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Essays on the Economics of Innovation and Intellectual Property Rights

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Essays on the Economics of Innovation and Intellectual Property Rights

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0.1 ACKNOWLEDGEMENT

0.2 ABSTRACT

Innovation, which is a major driving force of economic growth, has received much attention from economists. As a result, intellectual property rights, which allow the innovator to recover their R&D cost from monopoly pricing, have obtained wide acceptance. On one hand, these rights promote innovation and improve the social welfare in the long run. On the other hand, they hurt the short-run consumer surplus due to their exclusivity rights. Creating a balance between such dynamic and static efficiency is a primary concern for the policy makers. Many studies have addressed this question but reached no consensus.

In chapter one, I reexamine the debate in the context of incremental innovation in the pharmaceutical industry. I try to answer the following question: Should we grant additional market exclusivity to incremental innovators in the pharmaceutical industry? I assesses the welfare gains from incremental innovation in pharmaceuticals. Such innovation can yield consumer gains through improved quality, but the additional market exclusivity granted to innovators may also delay generic entry, a practice referred to as "evergreening", and reduce consumer surplus. Quantifying this tradeoff is vital in determining the optimal patent policy and regulatory treatment of incremental innovation. To shed light on this problem, I focus on incremental innovations in selective serotonin reuptake inhibitor (SSRI) anti-depressant drugs. I estimate the patients' demands for antidepressants with a random coefficient logit model, based on individual-level prescription drug data. By comparing scenarios of either withdrawing or allowing market exclusivity for incremental innovations with scenarios of withdrawing or retaining incremental innovations, I found that the consumer benefits from incremental innovation are overwhelmed by the consumer surplus loss due to market exclusivity when considering a single incremental innovation, whereas the consumer benefits from innovation outweigh the consumer losses from exclusivity when considering the counterfactual of withdrawal of all incremental innovations and market exclusivities. This result suggests that innovation benefits are primarily driven not by the quality improvements of products but by the competition effect of the introduction of several incremental innovation products in the market.

In chapter two (coauthored with Roberta Dessí), we turn our attention to the financial aspects of the innovative activities. As we all know, there is a great monetary and creative distance between an invention and its final market benefits. Venture capital specializes in financing high-tech start-ups and therefore plays an important role in bridging scientific discoveries and valuable business practices. Therefore, in this chapter, we review the empirical evidence on the impact of venture capital on innovation. We identify some of

the key challenges to empirical research in this area and discuss the methods that have been used to address them. We propose a simplified theoretical model to illuminate the potential endogeneity caveats by identifying the causal effects of venture capital on innovation.

In chapter three (coauthored with Margaret K. Kyle), we revisit the work in chapter one and continue to investigate the relationship between innovation and intellectual property rights. In modern science and technology development, no advance is truly original; all work is built upon previous innovations. Increasingly, scientists and researchers are realizing the impedimentary effect of intellectual property rights on the cumulative follow-up innovation (Bessen & Maskin (2009), Heller & Eisenberg (1998), Murray & Stern (2007) and Williams (2013) etc.). Here we explore the potential effects of intellectual property rights and research exemptions on cumulative advances in drug development. We use new clinical trials as a measure of innovative effort and explore both the variations in patent protections over time and countries as well as national statutory research exemptions in different countries to identify the effect of patents on innovation. Our results show that the overall effect of patent protection tends to promote innovative activities; post-launch drugs facilitate the clinical trials conducted on them. Research exemptions turn out to be associated with a lower level of follow-up innovation activities.

These three chapters of the thesis are self-contained, and each explores the economics of innovation and intellectual property rights. Chapters one and three investigate the relationship between intellectual property rights and innovation, i.e., the rationale of granting the innovator intellectual property rights by exploring the pros and cons of intellectual property rights. In chapter one, our conclusion is based on the consumer welfare derived from innovation, and in chapter three we focus on promoting the future innovation. Chapter two is more independent and investigates the financial provisions of innovation activities.

Chapter 1 Pharmaceuticals, Incremental Innovation and Market Exclusivity

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1   Introduction

"Incremental Innovations are not small achievements. Heat stable version of anti-retroviral drugs may not be critically important to HIV patients in large cities where there is easy access to electricity and refrigeration, but they are surely important to people in rural areas."

Greg Kalbaugh, Director of US-India Business Council[1]

*"Over the next few years, a number of blockbuster drugs face patent expiration. ... it is estimated that by 2012, brands with more than \$30 billion in sales will face new competition from generics. As more brands face patent expiration, many manufacturers will face the dilemma of how to grow revenue and minimize operational cutbacks as reliance on the new drug pipeline is unrealistic. One tactic is to develop an extended release formulation of an existing brand. Whether you call it extended release (ER, XR), long-acting (LA), or extra-long (XL), the modified formulation is intended to simplify dosing, improve compliance and **extend the life of the patent**. (emphasis added)"*

Kelly Renfro, Marketing Manager for McKesson Patient Relationship Solutions[2]

Innovation drives growth, but competition may undermine the incentives for innovation due to the nonrivalrous nature of ideas. Market exclusivity, provided by intellectual property rights and data exclusivity provisions, aims to incentivize innovation by allowing firms recoup their R&D expenditures and extract the returns to investments in the marketplace. These policies are controversial: How can we minimize dead-weight loss due to monopoly pricing without undermining incentives to innovate? This paper examine the welfare effects of incremental innovation

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[1]http://www.thaindian.com/newsportal/health1/allow-patents-for-incremental-innovation-of-medicines-study_100238527.html

[2]http://www.pharmaphorum.com/2011/03/18/battling-patent-expiration-by-building-brand-loyalty/

and delayed generic entry that results from granting additional market exclusivity periods to incremental pharmaceutical innovations.

"Incremental innovation" in pharmaceuticals, in contrast to the radical innovation of a new molecule to treat diseases, involves improvements over existing drugs such as the discovery of a new therapeutic use, new formulation, additional pediatric use, or improved efficacy and safety. The Hatch-Waxman Act (1984) grants innovators additional market exclusivity for incremental innovations (details in Section 2). Although incremental innovation may generate social benefits, additional market exclusivity may impose social costs. Market exclusivity implies an extension of monopoly, which hurts consumer surplus: budget-constrained patients are may be unable to purchase a treatment at all, or too little; this may in turn affect health status measures. I measure the value of incremental innovation from an economic perspective. I estimate demand based on individual prescription-level data for antidepressant use, and then calculate welfare under various counterfactual policy scenarios. Specifically, I am interested in determining whether the value of incremental innovation to patients exceeds the costs of extending market exclusivity.

This study contributes to policy debates in the regulation of pharmaceuticals, healthcare, and intellectual property. Many have accused the pharmaceutical industry of "evergreening, " or extending patent protection through the introduction of new products that represent minor advances over older drugs. An oft-cited example is the case of Prilosec, a best-selling prescription heartburn drug. Just before the expiration of Prilosec's patent in April 2002, the producer of Prilosec, AstraZeneca got approval for another drug, Nexium, in February 2001 and marketed it from March 2002. Nexium is one-half of the Prilosec molecule. Most clinical studies found no increase in efficacy. However, AstraZeneca obtained another patent that will expire in November 2018. But others point to examples of incremental innovation with important benefits. The anti-retroviral drug Norvir, a first-line treatment of HIV/AIDS, was approved by FDA in 1996 but requires refrigeration. In 2010, a heat-stable version of Norvir was introduced. While this incremental advance may not be important for developed country patients, it may make treatment far more accessible in countries without widespread refrigeration.

Even if incremental innovation yields real clinical benefits, the costs associated with extending a monopoly – either through new patents or through Hatch-Waxman exclusivity extensions – may be significant. Many developed countries are facing rising health care expenditure, a large portion of which is due to pharmaceuticals. Regulators use a variety of mechanisms to control pharmaceutical expenditure, including price controls and the promotion of generics. As Lichtenberg (2001) [20] has emphasized, the introduction of new drugs may reduce total health expenditure and create other benefits, such as fewer inpatient visits and lost workdays due to illness. A full examination of these trade-offs is essential in assessing efforts to balance cost, innovation and access. Market exclusivity extensions are another policy tool that allows regulators to balance incentives for incremental innovation that increases welfare against the static gains from earlier generic entry (Grabowski (2006, 2008) [14] [13]; Engelberg (2009) [11]).

In the intellectual property area, there is a debate about the standards of patentability, particularly whether incremental innovation satisfies the novelty and nonobviousness requirement of most patent systems. Some countries, including India, refuse to grant patents for some types of incremental innovation. Giving innovators the same period of patent protection on an incremental advance as on a new molecule may distort incentives. Although this study doesn't explicitly consider the shift between incremental innovation and radical innovation, it might shed light on the future research related to the substitution effects of these two types of innovation.

In this study, I focus on incremental innovations in selective serotonin reuptake inhibitor (SSRI) anti-depressant drugs, including the pediatric use of existing drugs, which has been granted a six-month exclusivity extension over existing patents, and two new formulations of existing

branded drugs (Lexapro and Paxil CR), which have been granted new patents. I estimate the patients' demands for antidepressants with a random coefficient logit model, based on individual-level prescription drug data. I then recover the marginal cost for the branded and generic firms based on the Bertrand Nash model. Before calculating the welfare change from status quo to counterfactual scenarios, I estimate counterfactual equilibrium prices from firms profit maximizing model, given the simulated demands over counterfactual alternative choice set (for example, incremental innovation products might be removed, or the generic entry might occur one year earlier due to the withdrawal of market exclusivity). Consumer surplus change is measured using the compensating variation between two scenarios.

By comparing scenarios of either withdrawing or allowing market exclusivity for incremental innovations with scenarios of withdrawing or retaining incremental innovations, I found that the consumer benefits from incremental innovation are overwhelmed by the consumer surplus loss due to market exclusivity when considering a single incremental innovation, whereas the consumer benefits from innovation outweigh the consumer losses from exclusivity when considering the counterfactual of withdrawal of all incremental innovations and market exclusivities. This result suggests that innovation benefits are primarily driven not by the quality improvements of products but by the competition effect of the introduction of several incremental innovation products in the market.

This paper is structured as following: sections 2 and 3 explain market exclusivity policies for pharmaceuticals and the antidepressant market, respectively. Section 4 details the estimation strategy. Section 5 describes the data, including data sources, sample choice, products and variables. Section 6 presents the estimation results, and I conclude section 7.

