28	-	0	0	366	366	6	5	1	

*: Administrative censoring (pre-GDUFA) with cutoff time as 2012-09-30 applied.

A.4. Number of generic entries by month and order

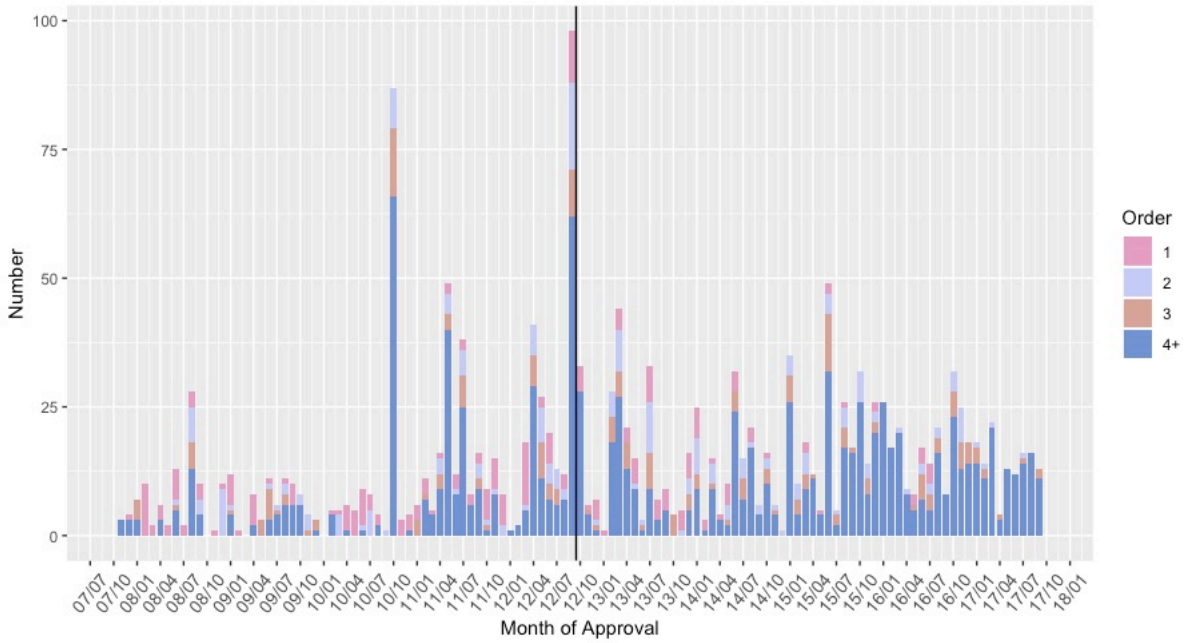

Figure A.1: Number of Generic Entry by Month and Order (With PC).

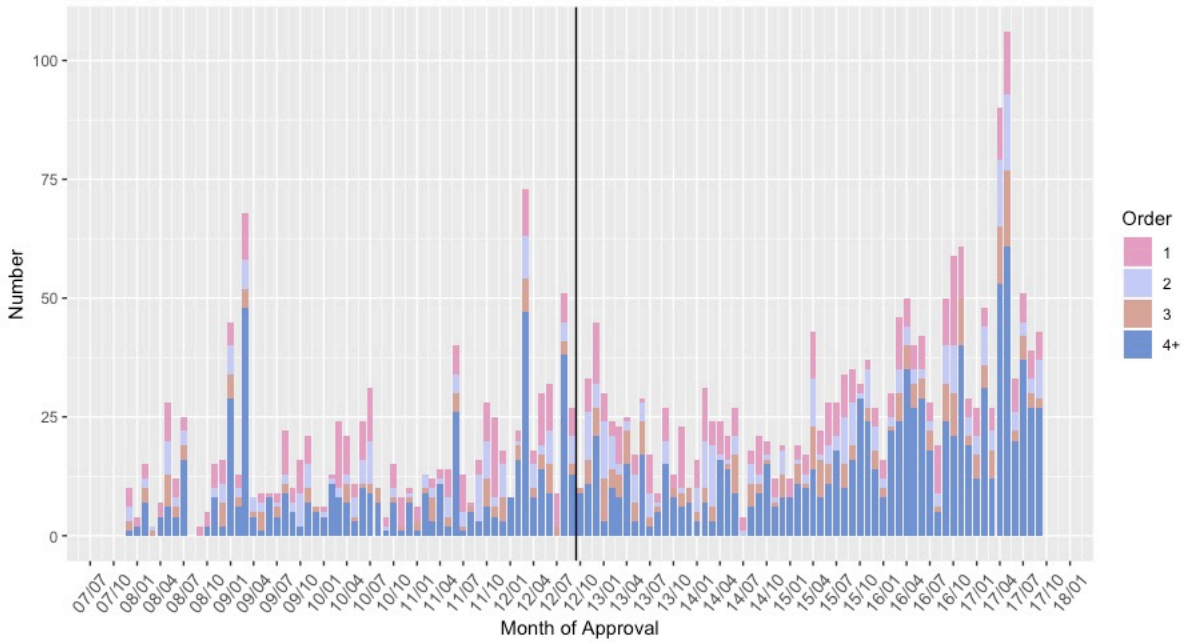

Figure A.2: Number of Generic Entry by Month and Order (Without PC).

A.5. Sensitivity analyses for the "With PC" group

Table A.3: Sensitivity analyses for the "With PC" group

Scenarios	Model		Effect of GDUFA For each stratum (# of generic competitors upon entry)					
			0 β_0	1 β_1	2 β_2	3 β_3	4 β_4	5 β_5
1) Base case	With PC (n = 897)	Conditional-TT	-	0.54** (0.39, 0.76)	1.50* (1.02, 2.22)	1.26 (0.79, 2.02)	1.25 (0.81, 1.92)	1.63 (0.96, 2.75)
		Conditional-GT	-	0.44** (0.31, 0.63)	1.43 (1.05, 1.96)	1.12 (0.77, 1.61)	1.21 (0.85, 1.74)	1.28 (0.85, 1.93)
2) Conditional frailty model	With PC (n = 897)	Conditional-TT	-	0.38** (0.22, 0.64)	1.25 (0.78, 2.00)	0.99 (0.60, 1.64)	1.02 (0.61, 1.72)	1.70 (0.95, 3.07)
		Conditional-GT	-	0.33** (0.19, 0.59)	1.29 (0.82, 2.00)	0.98 (0.61, 1.59)	1.00 (0.61, 1.65)	1.09 (0.64, 1.87)
3) Marginal model	With PC (n = 1185)	Marginal (TT)	-	0.52** (0.33, 0.83)	1.29* (1.06, 1.58)	1.13 (0.86, 1.50)	1.05 (0.76, 1,47)	0.93 (0.65, 1.34)
3) Control for impact of ACA	With PC (n = 897)	Conditional-TT	-	0.63* (0.43, 0.93)	1.54* (1.05, 2.26)	1.30 (0.82, 2.07)	1.33 (0.87, 2.02)	1.71* (1.02, 2.86)
		Conditional-GT	-	0.60* (0.40, 0.89)	1.56** (1.13, 2.14)	1.23 (0.85, 1.76)	1.36 (0.96, 1.95)	1.45 (0.98, 2.15)
4) Subgroup with multiple drugs challenged the patent	With PC (n =169)	Conditional-TT	-	0.84** (0.22, 0.69)	2.43* (1.18, 5.00)	6.32** (1.96, 20.42)	10^-8**	1.71** (3.79, 76.92)
		Conditional-GT	-	0.33** (0.17, 0.65)	2.71** (1.31, 5.57)	4.79** (1.71, 13.41)	3.17* (1.03, 0.98)	3.43* (1.01, 1.17)