2 Background of Market Exclusivity

The pharmaceutical industry is innovation intensive, with firms investing a very high proportion of annual sales into R&D; Additionally, their profitability relies heavily on patent protection. This salient feature of the industry results from the characteristics of innovation and the production process of the pharmaceuticals. The development of a successful branded drug is highly risky. To get approval from government regulatory authorities such as FDA in the US, the median time duration from the start of clinical trials to NDA (New Drug Application) issuance was 98.9 months. In each phase, the attrition rate is surprisingly high (around 25%, 52%, 36% for phase I, II, III, respectively, see Scherer, 2000[30]), resulting in large costs for clinical trials.

In comparison, the cost to copy a branded drug is remarkably low, not only for production but also for approval from the government authority. According to the Hatch-Waxman Act passed in 1984, a generic producer could file an ANDA (Abbreviated New Drug Application) based only on proof of bio-equivalence to the branded drug as long as its data exclusivity has expired. Once generic drugs enter into the market, both the price and sales revenue of branded drugs tend to drop about 80% over the next year. In this way, the length of patent protection governs the profitability and effective life of pharmaceuticals.

Policy makers are continually trying to balance the need to develop new drugs and improving patients' access to existing drugs while maintaining affordable health expenditures. By allowing generic producers to easily get approvals and market share, patients have access to blockbuster drugs that otherwise might not be affordable. However, it greatly reduces the profits of innovators and therefore undermines the incentives for them to carry out R&D for a new generation of drugs. The objective of government regulator is to develop an optimal policy that maximizes total social welfare while taking into account all these considerations.

Market exclusivity is influenced by a complex interaction of several factors (Grabo-wski and Kyle, 2007 [15]). In short, it is determined by the complementary action of patents and data exclusivity. Patents granted by USPTO (The United States Patent and Trademark Office) protect drug innovations from pure price competition, enabling drug innovators to recover research and development expenditures and thereby encouraging further research investment. Data exclusivity approved by the FDA restores the patent period loss during the regulatory review and clinical trial period, as well as protects clinical data from being utilized by generic competitor to file abbreviated new drug application (ANDAs)[3].

To illuminate the importance of data exclusivity, one should examine the sophisticated nature of pharmaceutical innovation and the market regulatory system. To ensure the safety and efficacy of marketing drugs, the FDA sets a series of regulatory requirements throughout the whole development process from the moment a new chemical entity is synthesized until final FDA approval of a NDA. The process is divided into three main stages: preclinical research, clinical investigation, and NDA approval. It is well-known that the requirements are rigorous and demanding. However, the patent term for pharmaceuticals remains unchanged, allowing 20 years after the filing date for patents applied for after 1995; and 17 years after the issue date for patents applied for before 1995.

This means that the effective patent life of pharmaceuticals is substantially shorter due to the government requirements. When a firm discovers a promising new chemical compound, the first thing to do is to file for a patent. From that moment, the patents 20-year term is on the clock, well before knowing if the compound can be developed into a marketable medicine. The government then requires substantial chemical, animal and human testing, followed with FDA review process of a NDA. The testing and approval process usually takes about 7 to 13 years (Congress House Committee, 1980) [27]. Therefore, for pharmaceutical products, the 20-year patent term has become a legislative figment. In reality, the effective patent life for pharmaceuticals has been eroded, and on average has only 6.8 years. The incentives to invest in pharmaceutical R&D have been reduced substantially.

The Hatch-Waxman Act (1984) was enacted by Congress to alleviate this problem by restoring market exclusivity to pharmaceutical innovations. In this act, two seemingly contradictory goals have guided the federal government's legislation: encouraging pioneer companies to continue developing innovative technologies while also making inexpensive generic pharmaceuticals available to consumers.

According to Hatch-Waxman Act, the generic manufacturer is allowed to use the clinical data of the patented drug to prepare its own FDA application prior to expiration of the patent rights, thus providing an abbreviated process for FDA approval of generic drug applications. The generic manufacturers can file abbreviated new drug applications (ANDAs) without their own clinical trials data as long as they provide proof of bio-equivalence to the branded drug. This substantially facilitates the entry of generic drugs (from 3 or more years to a few months, see CBO, 1998[26]). On the other hand, the Act provides a partial restoration of the patent life of the research-based drug company (the "pioneer") by adding 5 years of data exclusivity without surpass the maximum effective patent life of 14 years. The 5-year exclusivity is the period in which generic firms are forbidden from filing any ANDAs based on pioneer's clinical trial data. Besides the NCE exclusivity, Hatch-Waxman Act also provides other terms of data exclusivity:

1. **Three years** of exclusivity granted for a change in an approved drug product. The changes include new indications, dosage strength, dosage form, route of administration, patient pop-

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[3]Hutt (1982)[19] discusses the importance of patent term restoration to pharmaceutical innovation.

ulation, and conditions of use. The changes require new clinical investigations and the exclusivity could prevent effective approval (but not submission) of ANDAs.

2. **Seven years** of orphan-drug exclusivity. A company that develop such a drug (to treat a rare medical condition which implies the condition affects fewer than 200, 000 people in the US) could be protected from competition for seven years.

3. **Six months** of pediatric exclusivity. Unlike other exclusivity, the pediatric exclusivity could be attached to existing periods of exclusivity and patent protection. It can be extended to all approved formulations, dosage forms and indications for products that contain the same active ingredient so long as they are protected by an exclusivity or patent. More than one period of pediatric exclusivity is possible, e.g., new indication.

Within these three exclusivity periods, generic firms could file ANDAs, but they cannot get approval from the FDA. Only after the expiration of the data exclusivity, their generic products could be approved. However, only when the patent expires, the approved generic ANDAs could be marketed.

In this sense, data exclusivity adds a new hurdle for the generic firms to enter the market. Generic firms could also file and get approval of new drug application based on their own safety and efficacy data, however, that implies they should carry out their own clinical trial, and it introduces an immense amount of costs and uncertainty.

For pharmaceutical manufacturers, whether innovator or generic, their objective is to exploit every market potential and extract maximum returns. For the innovator, they are protecting their product from competition, restoring their patent terms and obtaining as long a data exclusivity as possible. However, for the generic firm, they are trying every shot to challenge current patents, and apply for ANDAs as early as possible to capitalize on market share. According to the Act, the first-to-file ANDA generic can obtain a 180-day exclusivity in which FDA will not approve a subsequently filed ANDA for the same product. Therefore, the competition of the branded and the generic passed on to the arena of patent and data exclusivity. As quoted at the beginning of our paper, the incremental innovation is one of the important strategies for the innovator to win in this battle.

3   The Anti-depressant industry and SSRIs

In this paper, we focus on the antidepressant industry, more specifically, the Selective Serotonin Reuptake Inhibitor antidepressants (SSRIs). The reason to concentrate on this market lies in the following: molecules in this class are relatively homogeneous with individually idiosyncratic therapeutic responses and side effects. Therefore, it is a differentiated but mutually exclusive market. The products with patent protection, incremental innovations, and generic entry coexist. In this sense, the market structure forms the indispensable ingredients (incremental innovation, market exclusivity, consumer loss without generic entry) for answering our question. Market is competitive with balanced share across brands, which facilitates the demand estimation.

The antidepressant manufacturing industry is the largest prescription industry in the United States, with more than 200 million prescriptions dispensed annually for 2007-2011 (IMS Health).[4] Trends will likely continue upward with the rising diagnosis rates and increasing public awareness of the disease. In fact, the World Health Organization forecasts that unipolar major depression will displace heart disease as the heaviest disease burden by 2020. [22] Furthermore, anxiety

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[4]See the Top-line Market Data "Top Therapeutic Classes by U.S. Dispensed Prescriptions" in www.imshealth.com.

disorders affect about 40 million American adults in any given year. They include panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, generalized anxiety disorder, and phobias. For these anxiety disorders, antidepressants are standard treatment.

Antidepressants are almost equal in their successes in relieving depression. The differences determining patient choices, come down to safety, effectiveness, costs, side effects and the presence of other medical conditions that could affect the drug's safety and effectiveness. Among them, side effects are especially crucial considerations. Common antidepressant side effects are nausea, weight gain, sexual dysfunction, and anxiety. Moreover, antidepressants are addictive, and discontinuing use may cause withdrawal symptoms in patients. Reducing these side effects is a vital area of research for pharmaceutical companies.

The diagnosis of depression involves more subjective criteria than other common diseases such as arthritis, cancer, or diabetes. As a result, Direct-To-Consumer (DTC) advertising has historically played a large role in creating popular recognition of depressive symptoms, "growing market" and fostering a demand for specific medications. Studies show that only half of people with depression are treated.[33] Thus, the success of new antidepressant treatments hinges on the ability of manufacturers to effectively market their products to the public.

According to action mechanisms, the antidepressants can be categorized into several therapeutic subdivisions, [5] in which SSRIs are the most commonly used as the first-line treatment of depression because of their favorable side effect profile and low toxicity. SSRIs also amount to the top prescribed antidepressants in the US retail market in 2010.[6] They work by preventing the reuptake of serotonin by the presynaptic neuron, thus maintaining a higher level of serotonin in the synapse. This allows the brain to better transmit signals, thus improving mood.

Prozac was the first SSRI marketed by Eli Lilly with FDA approval in 1987, later followed with other SSRIs including Zoloft (1991), Paxil (1992), Celexa (1998), Lexapro (2002) and updated versions, such as Prozac Weekly, Paxil CR etc.. After the added six-month of data exclusivity for Prozac due to its pediatric studies expires in Aug. 2001, the generic competitors enter. Generic counterparts for Paxil, Celexa and Zoloft then entered into the market in 2003, 2004 and 2006. The most recent SSRI Lexapro also began to face its generic competitor after Mar. 2012.

Unlike most markets where consumers hold the full discretion in making choices, demand for pharmaceuticals relies not only on ultimate patients' tastes (the efficacy and side effects response, brand loyalty), but also on the behaviors of physicians who prescribe these drugs and pharmacists who dispense the prescriptions. Fortunately, unlike other therapeutic classes of drugs[7], anti-depressants leave little scope to physicians when they decide what to prescribe. The efficacy and side-effect responses of anti-depressants are quite idiosyncratic across individuals. The traditional way to prescribe anti-depressants is to try one or two molecules to see which works with the fewest adverse reactions. According to patients' responses, doctors then write the prescription afterwards. In addition, people usually believe that physicians have incomplete or no information about relative prices (Ellison et al., 1997 [10]), however, for the treatment of chronic disease, exceptions happen (Caves et al. 1991[6]). Therefore, in our study, agency problems play little role in choice decisions, which justifies the rationale of applying discrete choice model in our problem.

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[5]The antidepressants mainly include the monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs), selective serotonin reuptake inhibitors (SSRIs), and Serotonin-norepinephrine reuptake inhibitors (SNRIs).

[6]From the statistics in "2010 top 200 generic drugs by total prescriptions" and "2010 top 200 branded drugs by total prescriptions" provided by www.drugtopics.com.

[7]Such as several chemically distinct but similarly working H2 antagonists used to treat duodenal ulcers; Several ACE inhibitors used in the treatment of hypertension; And also numerous chemically distinct antibiotics.

4 Estimation Strategy

The existing empirical literature has generally focused either on costs of market exclusivity or the benefits of innovation. Several papers have examined the consequences of early generic entry through Paragraph IV challenges (Branstetter et al. 2011)[5]; others have estimated consumer losses that would result from market exclusivity (Chaudhuri et al., 2006). [7] There is also a large body of work on the benefits of innovations in healthcare. The representative studies include: Trajtenberg (1989) [32] evaluates the value of CT scanners; Cleanthous (2011) [8] quantifies the patient welfare benefits from innovation in the depression drugs class; Lucarelli and Nicholson (2009) [23] and Dunn (2010) [9] calculate quality adjusted price indexes for colorectal cancer drugs and anti-cholesterol drugs respectively, suggesting that the price increase in pharmaceuticals are coming from the quality innovation.[8] However, few analyses have considered both sides simultaneously to answer whether the benefits of incremental innovation exceed the consumer surplus loss from market exclusivity. Our study fills this gap by focusing on the effects of incremental innovations in pharmaceuticals. Our approach roots from BLP random coefficient logit model. This method has been adopted by many people to study the value of new products in non-health related fields[9] or health-related area. This paper is closely related to Dunn (2010) [9] which applies BLP model with micro-level data in pharmaceutical industries.[10]

4.1 Demand Side Estimation

The patient choice decision of prescription drugs is complicated. Given the purchasing decision, it could be viewed as the joint choice of the patient, the physician and the insurer. The patient relies on his doctors to tell them which drug, if any, is best suited to treat his condition. At the same time, the third-party payers might restrict the choice set according to the patient's insurance plan or induce price sensitivity through the structure of the insurance plan. However, the most pivotal role in this choice making process is played by the patient's heterogeneous reactions to the drugs, especially in anti-depressant drugs where each individual responds very differently to the drugs, regardless of the efficacy or side-effects. Therefore, in our modeling, we will ignore the principal-agent relationship but regard the patient's demand as a black box determined simultaneously by individual characteristics and drug attributes.

Random coefficient model is a best fit to deal with this problem. In this model, consumer's utility is determined by the interaction of drug characteristics (including prices)with both observable and unobservable demographic characteristics, which allows for flexible substitution patterns. The patient choice in antidepressants is best suited to discrete choice model: patients consume only one anti-depressant at a time which is exactly an underlying assumption of the discrete choice model.[11].

Consider that a utility-maximizing patient i, where $i = 1, \ldots, I_t$, in a given time period t, where $t = 1, \ldots, T$, faces $J_t + 1$ alternatives: J_t different antidepressant drugs and the option of not purchasing any of the drugs, the outside option, $j = 0$. As in Berry, Levinsohn and Pakes (1995,

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[8]There are still a lot, such as Lichtenberg (2001, 2005) [20] [21] has studied the impact of the introduction of new chemical entities on the health status. Hsieh and Sloan (2008) [17] underline that the estimated benefits of adopting pharmaceutical innovation generally far exceed the costs.

[9]Based on BLP model, Petrin (2002) [28] studies the value of minivan introduction; Nevo (2003) [25] measure the welfare effect of new products and quality change in breakfast cereal industry.

[10] However, Dunns paper does not allow random coefficients but uses a conditional logit model.

[11]In our sample, we observe that some of the individuals may choose different drugs in different time, which is the evidence that patients are changing to a more suitable drug. Therefore, we will drop the former drug choice and only keep the latter one since it better reflects the patient's characteristics

2004) [2] [3] and Nevo (2000) [24], the indirect utility of any patient i, in market t choosing drug j can be expressed as

$$u_{ijt} = \beta_{ipt} x_{jpt} + \sum_k x_{jkt} \beta_{ikt} + \xi_{jt} + \epsilon_{ijt}.$$

with

$$\beta_{ict} = \bar{\beta}_c + \sum_r z_{irt} \beta^o_{cr} + v_{ic}, \ c = p,k.$$

The payoff of patient i purchasing drug j at date t depends on the drug price x_{jpt} and drug characteristics, including x_{jkt} (observable) and ξ_{jt} (unobservable). We allows patients to have heterogeneous preferences over observed drug attributes $x_{jct}, c = p, k$, [12] through the coefficients β_{ict}. The coefficients vary both with observable patient characteristics z_{irt}, indexed $r = 1, \cdots, R$ and unobservable household characteristics v_{ic}, indexed $c = 1, \cdots, K$.[13] We assume $v_{ic} \sim N(0, \Sigma)$, ϵ_{ijt} to be a zero-mean stochastic term.

For notation simplicity, in the following we will omit the market notation t. By grouping the drug-specific common term together, we get:

$$u_{ij} = \delta_j + \sum_{cr} x_{jc} z_{ir} \beta^o_{cr} + \sum_c x_{jc} v_{ic} + \epsilon_{ij}, \tag{1}$$

with $\delta_j = \sum_c x_{jc} \bar{\beta}_c + \xi_j$, we call it as the mean utility component of drug j, which is common to all patients in market t.

For the outside option, as in Griffith et al. (2010) [16], the individual utility takes the following form

$$u_{i0} = \delta_0 + \sum_r z_{ir} \beta_{1r} + \epsilon_{i01}.$$

where z_{ir} for $r = 1, \cdots, R$, is a vector of observable individual characteristics. We interact the payoff provided by selecting the outside option with observable individual characteristics to allow for heterogeneity in choices to buy or not. The parameter δ_0 capture the baseline payoff from the outside option and for each r, β_{1r} captures the variation in payoffs across individuals due to z_{ir}.

Individual i chooses drug j which gives him/her the highest payoff, i.e., $u_{ij} > u_{il}, \forall l \neq j, l \in \{0, \cdots, J\}$. Then, by assuming the random utility component ϵ_{ij} to be independent and identically distributed across both drugs and patients and follows an extreme value distribution, we can write the probability of individual i choosing drug j as

$$Pr_i(j \mid z, v, x, \delta, \beta) = \frac{exp(\delta_j + \sum_{cr} x_{jc} z_{ir} \beta^o_{cr} + \sum_c x_{jc} v_{ic})}{\sum_{l=0}^{J} exp(\delta_l + \sum_{cr} x_{lc} z_{ir} \beta^o_{cr} + \sum_c x_{lc} v_{ic})}. \tag{2}$$

In the above formula, we can observe the patient's choice results (therefore, $Pr_i(j)$), the drug characteristics x_{lc}, and the individual characteristics z_{ir}. For the unobservable individual characteristics, by assumption, we have $v \sim N(0, \Sigma)$, [14] then after integrating out v,

$$Pr_i(j \mid z, x, \delta, \beta) = \int Pr_i(j \mid z, v, x, \delta, \beta) P_v(dv). \tag{3}$$

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[12] p denotes price, k denote other drug characteristics, c denotes all the drug attributes.

[13] It implies the unobservable individual preference specific to drug characteristics.

[14] Here, v is a coefficient vector which corresponds to the drug characteristics x_{lc}.

A general concern in demand estimation is that unobservable drug characteristics lead to correlation between the error term and price resulting in inconsistent estimates of the price coefficients. The traditional way to circumvent this problem in mixed logit model is to introduce the mean utility term δ_{jt} which encompasses the price and unobserved product characteristics (BLP, 1995, 2004 [2] [3]). Therefore, a consistent estimates of δ_{jt}, β_{cr}^o and Σ are implementable. And then we could deal with the endogeneity problem in linear model

$$\delta_j = \bar{\beta}_p x_{jp} + \sum_k x_{jk} \bar{\beta}_k + \xi_j. \tag{4}$$

by instrumental variable estimation. In this way, the model can be estimated in two stages: δ_j, β_{cr}^o, and Σ are estimated from (2) by simulated maximum likelihood estimation; And then based on the estimates of δ_j in the first stage, $\bar{\beta}_c$ and ξ_j are estimated from (4) by IV estimation.

4.2 Instrumental Variables

Finding relevant and valid instruments is always challenging in demand estimation. It should correlate with the drug price but be uncorrelated with unobserved drug characteristics ξ_{jt}. A usual way in the literature is to find the cost factors in other countries or the competitors which affects the firms' pricing strategy but irrelevant to the product characteristics.

In our study, to exploit the detailed individual-level data, we adopt a different approach by Dunn (2010) [9] and adapt the demand predicts in the first stage logit estimates as IVs, but with drug prices and the unobserved product characteristics set to zero. The intuition behind the IV strategy is to employ the demographic information in the patient-level data which is reflected in the first stage demand estimates since choices are affected by individual characteristics. The individual information is controlled in the logit model and it shouldn't enter the unobserved component of model, ξ_{jt}. Therefore individual demographics should not be correlated with the unobserved component of demand; but the aggregate preferences of individuals in the market should be correlated with the price. As the firm's price strategy in oligopolistic model depends on both the demand of the drug and the derivative of demand with respect to price, Dunn (2010) [9] provides a detailed proof regarding the use of aggregated demographics as instrumental variables in the context of a simple linear demand model. Graynor and Vogt (2003) [12] utilized the first-stage demand estimates from the logit maximum likelihood equation as an instrument for price. Similar to their methods, assume that firms choose price based on a mark-up term derived from an oligopoly pricing model that depends on both the demand for the product and the derivative of demand with respect to price, $markup = p_{jt} - mc_{jt} = -\frac{D_{jt}}{\frac{\partial D_{jt}}{\partial p_{jt}}}$. Both the demand function and the derivative can be calculated by summing individual decisions and their responses to price. Specifically, the market demand for product j at date t is simply:

$$D_{jt}(j \mid z, x, \delta, \beta) = \sum_{i=1}^{I_t} Pr_{it}(j \mid z, x, \delta, \beta) \tag{5}$$

and the responsiveness to price is measured as:

$$\frac{\partial D_{jt}}{\partial p_{jt}} = \sum_{i=1}^{I_t} \frac{\partial Pr_{it}(j \mid z, x, \delta, \beta)}{\partial p_{jt}}. \tag{6}$$