*: p value less than 0.05

**: p-value less than 0.01

The negative impact of GDUFA on the second generics is present in all models. Some models including the Conditional-TT and the marginal model found a slightly significant and positive impact of GDUFA on the third entrant. Insignificant effects are present for the successive entrants. Based on feedback from the American Society of Health Economists (ASHEcon) Conference, we also examined a special case when multiple generics successfully challenged the patent and shared the 180-day exclusivity time. However, due to the limited number of observations, the results are different compared to the other scenarios.

A.6. Sensitivity analyses for the "Without PC" group

Table A.4: Sensitivity analyses for the "Without PC" group

Scenarios	Model		Effect of GDUFA For each stratum (# of generic competitors upon entry)					
			0 β_0	1 β_1	2 β_2	3 β_3	4 β_4	5 β_5
1) Base case	Without PC (n = 1252)	Conditional-TT	1.04 (0.55, 1.95)	0.38** (0.19, 0.78)	1.44 (0.65, 3.22)	0.48 (0.19, 1.24)	0.37 (0.56, 2.45)	0.43 (0.05, 4.04)
		Conditional-GT	0.97 (0.49, 1.92)	0.37** (0.20, 0.65)	0.80 (0.44, 1.44)	0.41* (0.18, 0.89)	0.47 (0.17, 1.33)	0.71 (0.24, 2.09)
2) Conditional frailty model	Without PC (n = 1252)	Conditional-TT	0.76 (0.37, 1.55)	0.51 (0.25, 1.02)	2.03 (0.83, 4.97)	0.40 (0.15, 1.05)	0.51 (0.09, 2.84)	0.47 (0.06, 3.94)
		Conditional-GT	0.95 (0.49, 1.84)	0.53* (0.28, 0.99)	0.87 (0.44, 1.72)	0.49 (0.21, 1.11)	0.58 (0.21, 1.60)	0.87 (0.28, 2.68)
3) Marginal model	Without PC (n = 5232)	Marginal (TT)	1.38 (0.46, 4.17)	0.63** (0.48, 0.83)	0.68* (0.47, 0.99)	0.56* (0.33, 0.95)	0.33** (0.17, 0.65)	0.42* (0.21, 0.85)
4) Use latest patent expiration dates	Without PC (n = 1498)	Conditional-TT	0.62* (0.41, 0.94)	0.58* (0.36, 0.93)	0.39** (0.22, 0.70)	0.92 (0.43, 1.94)	0.98 (0.27, 3.58)	1.47 (0.25, 8.72)
		Conditional-GT	0.57** (0.39, 0.83)	0.51** (0.34, 0.77)	0.48** (0.31, 0.75)	0.63 (0.37, 1.07)	0.75 (0.41, 1.35)	0.28** (0.13, 0.62)
5) Use first entrants' approval date as the index date	Without PC (n = 2196)	Conditional-GT	-	0.48** (0.39, 0.59)	1.24 (0.95, 1.61)	0.92 (0.67, 1.26)	0.87 (0.62, 1.23)	0.72 (0.49, 1.05)
4) Control for impact of ACA	Without PC (n = 1252)	Conditional-TT	0.96 (0.52, 1.75)	0.26** (0.12, 0.57)	0.96 (0.41, 2.26)	0.29* (0.11, 0.76)	0.29 (0.04, 2.00)	0.34 (0.03, 3.42)
		Conditional-GT	0.87 (0.45, 1.70)	0.25** (0.12, 0.50)	0.53 (0.26, 1.09)	0.26** (0.10, 0,64)	0.33 (0.11, 1.03)	0.53 (0.17, 1.60)

*: p value less than 0.05

**: p-value less than 0.01

Using the latest patent rather than the earliest one does not change the main conclusions. Since for some branded drugs, their patent information is not available in our dataset, we also used the first entrants' approval date as the index date, as it is available in the OB. For this scenario, the model is similar to the "With PC" case, where we only examined second entrants and beyond. We were able to capture more drugs that were previously being excluded due to the missing index date. Since we used the 1st entrants' approval date as the index date, a TT model is not so meaningful. Instead, we only examined the GT model here. Again, a slower time-to-entry for the second entrant since the 1st entrant's entry date is found post-GDUFA.

A.7. Post-GDUFA trend in time-to-entry

Since our main analysis is a pre-post analysis for a policy that is has a 5-year duration, it may not capture changes in time-to-entry post-GDUFA. Thus, we applied a 2-year censoring window for drugs with index dates in each 1-year window. In specific, for index dates between October 1st, 2012 and September 30th, 2013 (denoted as group "12/13"), every generic drug is censored on September 30th, 2014. While if the index date is between October 1st, 2013 and September 30th, 2014 (denoted as group "13/14"), censoring is applied on September 30th, 2015. In total, there are four groups, namely "12/13", "13/14", "14/15", and "15/16". Then, for each order of entry, we could compare the time-to-entry for different time groups to examine whether there is a trend over time. Using second entrants as an example, we plotted the K-M curves for four groups in both the "With PC" and "Without PC" scenarios. As shown in Figure A.3, for the "With PC" scenario, there is a quicker time-to-entry for the "15/16" group compared to the previous years. For the "Without PC" scenario (see Figure A.4), sharper K-M curves for year 2014 through 2015 and 2015 through 2016 suggests a potential speed up in entry post-GDUFA.

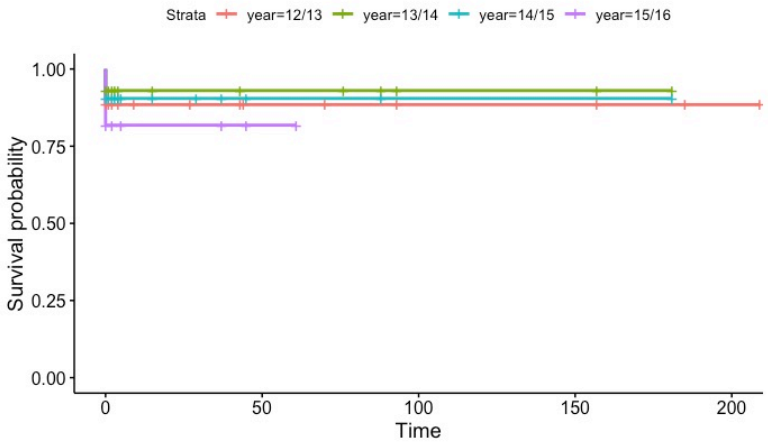

Figure A.3. Time-to-Entry for Second Entrants, with PC.