The first-stage estimates may be used to construct these demand measures, but they are likely to be endogenous because the function $Pr_{it}(j \mid z, x, \delta, \beta)$ depends on the market price, p_{jt}, and

the unobservable, ξ_{jt}. Therefore, in order to use the first-stage estimates, the terms containing price, p_{jt}, and the unobservable, ξ_{jt}, must be removed from the equation; so to construct the instruments all parameters interacted with price, $\bar{\beta}_p$, β_{pr}^o, v_{ip}, are set equal to zero, and the mean utility of product δ_{jt} is also equal to zero. That is, (5) and (6) are estimated at the point where $Pr_{it}(j \mid z, x, \delta = 0, \bar{\beta}_p = 0, \beta_{pr}^o = 0, v_{ip} = 0, \beta_{ic})$. Therefore, by representing all these price related parameters $\bar{\beta}_p$, β_{pr}^o and v_{ip} as β_p, we could construct the instruments as

$$D_{jt}(j \mid z, x, \delta = 0, \beta_p = 0, \beta_k),$$
$$and \quad \frac{\partial D_{jt}(j \mid z, x, \delta = 0, \beta_p = 0, \beta_k)}{\partial p_j}.$$

For generic drugs, we could expect that the pricing behaviour of generic firms be different from branded firms and the competition extent also different. By allowing the instrument to be distinct from the branded drugs, we have the instruments for generics as:

$$generic_{jt} \cdot D_{jt}(j \mid z, x, \delta = 0, \beta_p = 0, \beta_k),$$
$$and \quad generic_{jt} \cdot \frac{\partial D_{jt}(j \mid z, x, \delta = 0, \beta_p = 0, \beta_k)}{\partial p_j}.$$

Another group of IVs have also been considered in our study. Adopting the instruments employed in Branstetter et al. (2011) [5], we generate three alternative instruments to perform the robustness check. The variables includes: the number of dosages in which a product is available; years after the first generic entry; and number of firms (branded and generics) selling the same molecule in the market. The relevance and validity of all these instruments will be discussed in section 5.

4.3 Supply Side Estimation

Counterfactual simulations concerning the effects of incremental innovation withdrawal and market exclusivity removal require knowledge of the marginal costs of SSRI anti-depressants in the market. Adopting the traditional approach in the literature, we assume that the marginal cost mc_{jt} is constant and the industry is an oligopoly engaging in Bertrand competition with differentiated products. Firms myopically maximize profits each period, and then the firms' first-order conditions can be derived and used to infer the marginal costs.

Following the literature, we assume the firms are profit maximizers. Based on the typical Bertrand-Nash model, assume firm f produces subset J_t of the J total products[15]. It's profit function is:

$$\Pi_f = \sum_{j \in J_f} (p_j - mc_j) D_j \tag{7}$$

$$F.O.C.: \quad D_j + \sum_{l \in J_f} (p_l - mc_l) \frac{\partial D_l}{\partial p_j} = 0. \tag{8}$$

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[15]In our case, most of the firms have only one product except Forest Labs (producer of Celexa and Lexapro) and Glaxosmithkline (producer of Paxil and Paxil CR). Before the patent expiration of Celexa, Forest Labs developed a new transforms of Citalopram Hydrobromide (active ingredient of Celexa): Escitaloproam Oxalate. When pricing Celexa (Lexapro), Forest Labs should consider the substitive effects of Lexapro to Celexa.

Rewrite it in matrix form, the mark-up can be calculated by:

$$p - mc = \Delta(p, X, \beta)^{-1} D(p, X, \beta), \tag{9}$$

where the (j, l) element of Δ is

$$\Delta_{j,l} = \{ \begin{array}{ll} -\frac{\partial D_l}{\partial p_j} & \text{if } j \text{ and } l \text{ are produced by the same firm;} \\ 0 & \text{otherwise.} \end{array}$$

However, there are some exceptions in our study due to our data limitation. Our individual-level data, while providing detailed individual characteristics and purchasing history, contained inaccurate records about the drug manufacturers, especially for generics[16]. We could identify the producer if the patient purchased the branded one since there is unique branded producers corresponding to each molecule. For generics, it becomes a problem as there are dozens of pharmaceutical producers providing generics of the same molecule. Therefore, the only thing we can do is to treat all generics of one molecule as a single product although in fact they are provided by multiple competitors. In this case, the firm margins will be overestimated based on Bertrand-Nash model.

At the same time, there are two important phenomena in our market which illustrate us that simply assuming perfect competition or oligopoly market over all these years might be inappropriate. Phenomena 1: generic manufacturers enter the market sequentially following the patent expiration of the branded. Due to the Hatch-Waxman Act, the first generic entry could obtain 180 days of market exclusivity, which implies that within that period, the FDA cannot allow the second generics to enter and the first generics could enjoy a certain level of market power. While after the expiration of market exclusivity, generics firms flush into the market, for example (see Table 16), after Zoloft lost its patent protection, only Teva[17] entered in 2006, while in 2007, there were overall 16 generic producers entered. Phenomena 2: many generic firms simultaneously produce several product line. For example, Teva and Mylan (internationally well-known generic producers) produce four molecules. Phenomena 1 tells us that the market transition from oligopoly to perfect competition experiences a gradual process, it involves regulatory approval, entry into the market, and patient education about the availability of new drugs. Phenomena 2 implies that the firms also care about the substitution effects across generics with SSRI subclass when pricing. However, we can't capture this substitution effect based on our data.

Another issue we haven't tackled is the role of prescription drug copayment rates. According to Medicare Part D, the federal government started to subsidize the costs of prescription drugs for Medicare beneficiaries in the US from Jan. 2006. Several studies [18] have quantified the effects of Medicare Part D in overall drug utilization and generics use and illustrated that the assessment of Medicare Part D is complex due to its wide varieties of plans. There are rising concerns about pharmaceutical studies to recover price elasticity based on prices rather than copayment rate. [19] This is especially true with the introduction of Medicare Part D drug insurance.[20] Without tak-

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[16]The NDC (national drug code) recorded in MEPS which is used to link the products to manufacturers are highly inaccurate and incomplete. We could only observe the drug name and strength for each purchasing record. For the a large number of generics which are highly homogeneous in trade name and strength, we were unable to identify their manufacturers.

[17]Teva and Ivax Sub Teva Pharms are all from the same group.

[18]See Yin et al. (2008) [34] and Zhang et al. (2008) etc.. [35]

[19]Arcidiacono et al. (2012)[1] build a pharmaceutical pricing model incorporating the insurance co-payment rate and provide reasonable elasticity estimates. Brand et al. (2012)[4] also discusses the importance of copayments rather than prices in health care studies.

[20]Zhang et al.(2012) [36] has found that Medicare Part D coverage gap was associated with modest reductions in the use of antidepressants and those with generic drug coverage reduced their brand-name antidepressant prescriptions.

ing into account the copayment rate, price elasticity tends to be overestimated, which induces underestimated firm margins. While due to our data limitation, treating all generic competitors as a single producer tends to overestimate firm margins. These two biases act in opposite directions, making our cost recovering difficult and complicated. These issues remind us that the interpretation of Bertrand Nash model should be very careful. The method used to estimate the counterfactual prices with consideration of these issues will be discussed in the next section.

4.4   The Counter-factual Scenarios and New Equilibrium Prices

In assessing the effects of incremental innovation, we start by focusing on the most extreme case, in which incremental innovations are non-existent. Only the originals and their generics circulate in the market. Illustrating by Table 1, the product sets include only column 1 and 4. We use the results from the analysis of this case as a benchmark. In the next step, we consider withdrawal of each type of incremental innovation respectively. Therefore, in total, we have four cases:

- Withdrawal of all incremental innovations and the corresponding additional market exclusivity: remove column 2-3;

- Withdrawal of new formulated version of Celexa: Lexapro.

- Withdrawal of new formulated version of Paxil with safety improvement: Paxil CR;

- Withdrawal of pediatric usage for all products and the corresponding 6-month market exclusivity: drop column 3 and remove the pediatric usage for all the rest products;[21]

Although we have discussed several different types of data exclusivity granted to innovation in Section 2, the data exclusivity granted to incremental innovations in our market are only those for pediatric studies. Three years of data exclusivity granted to the firms for new indications were overlapped with patent protection and therefore they have played no role in extending market exclusivity.[22] However, the patent protection for the newly formulated products, such as Lexapro, create another barrier for generic competition. Therefore, in our counterfactual analysis, the market exclusivity we consider are the 6-month market exclusivity granted to Prozac, Paxil, and Zoloft for their pediatric studies[23] and the patent protection for Lexapro and Paxil CR.

As the above list suggests, we proceed from analyzing the effects of withdrawal of the entire incremental innovations to the analysis of eliminating a specific type of incremental innovation. This approach was motivated by the observations that market exclusivity extension, provided by Hatch-Waxman Act and intellectual property right, are specific to each type of incremental innovation. By considering separately the introduction of each incremental innovation and accompanied market exclusivity extension, the welfare effects could be evaluated and policy implications could be drawn.

Before carrying on the counter-factual analysis, the first step is to derive the new equilibrium prices under counter-factual scenarios. In deriving these prices, we start by assuming profit maximization pricing policy for the branded firms without generic entry. Such assumptions aim to be consistent with the price making assumptions in marginal cost estimation. Before generic entry,

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[21] It implies that the following products will no longer have the pediatric usage indication: Prozac (2006), generic Prozac (2003), Prozac (2006), generic Prozac (2006), Zoloft (1991), Zoloft (2002), Zoloft (2003), Generic Zoloft (2006).

[22] The reason that we don't consider new indications in SSRIs also lies in the fact that there is almost no significant effects of new indication dummies over the mean utility of drugs from our estimates.

[23] Although the safety and efficacy of the medication for the treatment of Major Depressive Disorder has been built only for Prozac. The safety and efficacy of the treatment for Obsessive Compulsive Disorder has also been developed for Zoloft.

the branded firms re-optimize in response to the market change and set new prices, taking the prices of all other firms as given. However, after the generics flood the market, as we explained in section 4.3, the counterfactual prices estimated from biased marginal cost in new equilibrium might be misleading. As we already know, Bertrand Nash model overestimates the margin of firms in case of generic competition, therefore underestimates the marginal cost in case of generic competition. Upon underestimated marginal costs and overestimated margins in Bertrand Nash Model, the estimates of counterfactual prices are inaccurate and the direction of bias is unpredictable, not to mention the copayment rate issue.