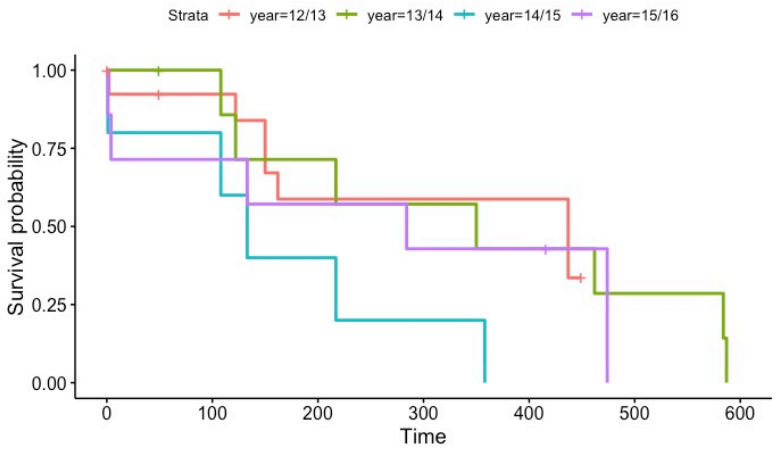

Figure A.4. Time-to-Entry for Second Entrants, without PC.

A.8. Technical appendix of detailed regression results

PWP-GT for PC

```
coxph(formula = Surv(genericPIV$gaptime_start, genericPIV$gaptime,
    entry2) ~ GDUFA + strata(ncompetitor) + route + AG + guidance_before +
    indexyear + ATCA + ATCB + ATCC + ATCD + ATCG + ATCH + ATCL +
    ATCM + ATCN + ATCP + ATCR + ATCS + ATCV + GDUFA:strata(ncompetitor),
    data = genericPIV, method = "breslow", cluster = index)

  n= 897, number of events= 763
   (68 observations deleted due to missingness)
```

	coef	exp(coef)	se(coef)	robust se	z	Pr(>|z|)	
GDUFA	-8.238e-01	4.388e-01	1.899e-01	1.787e-01	-4.610	4.03e-06	***
routeINJECTION	1.615e-01	1.175e+00	2.406e-01	2.096e-01	0.771	0.440926	
routeOTHER	-4.415e-01	6.431e-01	2.112e-01	1.880e-01	-2.348	0.018866	*
AG	-2.597e-01	7.713e-01	8.745e-02	8.654e-02	-3.000	0.002697	**
guidance_before	8.922e-02	1.093e+00	9.311e-02	9.263e-02	0.963	0.335423	
indexyear	1.438e-01	1.155e+00	3.212e-02	3.068e-02	4.686	2.79e-06	***
ATCA	8.303e-01	2.294e+00	2.204e-01	2.367e-01	3.508	0.000451	***
ATCB	4.314e-01	1.539e+00	4.175e-01	2.123e-01	2.032	0.042112	*
ATCC	7.573e-01	2.133e+00	1.807e-01	1.706e-01	4.439	9.03e-06	***
ATCD	5.345e-01	1.707e+00	3.549e-01	2.746e-01	1.947	0.051574	.
ATCG	4.311e-01	1.539e+00	3.467e-01	3.279e-01	1.314	0.188684	
ATCH	5.887e-01	1.802e+00	3.055e-01	1.804e-01	3.264	0.001098	**
ATCL	3.204e-01	1.378e+00	2.323e-01	2.108e-01	1.520	0.128536	
ATCM	1.303e+00	3.680e+00	2.617e-01	2.401e-01	5.426	5.76e-08	***
ATCN	4.991e-01	1.647e+00	1.800e-01	1.608e-01	3.103	0.001915	**
ATCP	-1.453e+01	4.873e-07	9.985e+02	1.017e+00	-14.293	< 2e-16	***
ATCR	5.022e-02	1.052e+00	5.152e-01	2.544e-01	0.197	0.843510	
ATCS	6.625e-01	1.940e+00	4.967e-01	4.884e-01	1.357	0.174895	

```
ATCV                                -3.590e-01  6.984e-01  7.375e-01  9.562e-01  -0.375 0.707321
GDUFA:strata(ncompetitor)ncompetitor=2  3.584e-01  1.431e+00  2.075e-01  1.603e-01   2.236
0.025355 *
GDUFA:strata(ncompetitor)ncompetitor=3  1.085e-01  1.115e+00  2.203e-01  1.863e-01   0.582
0.560387
GDUFA:strata(ncompetitor)ncompetitor=4  1.927e-01  1.213e+00  2.352e-01  1.836e-01   1.050
0.293833
GDUFA:strata(ncompetitor)ncompetitor=5  2.448e-01  1.277e+00  2.521e-01  2.095e-01   1.169
0.242465
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

                          exp(coef) exp(-coef) lower .95 upper .95
GDUFA                      4.388e-01  2.279e+00 3.091e-01 6.228e-01
routeINJECTION             1.175e+00  8.509e-01 7.794e-01 1.772e+00
routeOTHER                 6.431e-01  1.555e+00 4.448e-01 9.296e-01
AG                         7.713e-01  1.296e+00 6.510e-01 9.139e-01
guidance_before            1.093e+00  9.146e-01 9.118e-01 1.311e+00
indexyear                  1.155e+00  8.661e-01 1.087e+00 1.226e+00
ATCA                       2.294e+00  4.359e-01 1.443e+00 3.648e+00
ATCB                       1.539e+00  6.496e-01 1.015e+00 2.334e+00
ATCC                       2.133e+00  4.689e-01 1.526e+00 2.979e+00
ATCD                       1.707e+00  5.860e-01 9.964e-01 2.923e+00
ATCG                       1.539e+00  6.498e-01 8.092e-01 2.927e+00
ATCH                       1.802e+00  5.550e-01 1.265e+00 2.566e+00
ATCL                       1.378e+00  7.258e-01 9.114e-01 2.083e+00
ATCM                       3.680e+00  2.718e-01 2.298e+00 5.891e+00
ATCN                       1.647e+00  6.071e-01 1.202e+00 2.258e+00
ATCP                       4.873e-07  2.052e+06 6.641e-08 3.576e-06
ATCR                       1.052e+00  9.510e-01 6.386e-01 1.731e+00
ATCS                       1.940e+00  5.156e-01 7.448e-01 5.051e+00
```