Therefore, one way to deal with these issues, is to consider only the pre-2006 markets and calculate counterfactuals for the years before 2006. Another way to include all these years is to infer the counterfactual prices from the marketplace prices rather than from estimated marginal costs for the years after 2006. For example, consider the counterfactual of withdrawal of pediatric exclusivity of Prozac, the counterfactual price of Prozac in this scenario is set to be the marketplace price one year later (i.e., the generic competition come to the market one year earlier, which drop down the price one year earlier).

4.5 Measurement of Welfare Effect

The simulation of the new equilibrium under different scenarios can provide important insights into how consumers and firms will respond to the removal of incremental innovations and additional market exclusivity (for example, which products consumers will substitute or which prices will decrease the most). To get a more precise idea of how patient's well-being will ultimately be affected by the policy removal (withdraw the additional market exclusivity granted to the incremental innovation), we compute, as the last step in our analysis, the welfare effects if the regulators no longer grant additional market exclusivity to incremental innovations.

One point we should make it clear is that in this study we have no attempt to evaluate the responsiveness of incremental innovation to market exclusivity policies, which is left for future research. For this moment, we assume that if no additional market exclusivity is provided by regulators, no incremental innovation would take place. However, it should be acknowledged that the assumption might not hold as long as the expected gain of demand increases due to incremental innovation is greater than the investment cost, which might happen as improved quality can distinguish products from other competitors and therefore increase the demands. These issues are important and relevant to our study but we can't provide the answer to them with the current dataset. It involves requires additional study which might be the direction of our future research. But we are sure that incremental innovation would be reduced with the removal of market exclusivity provisions. By assuming the extent of withdrawal of incremental innovation, we could provide the lower bound and upper bound of the estimates to our question.

Social welfare, as defined, includes consumer surplus and firm profits. The easier part, firms' profits, can be calculated by demands multiplying the difference between price and marginal cost. Our data don't allow us to measure the investment cost of incremental innovation, which requires the R&D input in incremental innovations for each firms. We will put this issue tentatively aside and discuss it after we get the final results.

On the consumer side, we measure changes in consumer welfare by the compensating variation (CV), defined as the additional expenditure that consumers need in order to achieve the same utility level as before the product quality and price change. By denoting $u_{ij}^t = V_{ij}^t + \epsilon_{ij}^t$, the

compensating variation for individual i from period $t-1$ to period t is:

$$CV_{it} = \frac{u_i^t - u_i^{t-1}}{\beta_{ip}} = \Delta CS_{it}, \text{ where } u_i^t = \max_j V_{ij}^t,$$

where period $t-1$ and t are the different product characteristics corresponding to different scenarios (before and after the incremental innovation happens or before and after the market exclusivity expires). The total change of consumer surplus is:

$$\Delta CS = \sum_I \int CV_{it} dP(v,\epsilon) = \sum_I \int CV_{it} dP_v(v) dP_\epsilon(\epsilon)$$

$$= \sum_I \int \frac{\ln[\sum_{j=0}^{J_t} exp(V_{ij}^t)] - \ln[\sum_{j=0}^{J_{t-1}} exp(V_{ij}^{t-1})]}{\beta_{ip}} dP_v(v).$$

Note that the CV as computed above can be decomposed into two effects. To illustrate it, let's first clarify the notations: incremental innovation is denoted as II and additional market exclusivity as ME. The welfare change from the counter-factual scenario to the real situation can be written as:

$$\Delta = W(II, ME) - W(no\ II, no\ ME), \tag{10}$$

where $W(II, ME)$ implies the consumer welfare where there is incremental innovation and additional market exclusivity, similarly, $no\ II$, $no\ ME$ denotes the scenario where there is no incremental innovation and additional market exclusivity.

By manipulating equation 10, we have

$$\Delta = \{W(II, no\ ME) - W(no\ II, no\ ME)\} + \{W(II, ME) - W(II, no\ ME)\} \tag{11}$$

From equation 11, the consumer surplus can be interpreted as the sum of welfare loss resulting from withdrawal of incremental innovation and the gains from removal of additional market exclusivity, which is exactly the two blocks of values we are interested in.

If Δ is positive, then it implies that granting additional market exclusivity to incremental innovation is valuable since their loss is offset by their benefits. Therefore, we could separately measure the two terms in braces to get the estimate of Δ. For the first term, we will measure the welfare effect from product quality improvements without providing market exclusivity; Secondly, we will consider the price effects of extending market exclusivity while keeping the product quality unchanged with improved level.

Considering the four cases we discussed above, Δ will be calculated separately corresponding to each case. For example, for case 3, Δ is the sum of consumer gains from pediatric usage of the SSRIs without the market exclusivity extension plus the loss of providing the market exclusivity to all the pediatric studies.

5   Data

5.1   Data Sources

Three data sources are employed for this study: the consolidated individual data, medical condition data, and prescribed medicine event data from the Medical Expenditure Panel Survey (MEPS) from 1996 to 2009, the information about new drug application and patent/data exclusivity for

drugs from the U.S. Food and Drug Administration (FDA), and self-collected data about the drug characteristics from package insert labels.

MEPS provides nationally representative estimates of health care uses, expenditures, sources of payment, and health insurance coverage for the U.S. civilian non-institutionalized population. It follows all the individuals in randomly selected US families for 2 years with 5 rounds of questions, information recorded includes respondents' health status, demographic and socio-economic characteristics, health insurance, medical expenditure, etc.. More importantly, it supplements the survey data by contacting medical providers and pharmacies to acquire detailed and accurate consumption and billing information. For example, if the patient reports purchasing Norvir from a pharmacy, the pharmacy is contacted and required to provide the purchasing history of Norvir for the patient. The survey began 1996 and the most recent wave from 2010 is available. Overall, there are 239,720 individuals including in the survey from 1996 to 2009.[24]

Two datasets from the FDA (Drug@FDA and Orange Book) provide exhaustive information on the drug approvals, supplemental approvals, patent, and data exclusivity. For each approval, whether it is a radical innovation (new molecule entity) or incremental innovation (new formulation, new indication, and new combination) is documented. The subsequent supplemental approvals (including the safety, efficacy, new indication, new strength, new formulation, label change, patient population change) following each approved drug could be tracked in the FDA database. The information is critically indispensable for our study to identify incremental innovation from radical innovation.

Moreover, the drug characteristics (the strength, dosage form, active ingredient, producer, approval date, patent expiration date, data exclusivity expiration date, type of data exclusivity, etc.) are all available from the FDA. Based on this information, we could generate several important drug characteristics such as dummy of generics and age of molecule for each drug. The only flaws is that it only provides the unexpired data exclusivity information, i.e., once the data exclusivity expires, the information about expiration date, exclusivity type becomes absent from the available dataset. Fortunately, we could uncover the expiration date of the expired drugs from the entry of other competitors (ANDAs approval or marketing date). As a complementary source, USPTO provides more detailed information on the patent and their expiration. To link the MEPS consumption data with FDA drug data, NDC data file in FDA plays an important role in making the match.

A unique self-collected data is utilized in our study. By reviewing the package insert label for each drug, we construct several variables of drug attributes. These variables mainly lie in two aspects: the indications and side effects[25]. Indications are noted in each label and remain the same until the supplement approval has been granted for new indication. We generate several dummies of indications for each drug. We also collect the side effects information for each drug from the clinical trial data. Due to the heterogeneity of the clinical trial across drugs in the sense of the composition of the patients, the drug strength, the length of the clinical studies, etc., the original statistics is not comparable across drugs. To make the statistics meaningful across drugs, we generate variables for each symptom: the ratio of the occurrence rate of the symptom for the patients taking drugs over the occurrence rate for the patients taking placebo[26].

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[24]When we started the data cleaning, the data from 2010 wasn't yet available.

[25]There is also information about FDA safety alarms to health professionals and patients about drugs. The alarms usually happen several years later after the approvals, when the patients utilization of the drug reveals more safety problems. For this category (SSRI), all the drugs have been received the same FDA alarm and therefore, we cannot identify this variable without variation and therefore we didn't include it into our study.

[26]The details to construct side effect variables are illustrated in Appendix A.2.

5.2 Products and Incremental Innovations

Our focus is on four active ingredients in selective serotonin reuptake inhibitor (SSRI) anti-depressant drugs, denoted in ATC code as N06AB-. [27] It involves four new molecule entities following with 12 incremental innovations and subsequent generics. [28] Prozac Weekly, Sarafem, as incremental innovations of Prozac are not included in this study due to their limited number of observations.

As shown in Table 1, following the marketing of four new molecule entities: Celexa (1998), Paxil (1992), Prozac (1987), Zoloft (1991) [29], subsequent updated generations are innovated. In our paper, to consider the incremental innovation, we mainly focus on the pediatric use of SSRIs and newly formulated drugs with new drug application to the FDA, such as Lexapro and Paxil CR. New indication uses will not be considered in this paper because the data exclusivity granted to the new indications in our study doesn't extend the market exclusivity due to a longer patent period. Our results, as demonstrated below, illustrate that the utility from new indications is not significant and also ignorable. [30]

If we define products as the drug with constant characteristics, then an updated version implies a new product; therefore, overall there are 12 products plus an outside option in our analysis. The indications for each drug are listed in Table 13 and the side effects for each molecule are also shown in Table 14. [31] Unlike most of the literature which treat drugs in different formulation and different strength as different products, in my study, I treat them as one product, since most depression drugs are administered once daily, I use weighted price across strength and formulation as the product price without further adjustment. Treating these simialar drugs as different products will make the estimation computationally burdensome without gaining benefits.

Products from branded firms and generic producers are distinguished. But we find it from the Table 14 and 13 that the characteristics of the branded drug and the generic one are similar in terms of indications and side effects because of the current legislation (Hatch-Waxman Act: Generic drugs can provide only the proof of bio-equivalence to branded drugs to get abbreviated new drug approval from FDA without carrying on clinical trials but building their safety and efficacy on the clinical data of the branded counterpart). As shown in Table 14, side effects data remain the same for all drugs with the same molecule across years. Finally, the summary statistics of the attributes for these drugs are listed in Table 5.

The additional market exclusivities granted to the incremental innovations in SSRIs include:

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[27] According to the WHO ATC index, there are nine substances which have ever been approved as medicines. (See http://www.whocc.no/atc_ddd_index/ and search N06AB.) However, three of them have been withdrawn due to safety problem, leaving only 6 molecules in the US market: Citalopram Hydrobromide, Escitalopram Oxalate, Fluvoxamine Maleate, Fluoxetine Hydrochloride, Paroxetine Hydrochloride, and Sertraline Hydrochloride. Among them, Fluvoxamine Maleate is omitted in our analysis because of ignorable market share. Finally we only focus on the remaining five active ingredients.

[28] Escitalopram Oxalate is basically a new formulation of Citalopram Hydrobromide, and therefore, we will treat it as an incremental innovation instead of a new molecule entity.

[29] Enclosed in the parenthesis are the year of first approval.

[30] The market exclusivity granted to new indication or new formulation only protects the updated drug from generic competition, however, the exclusivity for original new molecule entities will expire as usual. We can see from Table 1 that, while the marketing of new version of branded drugs, the generics entered as well. Nevertheless, even with market exclusivity extension on the new indication, the drug producer would generally need a new dosing strength or formulation to make this commercially reasonable since doctors could, and would, write prescriptions for the old version for the new indication. In this sense, it can be expected that the generics could obtain the new indication characteristics as the branded one as long as the drug strength or formulation are the same.

[31] Side effects data keep the same for all drugs with the same molecule which is obtained from the clinical data of branded drug. After Hatch-Waxman Act in 1984, generics could enter into the market based on the clinical data of branded counter-parts with only providing the bio-equivalence to the branded one. Therefore, we could expect that the side-effects of the generics remain the same as the branded one.

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- Prozac was approved for additional six month pediatric exclusivity for its pediatric usage which extend their market exclusivity from Feb. 2001 to Aug 2001;

- Paxil obtained 6-month exclusivity for its pediatric studies extend its market exclusivity from Sep. 2015 to Mar. 2016;

- Zoloft obtained 6-month exclusivity for its pediatric studies extend its market exclusivity from Dec. 2005 to June 2006;

- Lexapro obtained 6-month exclusivity for its pediatric studies extend its market exclusivity from Sep. 2011 to Mar. 2012.[32]

5.3 Sample Selection

As shown in Table 3, among the 239,720 respondents in MEPS, only those with depression (25,001, 92.9 %) [33] [34] and those who has no depression but purchased SSRI anti-depressants (1,914, 7.1%) are included in our analysis. 12,815 (47.6%) of the whole sample have ever purchased SSRI drugs. The rest of the patients: 7,298 (27.1%) had never purchased the drugs, 6,802 (25.3%) purchased other anti-depressants. The individuals who purchased drugs construct the demand of these products, and the patients who had condition but didn't purchased SSRI drugs make up of the potential market size, we regard them as choosing the outside option.

There is another potential group of patients unobserved in our sample due to their mild condition for which they never sought treatment, and are not reported in the survey. Therefore, we cannot include them. We believe this approach is reasonable as depression is the type of condition that only becomes a disease when it disturbs the mood of the patients and severely affects thier daily life.

As we know, depression is a chronic disease which requires long-term medication treatments. Therefore, refills and repeated purchasing are very common in the survey. Implementing a maximum likelihood estimation based on the full sample is computationally burdensome. Therefore, we will drop them accordingly. In our data, 104,143 purchasing events for the 12,815 individuals are documented. 70,937 observations are refills and 18,186 are repeated purchasing, which are dropped from our sample and left with 15,020 observations. Among them, 2,205 observations are switching drugs. For the records with switching, we keep the later drug as their choice and drop the earlier ones. We believe that patients are switching to find a better fit for their condition. Therefore, we have 12,815 purchase records for 12,815 individuals plus 14,100 patients who chose outside option kept in our study.[35] As evidenced in Table 4, the deletion of refills and repeated purchasing has little effect on our demand estimation since the market share remains more or less the same between the MEPS survey sample and our analytic data.

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[32]We will not investigate the withdrawal of this exclusivity since the time span is out of our data scope.

[33]According to the ICD-9-CM diagnosis codes, if the respondent has condition with code 296 (Episodic mood disorders), 300 (Anxiety, dissociative and somatoform disorders) or 311 (Depressive disorder not elsewhere classified), then we regarded them as having depression.

[34]The condition can be recorded in MEPS for the following reasons: 1. reported by the household respondent for a particular medical event (hospital stay, outpatient visit, emergency room visit, home health episode, prescribed medication purchase, or medical provider visit); 2. reported as the reason for one or more episodes of disability days. 3. Reported by the household level respondent as a condition "bothering" the person during the reference period.

[35]Alternative sample selection method is to keep the observations in individual-year level rather than in individual level since in our analysis, years implies different market with different choice sets and prices. The difficulty in this lies in that the observations will be almost doubled (44,332 vs. 26,915): Estimating a maximum likelihood model with 12 products in 26,915 observations is already computationally burdensome, requiring around 100GB of memory and more than 3 days to process. Doubling the observations makes the current computation resources unsustainable.

5.4 Variables

The dependant variable used in this paper is the treatment choice dummy of each patient in a period. The treatment choices include the drugs products we illustrate above in section 4.2 and an outside option. Here, we assume if an individual purchase the drugs, he is considered to be taking the medicine, i.e., $choice_{it} = 1$. Patients' compliance to the medication isn't considered in our context.

The details of data construction for the individual characteristics and drug attributes are described in Appendix A. The individual demographics that we use include Age_{it}, $Adult_{it}$ [36], $Male_{it}$. The socio-economic variables include $Years\ of\ educat-ion_{it}$ and $Family\ income\ per\ capita_{it}$. Family income per capita is generated by average the total family income across individuals. Income is deflated and measured in 1996 dollars. For children and adolescents, I use their parents' education as the education level since we want to see whether education helps people obtain better health service.

The health-related variables we employed in the study includes health insurance variables (i.e., $Having\ medical\ insurance_{it}$, $Having\ Medicare_{it}$, $Having\ Medicaid_{it}$, $Drug\ Insurance_{it}$ and subjective perceived status $Perceived\ health_{it}$). As we all know, besides drug price, the insurance coverage plays an important role in the patients choice making as well, especially the drug insurance. Therefore, we include dummies for whether having medical insurance, having Medicare, having Medicaid to control the insurance status for each individual. Unfortunately, the drug insurance coverage is not observable in the survey. To proxy the drug insurance, we construct $out\ of\ pocket\ ratio_{it}$ for each individuals based on their purchasing history.[37]

The drug attribute variables mainly include $Price_{it}$, $Age\ of\ Molecule_{it}$, $Generic_{it}$, indication dummies and side effect variables[38]. $Price_{it}$ is deflated to 1996 price level using CPI in Managed Care Commodities category[39]. $Age\ of\ Molecule_{it}$ is the same for the branded and generics in the same year. It is the period length from the birth of new molecule till the year when purchasing happens. A dummy variable $outside$ is generated to denote whether the individual chooses SSRIs ($outside = 0$) or outside option ($outside = 1$). The variable is introduced to facilitate the estimation for outside option.

SSRIs are primarily used to treat major depressive disorder (MDD), besides that, they can also be used to treat obsessive compulsive disorder (OCD), panic disorder (PD), post-traumatic stress disorder (PSD), premenstrual dysphoric disorder (PDD), social anxiety disorder (SAD), bulimia nervosa (BN). As we can see in Table 13, when a drug is initially developed, its clinical trial data only supports the safety and efficacy of one or two indications. As time goes by, the manufacturers carried on subsequent investigation and then more and more indications is supported after the supplemental approval by FDA. This process is one type of incremental innovation that we want to investigate in this paper. Therefore, the same drugs across year may have different indications and therefore bring to the patients different utility, in the following studies, we will control the year and the indication.

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[36] We define $Adult_{it} = 1$ if $Age_{it} \geq 18$

[37] In Prescribed Medicines Files of MEPS, the listed price as well as the price paid by patients are all provided.

[38] Indication dummies and side effect variables have been introduced in the above data subsection and they are listed in Table 12 and Table 13.

[39] CPI source: US Bureau of Labor Statistics.

6 Results

6.1 Descriptive Statistics

Figure 1 shows the market share of SSRIs (branded and generics) and an outside option. Just as we mentioned above, the market share of outside option is around 50 % in our data, including those who have been diagnosed as depressive but didn't purchased SSRIs. The overall diagnosed depressive patients are increasing from less than 500 MEPS respondents in 1996 to more than 3500 individuals in 2009. The demand for SSRI antidepressants shifted gradually from the branded to the generic starting from 2001, the first year when generic Prozac was available. The market share of generics surpassed that of the branded in 2009. With the expansion of the generics, the patients who prescribed SSRIs reach the highest level in 2009. However, the total sale of SSRIs changes in another direction (see Figure 2)[40]. Although the total demand of SSRIs remains high as shown in Figure 1, the sales revenue of SSRIs dropped dramatically in 2007, driven by the sharp decreasing of drug price (See Figure 5). This pattern illustrates that the tough generic competition in this market make Bertrand-Nash model no longer applicable in the last three or four years.

By separating the market share and sales by brands, it's clear to see the strategic behavior of producers (See Figure 3 and 4). For the first five years, the market is mainly divided by three branded products: Paxil, Prozac and Zoloft. With the entry of Celexa and its new formulation Lexapro (produced by Forest Labs), the share of Paxil and Prozac begun to shrink in 2003-2005. The new formulation of Paxil, Paxil CR is not as successful as Lexapro in the market. Lexapro successfully grabbed market share from its ancestor and other brand competitors, achieving the highest sales among SSRIs in 2006, while the sales of Paxil CR become negligible until the end. Another interesting phenomenon about the Celexa and Lexapro is that two or three years before the patent expiration of Celexa (2004), Lexapro is marketed in 2002. Over that time, the demand for Celexa gradually shifted to Lexapro. When the generic Celexa entered into market in 2004, the overall use of Celexa had already gone down significantly, leaving only little market share for the generic counterparts. This observation is consistent with the evidence of Huckfeldt and Knittel (2011) [18], who find large decreases in overall use after patent expiration that begin in the two years before generic entry and continue in the years following. Furthermore, they suggest that it might be due to advertising which shifts demand from the now cheaper original molecule to another patented molecule.

The price trend of SSRI antidepressants across the years are provided in Figure 5. The bar graph indicates the number of generic firms producing the molecule in each year. With the number of generic entries increasing, both prices for the branded and generics go down, although the price reduction doesn't happen immediately after the first generic entry.[41] The turning point is in 2007, when most of the SSRIs prices dropped dramatically. It can be imagined that the pricing strategies should change afterwards from oligopolistic pricing to perfect competition.