ATCV 6.984e-01 1.432e+00 1.072e-01 4.550e+00
GDUFA:strata(ncompetitor)ncompetitor=2 1.431e+00 6.988e-01 1.045e+00 1.959e+00
GDUFA:strata(ncompetitor)ncompetitor=3 1.115e+00 8.972e-01 7.737e-01 1.606e+00
GDUFA:strata(ncompetitor)ncompetitor=4 1.213e+00 8.247e-01 8.461e-01 1.738e+00
GDUFA:strata(ncompetitor)ncompetitor=5 1.277e+00 7.828e-01 8.473e-01 1.926e+00

Concordance= 0.698 (se = 0.017)
Likelihood ratio test= 95.26 on 23 df, p=9e-11
Wald test = 391.8 on 23 df, p=<2e-16
Score (logrank) test = 88.76 on 23 df, p=1e-09, Robust = 70.13 p=1e-06

(Note: the likelihood ratio and score tests assume independence of
observations within a cluster, the Wald and robust score tests do not).

PWP-GT for no PC

coxph(formula = Surv(genericnoPIV$gaptime_start, gaptime, entry1) ~
GDUFA + strata(ncompetitor) + route + AG + ETASU + guidance_before +
indexyear + ATCA + ATCB + ATCC + ATCD + ATCG + ATCH +
ATCL + ATCM + ATCN + ATCP + ATCR + ATCS + ATCV + GDUFA:strata(ncompetitor),
data = genericnoPIV, method = "breslow", cluster = index)

n= 1252, number of events= 403
(293 observations deleted due to missingness)

	coef	exp(coef)	se(coef)	robust se	z	Pr(>|z|)	
GDUFA	-3.058e-02	9.699e-01	2.807e-01	3.473e-01	-0.088	0.92983	
routeINJECTION	3.773e-01	1.458e+00	2.773e-01	3.766e-01	1.002	0.31640	
routeOTHER	-8.213e-01	4.399e-01	2.373e-01	3.317e-01	-2.476	0.01328	*
AG	-1.669e-01	8.463e-01	1.327e-01	1.616e-01	-1.033	0.30171	
ETASU1	-2.753e+00	6.377e-02	1.007e+00	9.697e-01	-2.839	0.00453	**
guidance_before	6.902e-01	1.994e+00	1.292e-01	1.497e-01	4.609	4.04e-06	***

indexyear	4.279e-02	1.044e+00	4.695e-02	6.537e-02	0.655	0.51270
ATCA	-7.687e-01	4.636e-01	2.903e-01	3.433e-01	-2.240	0.02512 *
ATCB	-7.310e-01	4.814e-01	4.866e-01	3.715e-01	-1.967	0.04914 *
ATCC	-1.641e-02	9.837e-01	2.339e-01	2.486e-01	-0.066	0.94735
ATCD	-1.683e-01	8.451e-01	4.780e-01	4.817e-01	-0.349	0.72673
ATCG	-7.171e-01	4.882e-01	3.431e-01	3.033e-01	-2.364	0.01806 *
ATCH	6.195e-02	1.064e+00	4.982e-01	4.722e-01	0.131	0.89563
ATCL	-6.316e-01	5.318e-01	3.172e-01	4.632e-01	-1.364	0.17272
ATCM	-5.084e-01	6.015e-01	3.991e-01	4.491e-01	-1.132	0.25765
ATCN	2.775e-01	1.320e+00	1.930e-01	2.603e-01	1.066	0.28633
ATCP	3.246e-01	1.383e+00	6.156e-01	4.307e-01	0.754	0.45104
ATCR	-2.070e-01	8.130e-01	4.642e-01	4.555e-01	-0.455	0.64945
ATCS	-4.857e-01	6.153e-01	7.468e-01	9.503e-01	-0.511	0.60928
ATCV	-1.587e+01	1.284e-07	1.229e+03	3.728e-01	-42.568	< 2e-16 ***
GDUFA:strata(ncompetitor)ncompetitor=1	-1.006e+00	3.655e-01	2.886e-01	2.973e-01	-3.386	0.00071 ***
GDUFA:strata(ncompetitor)ncompetitor=2	-2.274e-01	7.966e-01	3.097e-01	3.010e-01	-0.755	0.44998
GDUFA:strata(ncompetitor)ncompetitor=3	-9.023e-01	4.056e-01	3.856e-01	4.027e-01	-2.240	0.02507 *
GDUFA:strata(ncompetitor)ncompetitor=4	-7.560e-01	4.695e-01	4.828e-01	5.301e-01	-1.426	0.15386
GDUFA:strata(ncompetitor)ncompetitor=5	-3.442e-01	7.088e-01	5.297e-01	5.526e-01	-0.623	0.53334

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

	exp(coef)	exp(-coef)	lower .95	upper .95
GDUFA	9.699e-01	1.031e+00	4.910e-01	1.916e+00
routeINJECTION	1.458e+00	6.857e-01	6.971e-01	3.051e+00
routeOTHER	4.399e-01	2.273e+00	2.296e-01	8.426e-01

AG	8.463e-01	1.182e+00	6.166e-01	1.162e+00
ETASU1	6.377e-02	1.568e+01	9.533e-03	4.265e-01
guidance_before	1.994e+00	5.015e-01	1.487e+00	2.674e+00
indexyear	1.044e+00	9.581e-01	9.182e-01	1.186e+00
ATCA	4.636e-01	2.157e+00	2.366e-01	9.085e-01
ATCB	4.814e-01	2.077e+00	2.324e-01	9.972e-01
ATCC	9.837e-01	1.017e+00	6.044e-01	1.601e+00
ATCD	8.451e-01	1.183e+00	3.288e-01	2.172e+00
ATCG	4.882e-01	2.048e+00	2.694e-01	8.846e-01
ATCH	1.064e+00	9.399e-01	4.217e-01	2.684e+00
ATCL	5.318e-01	1.881e+00	2.145e-01	1.318e+00
ATCM	6.015e-01	1.663e+00	2.494e-01	1.450e+00
ATCN	1.320e+00	7.577e-01	7.924e-01	2.198e+00
ATCP	1.383e+00	7.228e-01	5.948e-01	3.218e+00
ATCR	8.130e-01	1.230e+00	3.330e-01	1.985e+00
ATCS	6.153e-01	1.625e+00	9.554e-02	3.962e+00
ATCV	1.284e-07	7.791e+06	6.182e-08	2.665e-07
GDUFA:strata(ncompetitor)ncompetitor=1	3.655e-01	2.736e+00	2.041e-01	6.546e-01
GDUFA:strata(ncompetitor)ncompetitor=2	7.966e-01	1.255e+00	4.416e-01	1.437e+00
GDUFA:strata(ncompetitor)ncompetitor=3	4.056e-01	2.465e+00	1.842e-01	8.932e-01
GDUFA:strata(ncompetitor)ncompetitor=4	4.695e-01	2.130e+00	1.661e-01	1.327e+00
GDUFA:strata(ncompetitor)ncompetitor=5	7.088e-01	1.411e+00	2.400e-01	2.093e+00

Concordance= 0.755 (se = 0.015)
Likelihood ratio test= 161 on 25 df, p=<2e-16
Wald test = 3052 on 25 df, p=<2e-16
Score (logrank) test = 151.8 on 25 df, p=<2e-16, Robust = 127.9 p=9e-16

(Note: the likelihood ratio and score tests assume independence of
observations within a cluster, the Wald and robust score tests do not).