The individual demographic statistics of the sample are provided in Table 3 comparing to the national representative sample. Column 1 and 2 shows the mean and the standard deviation for the whole sample in MEPS and the analytic sample in our study; column 3-5 separately show the statistics of the subjects in the sample by three groups: for those who reported that he/she has depression but he/she didn't purchase SSRI drugs; for those who have depression and ever purchased SSRIs; and for those who have no depression condition but purchased SSRIs.

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[40]The sales is simulated by assuming each individual has a compliance rate of 0.75 over 365 days in a year when taking the once daily treatment. The price we used is the weighted price over different strengths and dosage forms.

[41]The Hatch-Waxman Act grants 180-days of market exclusivity to the first generic entry which exclude the generic competitors in the short run.

Table 3 reveals that those in the sample are quite distinct from the national population. Compared to the national representative sample, our study sample consists of individuals who are older (45.72 vs. 33.62), more likely to be female, have a lower perceived health status (2.93 vs. 2.21), have a higher prevalence of respiratory diseases (0.09 vs. 0.04), asthma (0.09 vs. 0.05), hypertension (0.28 vs. 0.13), cardiovascular heart disease (0.19 vs. 0.08), diabetes (0.12 vs. 0.05) and are, of course, more depressive (0.93 vs. 0.03). Our sample has higher insurance coverage (0.88 vs. 0.83), lower out of pocket rate (0.48 vs. 0.54), it might be due to the selection effects: individuals in our analytic sample tend to buy more insurance because of their worse health status. Our sample have lower household income (39, 610$ vs. 44, 600$) but higher household income per capita (16, 610$ vs. 15, 330$) which implies that they have fewer dependants in the family. Overall, it shows considerable variation in most of the demographic variables.

Within our sample, there are also significant differences across the three groups. For those who reported of having depression, those who chose SSRIs are significantly different from those who chose an outside option for most of the demographic variables, except for the dummies of having HIV, having depression (this doesnt make sense to me). For those who purchased SSRIs, those who are depressive are also distinguished by the all of these variables from sample who are not depressive except for age, household income per capita, having Medicare, having HIV and having cardiovascular heart diseases.

Table 5 shows the summary statistics of the drugs. All of the drugs can be used to treat Major Depressive Disorder.[42] A large proportion of the products can be used to treat obsessive compulsive disorder (0.68); around half of these products can be used to treat panic disorder (0.55), and premenstrual dysphoric disorder (0.45). Around one third of the products can be used to treat social anxiety disorder (0.32) and bulimia nervosa (0.32). Over one-fifth of the products can be used to treat posttraumatic stress disorder (0.23). The variation of side effects ratios across products seems not large except abnormal ejaculation and anorexia.

6.2 Demand Side

We estimate the model by simulated maximum likelihood estimation.[43] The model contains 109 branded-year fixed effects and 115 explanatory variables (including two random coefficients for price and generic dummy and 113 individual-drug characteristics interaction terms). The full set of parameter estimates is shown in Table 15 and Table 16. To avoid poor estimation of Maximum Likelihood in the existence of scale problem, the variables with large scale have been taken logarithm. These variables include *Age*, *Age_squared*, *Age of Molecule*, *Abnormal Ejaculation*, *Years of Education*. The interaction term of variable *outside* with individual characteristics from Table 15 shows the estimates for β_{1r} which capture the variations of payoffs of outside option across individuals.

The selected estimates of parameters for the interacted explanatory variables are listed in Table 6. Factors such as *Drug Insurance*, *Household Income per Capita*, *Prices*, *Age of Molecule*, *Generic Dummy*, *Pediatric Usage* matter for patients' choice making. The estimates reveal that several individual attributes affect price sensitivity. Those with higher incomes, with drug insurance (lower out of pocket ratio), without Medicaid tend to be less sensitive to price. Age has a U-shape relationship with price sensitivity: the young and the elderly tend to be more price sensitive than middle aged adults. In additional to reducing price sensitivity, having drug insurance has a positive and significant effect on the probability of taking medications (see from the coefficient of the interaction of *Out of Pocket Ratio* and *Outside Option*). Patients with drug insurance tend to

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[42]Due to lack of variation, in the following analysis we will ignore this dummy.
[43]See Train [29][31] for detailed discussions.

purchase the younger medications and generics. The potential explanation for this phenomenon is that the reimbursement conditions and regulations provided by drug insurers encourage insurees to purchase generic drugs. As shown in Table 6, patients with medical insurance tend to purchase drugs with pediatric usage; individuals with higher incomes tend to choose the generics and the drug with pediatric use.

Using estimates of mean utility derived from the first stage MLE estimation, the second-stage demand estimation regresses mean utility on price and other product characteristics. The exogenous variables in the second stage are the indication dummies and brand dummy variables with branded Celexa as the excluded alternative. As shown in Table 12, the dummies of OCD and BN coincide with brand fixed effects, which generates collinearity problem, and therefore they are excluded in the second stage estimation. Even if we couldn't estimate the parameters for these two indications, it doesn't affect our future counter-factual calculation. Our focus is the welfare effect on the discovery of new indications for existing drugs while there is no incremental innovation related to these two indications. Table 7 reports the second-stage results. The first column shows the results from OLS estimation without consideration of price endogeneity. Column 2-4 shows the IV estimation with different IV combinations. The results show that the coefficient on *Price* is negative and highly significant with a coefficient, -1.443. Note that the price coefficient is much larger than the coefficient on the interaction of *Price* and *Drug Insurance* of 0.61 (reported in Table 6), which implies that those with drug insurance are actually still responsive to market price. The IVs we used in our main model (column 2) is *Markup*Generic* and *Number of Dosage the Product Has*.

The relevance and validity of the IV have been checked in our study. Corresponding to the model specification in Table 7, Table 8 shows the first stage results of regressing price on IVs and other included exogenous explanatory variables. The results show that the instruments *Markup*Generic* and *Number of Dosage the Product Has* are significantly correlated with prices. The weak instruments tests have been rejected and the over-identification restriction test shows that the null hypothesis of the IVs is independent of the error terms are accepted. For the constructed IV:*years after the first generic entry*; and *number of firms (branded and generics) selling the same molecule in the market*, they didn't pass the overidentification test, therefore, we don't include them in the table. These two variables are all related to the life cycle of the products, therefore, they might be correlated with unobserved error term.

6.3 Supply Side

Based on the assumption of firms' pricing behavior, marginal costs of products in the market are backed up. For the Bertrand-Nash equilibrium, the recovered marginal costs satisfy equation 9: the estimates of marginal costs are built upon the knowledge of observable prices and estimates of demands and their derivatives. The estimated marginal costs and margins ($Margin = (Price - MC)/Price.$) are shown in Figure 6.

As we expect, based on the Bertrand-Nash model, the estimated firm margins are much higher for the years after 2006. Considering that the market structure after 2006 tends to be more competitive, as evidenced by numerous generic entries shown in Figure 5, the margins are overestimated. It highlights that our data limitations pose a severe problem in supply side modeling. Instead of using the estimated cost to recover the counterfactual prices for the years after 2006, we directly infer the counterfactual prices from the prices in market. This inference might not be accurate, but it will provide more reasonable estimates of price than those obtained from the Bertrand-Nash model.

Before computing welfare changes, the simulated equilibrium prices are estimated based on

the estimated consumer preferences and recovered marginal costs. Products characteristics are altered in counterfactual scenarios when we withdrawal incremental innovations. Corresponding to each scenario, there is no pediatric use, new prices, or the newly formulated drugs are removed from the choice set. Based on the simulated demands and recovered marginal costs from the status quo case, we estimate the equilibrium prices. The correspondence of different cases to different scenarios and the assumptions of prices and costs for each scenario are illustrated in Table 9 and 10.

The model used to simulate the prices is for Bertrand Nash Oligopolistic market structure. As we explained before, the Bertrand Nash model tends to overestimate the firm margin when we could identify the generic competitors. Therefore, to get a tentative estimation of welfare change for the years after 2006, we simply assume the price equal to the price we observed in the market, with setting the counterfactual prices without pediatric exclusivity with the price observed one year later. Because we didn't have the status quo of price for generic Paxil CR and generic Lexapro, we have adopted the prices of their ancestors, generic Paxil and generic Celexa.

Figures 7 to 14 show the estimated price changes across scenarios. For example, Figure 13 shows the prices changes from the scenario without pediatric use and pediatric exclusivity to the scenario with pediatric and without pediatric exclusivity. The pink points denote the prices in Scenario 7, while the blue points denote the prices in Scenario 8. The prices of Celexa, Lexapro and Paxil and Paxil CR are slightly lower than the case without pediatric use. Figure 14 shows the prices changes from the scenario with pediatric use and no exclusivity to the scenario with pediatric use and exclusivity. We find that the exclusivity results in overall price increases (from blue points to pink points). Not only have the branded firms charged a higher prices to the patients but so have the generics. Almost all of prices changed from the scenario without market exclusivity to the scenario with market exclusivity, involve price increases (as shown in Figure 8,10, 12, 14). In all these figures, we only considered the years before 2006. As we explained before, the standard Bertrand Nash model couldn't provide reasonable estimates for the case when Medicare Part D introduced and there are numerous generic entries. Therefore, the counterfactual estimates doesnt make much sense.

6.4 Welfare Analysis

As shown in Section 4.4, we measure four counter-factual cases by excluding all the incremental innovations and accompanied market exclusivities and then excluding three different types of incremental innovations separately to consider their different effects. To illustrate the magnitude of the benefits and costs side, we need to separate the welfare effect by two parts (see Equation (11)), which implies we have to investigate 8 different scenarios. For example, for case 4, we construct a counterfactual market withdrawing pediatric use from all drugs, and enabling the generics enter one year earlier (for Paxil, Prozac, Zoloft[44][45]) (i.e., $W(noII, noME)$), together with a counterfactual including the pediatric use but still making the generics enter earlier (i.e., $W(II, noME)$). Therefore, we are able to calculate the two effects: $W(II, ME) - W(II, noME)$, $W(II, noME) - W(noII, noME)$, noting that the purchasing records observed in data represent the case $W(II, ME)$.

As shown in Section 4.5, by dividing individual's utility change from an event with the price coefficient, and summing them up, we can obtain the measure of welfare change. The utility change compares the individual utility from status quo with the utility in counter-factual scenar-

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[44]Celexa didn't obtain 6-month pediatric exclusivity.