APPENDIX B

B.1. Search criteria

The specific question for the search is: **In the US, how do the number of generic drugs entered after patent expiration affects drug price (relative and absolute), market share, and drug utilization?** Literature search in PubMed, EMBASE, EconLit, Business Source Open, NBER (only the top 100), and Google Scholar (only the top 100) were conducted. Search strategy was finalized after consultation with a UW librarian (Diana Louden). Below are the database-specific search terms, additional requirements, time of search, and the total number of results identified.

1. PubMed

Search terms:

("Economics"[Mesh] OR "economics" [Subheading]) AND (“generic drug” OR generic OR generics OR "branded drug" OR "brand-name drug" OR originator) AND (drug OR medicine OR pharmaceutical*) AND (patent OR patents OR off-patent OR entry OR entries OR entrant* OR substitut* OR “market exclusivity” OR expiration OR expiry) AND (cost OR costs OR price OR prices OR pricing OR "mark up" OR markup* OR paradox OR rigidity OR "generic to branded" OR penetrat* OR segment* OR erosion OR saturation OR “drug volume” OR demand OR sales OR output OR dynamic* OR manufactur* OR competiti* OR sellers OR market*) NOT (("Asia"[mesh] OR "africa"[mesh] OR "south America"[mesh] OR "central America"[mesh] OR "Caribbean Region"[Mesh] OR "oceania"[mesh] OR "Europe"[mesh] OR

"Canada"[mesh] OR "Mexico"[mesh]) NOT ("United States"[mesh])) NOT(“case study”) AND (number OR order OR count)

Additional requirements:

- English only
- Year 1984 and forward

Exported as RIS

Date of search: 2019/09/19

85 items found

2. EconLit + Business Source Complete

Access through UW library

Search terms:

(“generic drug” OR generic OR generics OR “branded drug” OR “brand-name drug” OR originator) AND (drug OR medicine OR pharmaceutical) AND (patent OR patents OR off-patent OR entry OR entries OR entrant OR substitut* OR “market exclusivity” OR expiration OR expiry) AND (cost OR costs OR price OR prices OR pricing OR “mark up” OR markup OR paradox OR rigidity OR generic to branded OR penetrat* OR segment* OR erosion OR saturation OR “drug volume” OR demand OR sales OR output OR dynamic* OR manufactur* OR competiti* OR sellers OR market*) AND (“United States” OR US) AND (number OR order OR count)

Additional requirements:

- English only
- Year 1984 and forward

- Expanders: apply equivalent subjects
- Search modes: Boolean/phrase

Exported as RIS

Date of search: 2019/09/19

102 items found (96 after excluding duplicates)

3. NBER

Full text search for working papers

Search terms:

(“generic drug” OR generic OR generics OR “branded drug” OR “brand-name drug” OR originator) AND (drug OR medicine OR pharmaceutical) AND (patent OR patents OR off-patent OR entry OR entries OR entrant OR substitut* OR “market exclusivity” OR expiration OR expiry) AND (cost OR costs OR price OR prices OR pricing OR “mark up” OR markup OR paradox OR rigidity OR generic to branded OR penetrat* OR segment* OR erosion OR saturation OR “drug volume” OR demand OR sales OR output OR dynamic* OR manufactur* OR competiti* OR sellers OR market*) AND (“United States” OR US) AND (number OR order OR count)

Additional requirements:

- Check top 100
- **Search what kinds of research output:** Working Papers; Books; Research Projects; Conferences and meetings

Date of search: 2019/09/30

4. EMBASE:

Access through UW library

Sources: Embase, MEDLINE

Search terms:

Query('economics'/exp OR 'economics') AND ('generic drug'/exp OR 'generic drug' OR generic OR generics OR 'branded drug'/exp OR 'branded drug' OR 'brand-name drug' OR originator) AND (drug OR medicine OR pharmaceutical*) AND (patent OR patents OR 'off patent' OR entry OR entries OR entrant* OR substitut* OR 'market exclusivity' OR expiration OR expiry) AND (cost OR costs OR price OR prices OR pricing OR 'mark up' OR markup* OR paradox OR rigidity OR 'generic to branded' OR penetrat* OR segment* OR erosion OR saturation OR 'drug volume' OR demand OR sales OR output OR dynamic* OR manufactur* OR competiti* OR sellers OR market*) AND 'united states' AND (number OR order OR count)

Additional requirements:

- Year 1984 and forward

Exported as RIS

Date of search: 2019/09/19

68 items found

5. Google Scholar:

Search terms:

Economics AND (generic drug OR generics) AND entry AND (number OR order OR count) AND (Price OR market share OR utilization OR market size)

Additional requirements:

- English only
- Year 1984 and forward
- Include top 100 search results

Exported as RIS not possible (EndNote or csv, did not provide abstract)

Date of search: 2019/11/08

B.2. Summary of Studies Regarding How Generic Drug Price was Modeled

Study	Model	Price	Variables included in the model	Model	IV	FE/RE	Estimated regression coefficients	SE
Dafny (2016)	1	Average revenue per prescription (upper bound for true price)	N, t (time since LOE), coupon, t*coupon, refill percentage, ln(previous branded price)	OLS	-	-	-0.094	0.008
Frank (1997)	1	Sum of generic sales divided by generic volume	N, ln(branded price), t	2SLS	sales prior to generic entry, market age, time off patent	time and drug FE	-0.097	0.0375969
Grabowski (2007)	1	NA (used IMS data, likely sales price used)	N	OLS	-	Class FE	-0.09	0.01
Helland (2016)	1	Total expenditures divided by the number of units purchased	N, warning label indicators, adverse event counts, the potential market proxy, the number of competitor molecules in the therapeutic class,	OLS	-	time and class FE	-0.053	0.009

			the time remaining on exclusivity					
	2	Total expenditures divided by the number of units purchased	N, warning label indicators, adverse event counts, the potential market proxy, the number of competitor molecules in the therapeutic class, the time remaining on exclusivity	2SLS	headquarter, adjusted # of patent citations	time and class FE	-0.108	0.031
Regan (2008)	1		N, t, number of other generic drugs, Medicaid share of generics, third-party share of generics, average percentage change in real branded revenue pre-entry	OLS	-	RE	0.0023	0.0018
	2		N, t, number of other generic drugs, Medicaid share of generics, third-party share of generics	2SLS	revenue pre patent expiration	FE	-0.0012	0.0039

B.3. Summary of Studies Regarding How Branded Drug Price was Modeled

Study	Model	Price	Variables included in the model	Model	IV	FE/RE	Estimated regression coefficients	SE
Dafny (2016)	1	Average revenue per prescription (upper bound for true price)	N, t (time since LOE), coupon, t*coupon, refill percentage, ln(previous branded price)	OLS	-	-	0.012	0.006

Frank (1997)	1	Sum of sales divided by volume	N	OLS	-	time and drug FE	0.007	0.00311111
	2		N	2SLS	sales prior to generic entry, market age, time off patent	time and drug FE	0.016	0.0040404
Regan (2008)	1		N, t, number of other substition branded drugs, number of other substition generic drugs, number of oral solid presentations, Medicaid share of branded, third-party share of branded	OLS	-	RE	0.0104	0.0017
	2		N, t, number of other substition drugs, Medicaid share of branded, third-party share of branded	2SLS	revenue pre patent expiration	RE	0.0199	0.0033

B.4. Distribution of different generic entrants

In order to simulate the proportion of different order of entrants, we first used OB data to fit a negative binomial distribution (see graphs below, for different years). As illustrated, the distribution fits data well.

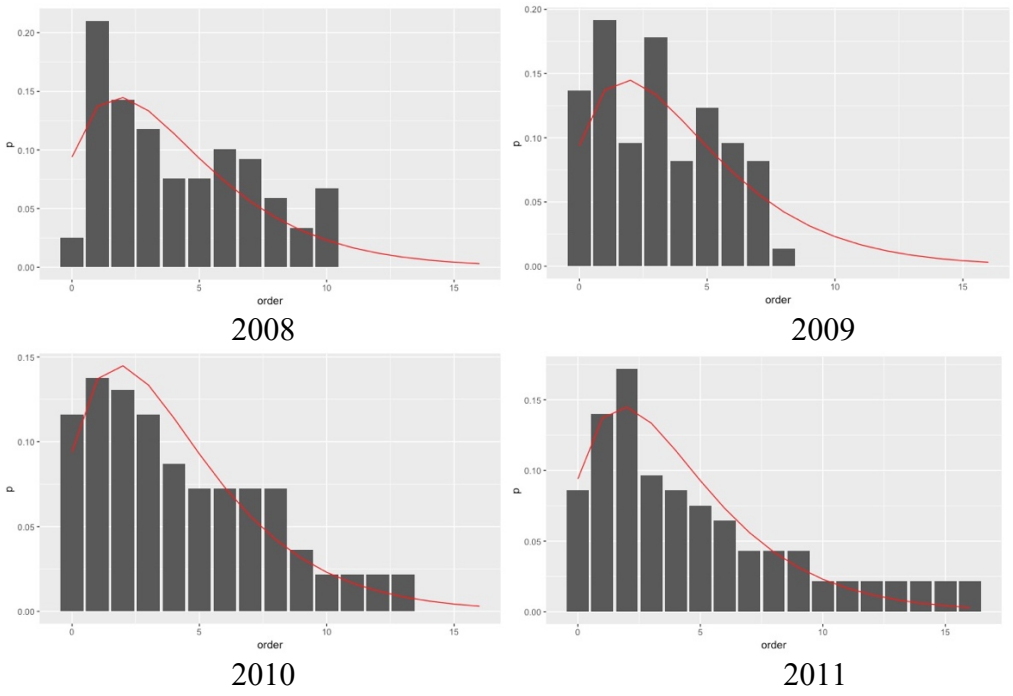

Table B.4: Summary of the distribution of the number of generics, from OB

	2008	2009	2010	2011	2012	2013
mean	4.23	3.12	4.30	4.87	4.63	3.56
variance	8.52	5.25	11.80	18.14	11.37	6.19
Fitted using NB2						
Dispersion	3.66	3.44	2.00	1.69	2.65	4.56
1/sqrt(dispersion)	0.523	0.539	0.707	0.769	0.614	0.468

1/sqrt(dispersion) has mean 0.60 and standard deviation 0.12. Therefore, we used NB(mean = 0.60, variance = 0.01) for the simulated distribution of different order of entrants.

B.5. NDC conversion

FDA NDC code is in 10-digit, and MEPS NDC code is in 11-digit. In order to map MEPS data to FDA NDC and therefore FDA OB, we converted the FDA NDC code to 11-digit, using the rule below [96].

09999-9999-99

99999-**0**999-99

99999-9999-**0**9

Using the 11-digit NDC to map, only 20% to 30% of the unique drugs in MEPS can be linked to FDA NDC. We dropped the last two digits (package code/size) and reconducted the mapping, which resulted in increased matching (35% to 45% of the unique drugs in MEPS can be matched). Over time, we see an increase in the proportion of drugs that can be matched.

B.7. Change in sample size

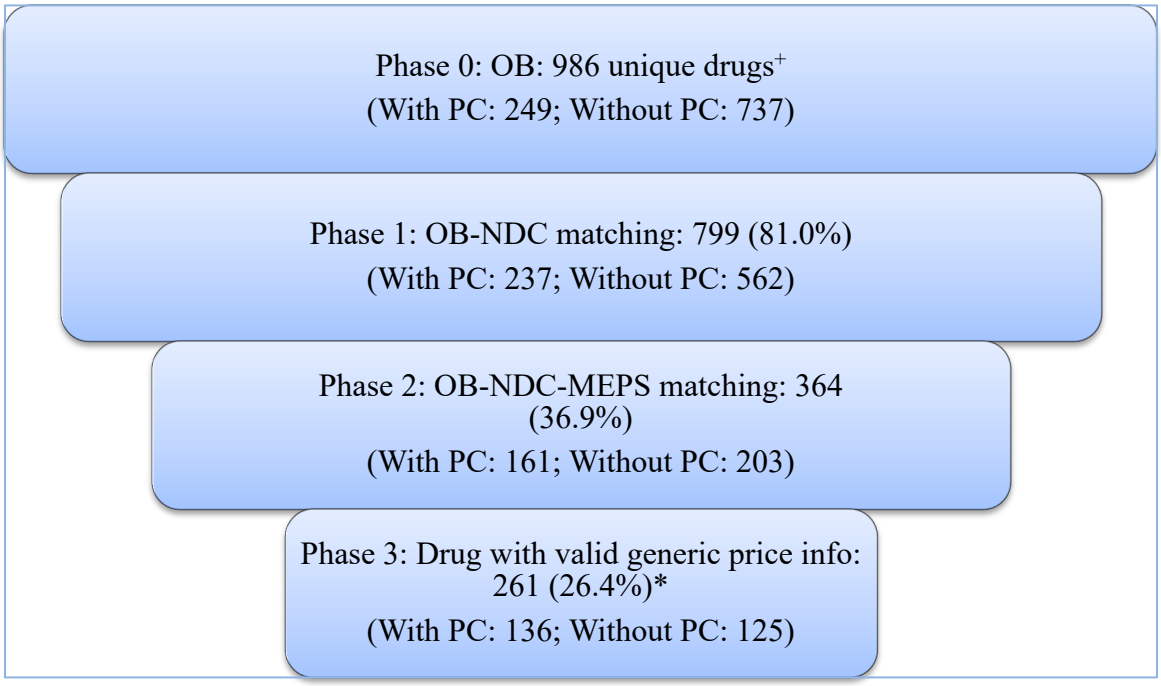

Figure B. Flow Diagram of Sample Size Change in Different Phases

Note:

+: Each unique drug represent a unique molecule-route-strength(dose) combination.

*Compared to the regression, for model fitting in Chapter 3, this count further decreased if we miss branded drug price prior to loss of exclusivity, or assigned all observations to the test set (thus the drug would be excluded).

In Phase 1, we first linked OB to FDA NDC. Since the NDC dataset does not provide product number (the identifier for different route/strength for drugs with the same ANDA number), while there is a great inconsistency in how drug strength was coded between two datasets, we have 81.0% (799/986) of the unique drugs left. We denote this subset the OB-NDC dataset.

Next, in Phase 2, we linked NDC code in MEPS with OB-NDC. A bigger sample size reduction occurred due to failure to match NDC code. Only 45.6% (364/799) of the unique drugs in OB-NDC can be matched to NDC in MEPS, even after adding historical FDA NDC code, excluded NDC code, and the "NDC universe" constructed from NBER data archive [95].

In Phase 3, drugs in MEPS that do not have at least one observation of generic drug price and branded drug price before generic entry were further excluded. The missingness in Phase 2 also lead to more drugs being excluded (e.g. if only branded drug NDC can be matched, but not the generic version, then this drug would be dropped). There are also cases of missing branded drug information in OB (see the screenshot below). As illustrated, only generics but not the corresponding branded drug information were documented in OB. OB only reports an updated "evergreen" version of the branded drug with a different route. Drugs like this were also dropped.

RX	TRAMADOL HYDROCHLORIDE	CONZIP	N022370	CAPSULE, EXTENDED RELEASE	ORAL	300MG		RLD		CIPHER PHARMACEUTICALS INC
RX	TRAMADOL HYDROCHLORIDE	TRAMADOL HYDROCHLORIDE	A200503	TABLET, EXTENDED RELEASE	ORAL	300MG	AB1			LUPIN LTD
RX	TRAMADOL HYDROCHLORIDE	TRAMADOL HYDROCHLORIDE	A205257	TABLET, EXTENDED RELEASE	ORAL	300MG	AB1			MYLAN PHARMACEUTICALS INC
RX	TRAMADOL HYDROCHLORIDE	TRAMADOL HYDROCHLORIDE	A201384	TABLET, EXTENDED RELEASE	ORAL	300MG	AB1			SUN PHARMACEUTICAL INDUSTRIES LTD
RX	TRAMADOL HYDROCHLORIDE	TRAMADOL HYDROCHLORIDE	A091609	TABLET, EXTENDED RELEASE	ORAL	300MG	AB2			ACTAVIS ELIZABETH LLC
RX	TRAMADOL HYDROCHLORIDE	TRAMADOL HYDROCHLORIDE	A200491	TABLET, EXTENDED RELEASE	ORAL	300MG	AB2			ANCHEN PHARMACEUTICALS INC
RX	TRAMADOL HYDROCHLORIDE	TRAMADOL HYDROCHLORIDE	A091607	TABLET, EXTENDED RELEASE	ORAL	300MG	AB2			SUN PHARMACEUTICAL INDUSTRIES LTD

B.8. Model results using varying-intercept, varying-slope (N only) regression model

Model	Prior for N	Beta-coefficient in Training	% of test data covered by 95% CI
Generic drug price, log-transformed	Non-informative	-0.06802 [-0.08901, -0.04741]	93.6%
	From BMA (base)	-0.07061 [-0.08922, -0.05254]	93.4%
	From BMA (bias corrected)	-0.06889 [-0.08965, -0.04828]	93.1%
Branded drug price, log-transformed	Non-informative	-0.04754 [-0.07462, -0.02130]	94.1%
	From BMA (base)	0.00355 [-0.00580, 0.01289]	93.9%
	From BMA (bias corrected)	-0.02582 [-0.04822, -0.00355]	94.1%
Generic drug market share	Non-informative	0.03312 [0.02487, 0.04227]	93.4%
Total utilization (generic + branded), log-transformed	Non-informative	0.07778 [0.03238, 0.12388]	94.8%

B.9. Model results using varying-intercept, varying-slope (all covariates) regression model

Model	Prior for N	Beta-coefficient in Training	% of test data covered by 95% CI
Generic drug price, log-transformed	Non-informative	-0.07995 [-0.09893, -0.06147]	92.4%
	From BMA (base)	-0.07994 [-0.09700, -0.06305]	92.9%
	From BMA (bias corrected)	-0.08060 [-0.09886, -0.06215]	92.8%
Branded drug price, log-transformed	Non-informative	-0.04718 [-0.07142, -0.02307]	94.1%
	From BMA (base)	0.00257 [-0.00684, 0.01202]	93.7%
	From BMA (bias corrected)	-0.02877 [-0.04894, -0.00825]	93.8%
Generic drug market share	Non-informative	0.03335 [0.02598, 0.04128]	93.1%
Total utilization (generic + branded), log-transformed	Non-informative	0.07414 [0.03078, 0.11879]	93.6%

B.10. Sensitivity analyses results using the varying-intercept model

Model	Prior for N	Beta-coefficient in Training	% of test data covered by 95% CI
Generic drug price, log-transformed; Controlling for routes	Non-informative	-0.06701 [-0.08763, -0.04599]	88.2%
	From BMA (base)	-0.06683 [-0.08788, -0.04580]	88.2%
	From BMA (bias corrected)	-0.06793 [-0.08876, -0.04716]	87.9%
Generic drug price, log-transformed; Controlling for ATC level 1	Non-informative	-0.05778 [-0.07919, -0.03601]	89.1%
	From BMA (base)	-0.05780 [-0.07927, -0.03616]	89.4%
	From BMA (bias corrected)	-0.05913 [-0.08011, -0.03827]	89.2%
Generic drug price, log-transformed; Controlling for AG	Non-informative	-0.06584 [-0.08539, -0.04539]	88.2%
	From BMA (base)	-0.06589 [-0.08631, -0.04536]	88.0%
	From BMA (bias corrected)	-0.06659 [-0.08624, -0.04665]	87.9%
Generic drug price, log-transformed; Using molecule rather than molecule-route-strength as the unit of analysis	Non-informative	-0.05255 [-0.07424, -0.03057]	89.1%
	From BMA (base)	-0.05280 [-0.07464, -0.03107]	89.1%
	From BMA (bias corrected)	-0.05410 [-0.07613, -0.03264]	89.2%

B.11. Regression Results on the training set

1) Log-transformed generic price (varying intercept model)

Family: gaussian

Links: mu = identity; sigma = identity

Formula: Y ~ competitor + t_LOE + P_b_prior_LOE + (1 | index)

autocor ~ tructure(list(), class = "formula", .Environment = <environment>)

Data: generic_price_train (Number of observations: 659)

Samples: 4 chains, each with iter = 6000; warmup = 1000; thin = 1;

total post-warmup samples = 20000

Group-Level Effects:

~index (Number of levels: 261)

	Estimate	Est.Error	l-95% CI	u-95% CI	Rhat	Bulk_ESS	Tail_ESS
sd(Intercept)	0.57948	0.04595	0.49108	0.67010	1.00071	6593	11314

Population-Level Effects:

	Estimate	Est.Error	l-95% CI	u-95% CI	Rhat	Bulk_ESS	Tail_ESS
Intercept	3.06911	0.27235	2.52811	3.59125	1.00017	14905	15125
competitor	-0.06631	0.01014	-0.08615	-0.04638	0.99999	14460	16171
t_LOE	-0.02846	0.01451	-0.05667	0.00007	1.00009	22808	17878
P_b_prior_LOE	0.41605	0.05197	0.31510	0.51885	1.00013	14535	16258

Family Specific Parameters:

	Estimate	Est.Error	l-95% CI	u-95% CI	Rhat	Bulk_ESS	Tail_ESS
sigma	0.71206	0.02509	0.66483	0.76295	1.00038	13651	15802

<u>2) Log-transformed branded price (varying intercept model)</u>

Family: gaussian

Links: mu = identity; sigma = identity

Formula: Y ~ competitor + t_LOE + P_b_prior_LOE + (1 | index)

autocor ~ tructure(list(), class = "formula", .Environment = <environment>)

Data: branded_price_train (Number of observations: 621)

Samples: 4 chains, each with iter = 6000; warmup = 1000; thin = 1;

total post-warmup samples = 20000

Group-Level Effects:

~index (Number of levels: 283)

	Estimate	Est.Error	l-95% CI	u-95% CI	Rhat	Bulk_ESS	Tail_ESS
sd(Intercept)	0.57472	0.05140	0.47519	0.67608	1.00028	6770	12191

Population-Level Effects:

	Estimate	Est.Error	l-95% CI	u-95% CI	Rhat	Bulk_ESS	Tail_ESS
Intercept	2.81244	0.28859	2.24649	3.37928	1.00021	19660	16985
competitor	-0.04381	0.01119	-0.06601	-0.02203	1.00007	20140	16354
t_LOE	-0.00600	0.01668	-0.03882	0.02684	1.00004	27321	17179
P_b_prior_LOE	0.51026	0.05545	0.40160	0.61887	1.00015	20080	17299

Family Specific Parameters:

	Estimate	Est.Error	l-95% CI	u-95% CI	Rhat	Bulk_ESS	Tail_ESS
sigma	0.79602	0.02942	0.74072	0.85621	1.00045	11861	15087

3) Generic market share (varying intercept model)

Family: gaussian

```
  Links: mu = identity; sigma = identity
Formula: Y ~ competitor + t_LOE + P_b_prior_LOE + (1 | index)
   Data: generic_share_train (Number of observations: 441)
Samples: 4 chains, each with iter = 6000; warmup = 1000; thin = 1;
         total post-warmup samples = 20000

Group-Level Effects:
~index (Number of levels: 220)
              Estimate Est.Error l-95% CI u-95% CI    Rhat Bulk_ESS Tail_ESS
sd(Intercept)  0.16470   0.02094  0.12275  0.20544 1.00189     4404     7416

Population-Level Effects:
              Estimate Est.Error l-95% CI u-95% CI    Rhat Bulk_ESS Tail_ESS
Intercept      0.36200   0.09835  0.16694  0.55505 1.00029    14838    16185
competitor     0.03422   0.00355  0.02735  0.04131 1.00048    12675    15639
t_LOE          0.02630   0.00552  0.01559  0.03722 1.00012    22347    16708
P_b_prior_LOE -0.01695   0.01880 -0.05420  0.01995 1.00023    15080    15724

Family Specific Parameters:
      Estimate Est.Error l-95% CI u-95% CI    Rhat Bulk_ESS Tail_ESS
sigma  0.22844   0.01141  0.20748  0.25199 1.00084     6441     9619
```

4) Log-transformed total utilization (varying intercept model)

Family: gaussian

Links: mu = identity; sigma = identity

Formula: Y ~ competitor + t_LOE + P_b_prior_LOE + (1 | index)

Data: total_utilization_train (Number of observations: 441)

Samples: 4 chains, each with iter = 6000; warmup = 1000; thin = 1;

total post-warmup samples = 20000

Group-Level Effects:

~index (Number of levels: 220)

	Estimate	Est.Error	l-95% CI	u-95% CI	Rhat	Bulk_ESS	Tail_ESS
sd(Intercept)	1.24478	0.07161	1.11283	1.39191	1.00109	3957	6533

Population-Level Effects:

	Estimate	Est.Error	l-95% CI	u-95% CI	Rhat	Bulk_ESS	Tail_ESS
Intercept	13.98428	0.52889	12.95403	15.02813	1.00087	4359	7461
competitor	0.06641	0.01658	0.03361	0.09827	1.00165	4700	8017
t_LOE	-0.05206	0.01904	-0.08965	-0.01522	1.00063	8936	11583
P_b_prior_LOE	-0.18712	0.10229	-0.38653	0.01414	1.00104	4557	8056

Family Specific Parameters:

	Estimate	Est.Error	l-95% CI	u-95% CI	Rhat	Bulk_ESS	Tail_ESS
sigma	0.60889	0.02984	0.55385	0.67026	1.00033	6963	12141

VITA

Before joining UW, Shuxian obtained her bachelor's degree from Nanjing University and master's degree from Duke University, both in economics. Her dissertation research studies the recent policies to accelerate generic drug entry and the impact on drug price, market share and health expenditures. She also participated in several research projects regarding performance-based risk-sharing arrangements, decision-making framework using real-world evidence, and dementia risk prediction. She has previous internship experience with Amgen (on cost-effectiveness analysis of innovative heart failure therapies), Flatiron Health (on the generalizability of Flatiron data to the broader patient population with cancer), and Facebook (on Brier Score decomposition).