[45]In our data, we could only identify individual who purchased drugs by years, not months. Therefore, here we can only measure the effect of generic entry one year earlier if we remove the 6-month market exclusivity.

ios. Hence, Table 11 and 12 provide the estimates of welfare changes for the years before 2006 and all the years respectively. The profit changes of the firm are for the branded firms. The profit changes of the generic firms are not listed here for several reasons: first, for the years prior to 2006, the generic market share are very small and the magnitude of welfare effects are ignorable; second, for the year after 2006 we couldn't accurately estimate the margin of the generics or their profits.

Overall, the social benefits from incremental innovation outweigh the loss from market exclusivity by a small margin: 1.2 billion dollars for the years before 2006, and 0.5 billion dollars for 1996-2009 (considering the net value of case 1). Considering the incremental innovation separately, the introduction of Lexapro brought large profits to the branded firms, as do the provision for pediatric use. However, the marketing of Paxil CR with exclusivity brings about net negative social welfare. For the consumer surplus from each incremental innovation, patients suffer from "granting exclusivity to incremental innovation;" the net consumer surplus loss from Lexapro is 9.22 billion dollars, from Paxil CR is around 6.29 billion dollars, and from pediatric use is around 6.64 billion dollars for 1996-2005. Due to the overall decrease in drug prices in 2007, the consumer loss for 1996-2009 are reduced for each type of incremental innovation. You might wonder why putting all the incremental innovation together increase the consumer surplus. As shown in the column 3 of Table 11 and 12, the consumer surplus of introducing all the incremental innovations is much higher than the sum of benefits from simply introducing one of the incremental innovations. The reason is that competition effect of multiple incremental innovations drags down the prices in the market. Compared with Figure 10, 12, 14, the counterfactual prices in Figure 8 is lower than their counterparts in other three figures. The competition effect also explains why the loss of branded firm profits is so high in the case of introducing all incremental innovation (20.6 billion dollars in Table 11.)

7   Conclusion

In this paper, I address the following research question: Should additional market exclusivity be granted to incremental innovations to allow innovators to recoup R&D investment cost from monopoly pricing, despite the fact that excluding competition could harm the consumer surplus?

By comparing scenarios of either withdrawing or allowing market exclusivity for incremental innovations with scenarios of withdrawing or retaining incremental innovations, I found that the consumer benefits from incremental innovation are overwhelmed by the consumer surplus loss due to market exclusivity when considering a single incremental innovation, whereas the consumer benefits from innovation outweigh the consumer losses from exclusivity when considering the counterfactual of withdrawal of all incremental innovations and market exclusivities. This result suggests that innovation benefits are primarily driven not by the quality improvements of products but by the competition effect of the introduction of several incremental innovation products in the market.

My research is novel to the literature in the following ways. First, to my knowledge, this is the first paper to combine a measurement of the value of innovated products with a quantification of loss from market exclusivity, which offers a number of interesting and critical policy implications. Second, unlike existing studies, which either adopt aggregate level data with random coefficient models or use individual-level data with conditional logit models to measure the value of pharmaceutical innovation, my paper applies a random coefficient model with patient-level data. I estimate the model with simulated maximum likelihood estimation, taking price endogeneity into account. Although this method brings about difficulties in estimation and is computationally

burdensome, it takes advantage of detailed demographic information in micro-level data and also enables individual heterogeneity, resulting in a better fit between model and data. Third, our results suggest that "granting market exclusivity" not only provides incentives to innovate but also fosters a market with improved high-quality products, which hasn't been emphasized in previous studies. Although it excludes generic competition, it justifies branded drug competition. Therefore, taking all these effects into account, "granting the market exclusivity" is favorable because it improves social welfare.

However, our results should be interpreted with caution. For starters, our results are drawn from the incremental innovations of SSRIs antidepressants. For other therapeutic classes of drugs, the conclusion may not hold. Development of innovative medicines is full of uncertainty, as is its value to the patients, which varies across diseases and treatments. Additionally, we haven't been able to consider the substitution effect of market exclusivity—motivating firms to invest their resources in incremental innovation results in decreased investment resources in radical innovation. "Granting additional market exclusivity to incremental innovations" might alter the relative marginal revenue of incremental innovation to radical innovation and therefore distort investment allocation between these two types of innovations. Furthermore, the responsiveness of incremental innovation to market exclusivity hasn't been investigated in this paper. We assume that without market exclusivity, no incremental innovation would be innovated. However, this is still an open question and it will be explored in our future research.

Several questions worthy of future investigation have arisen. First, how large is the role that advertising plays in promoting newly formulated drugs, and could we identify the advertising effects from the improved quality effects in expanding demands for newly formulated drugs? Second, what are the learning behaviors of patients using pharmaceuticals for chronic diseases, and how do patterns of switching from one drug to another differ based on different individual characteristics? Third, will pricing control on the insurer side discourage innovation activities of the branded firms? As we know, creating drug reference catalogues, legalizing generic substitutions, and setting price caps for brands all tend to encourage consumption of generics instead of their branded counterparts. These questions are potential directions for future research.

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Figure 1: Market Share of SSRIs across year
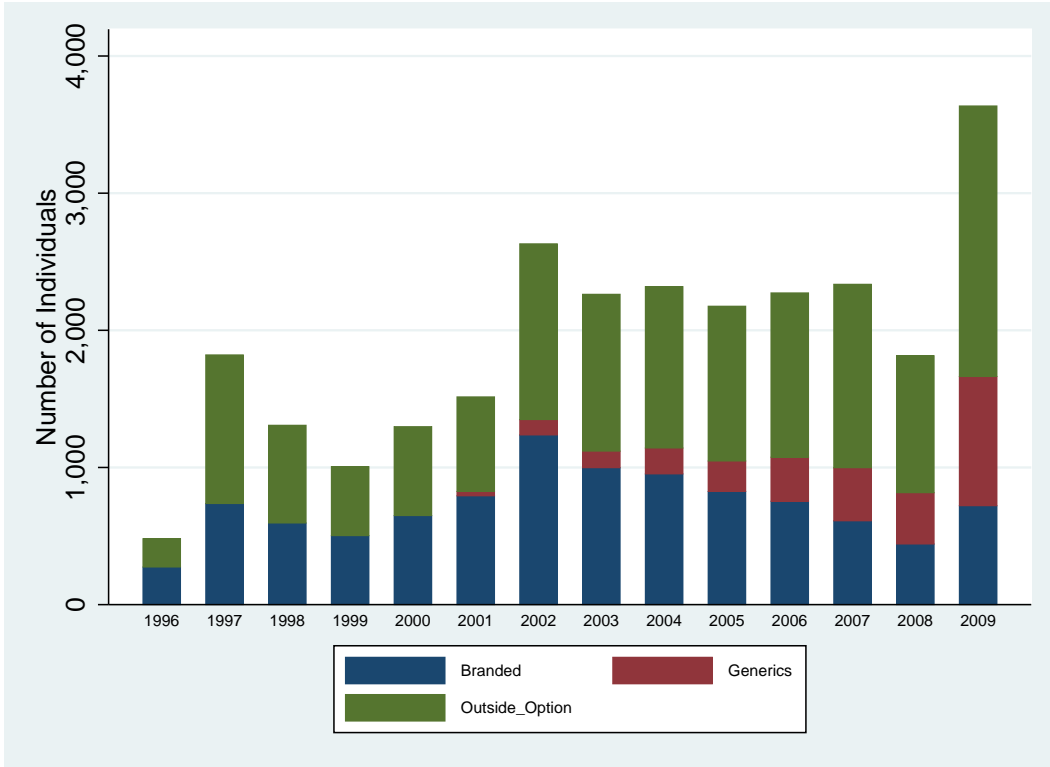
Figure 2: Annual Sales of SSRIs across year
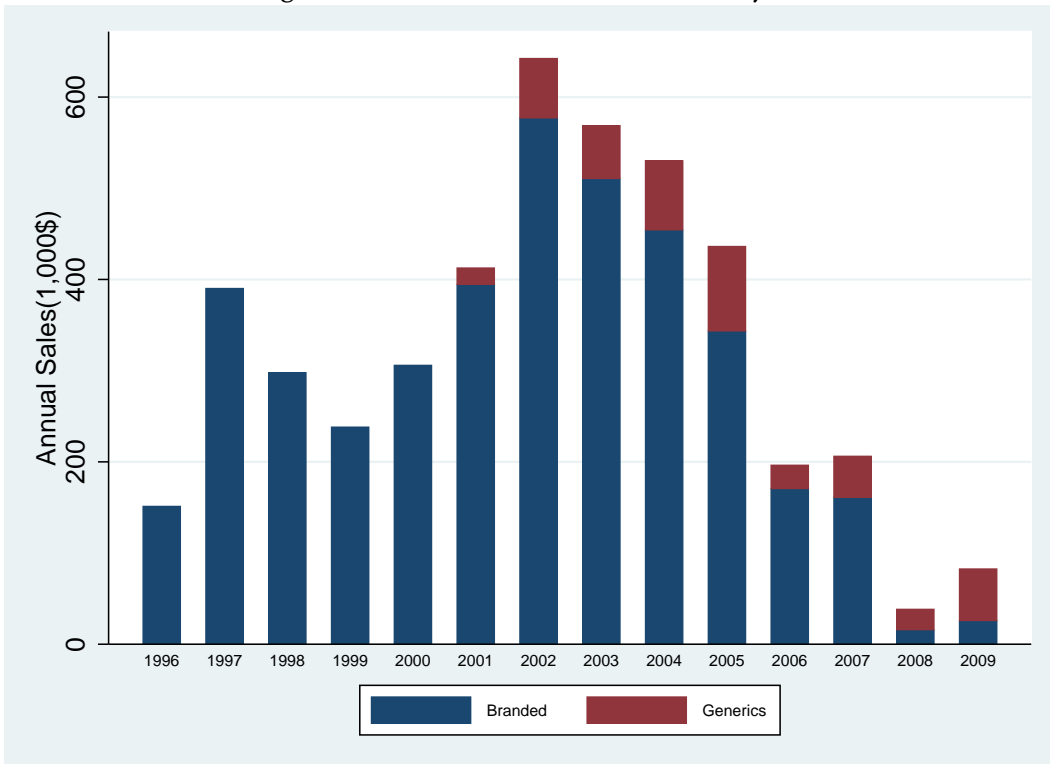
Figure 3: Market Share of SSRIs over Brands across Year
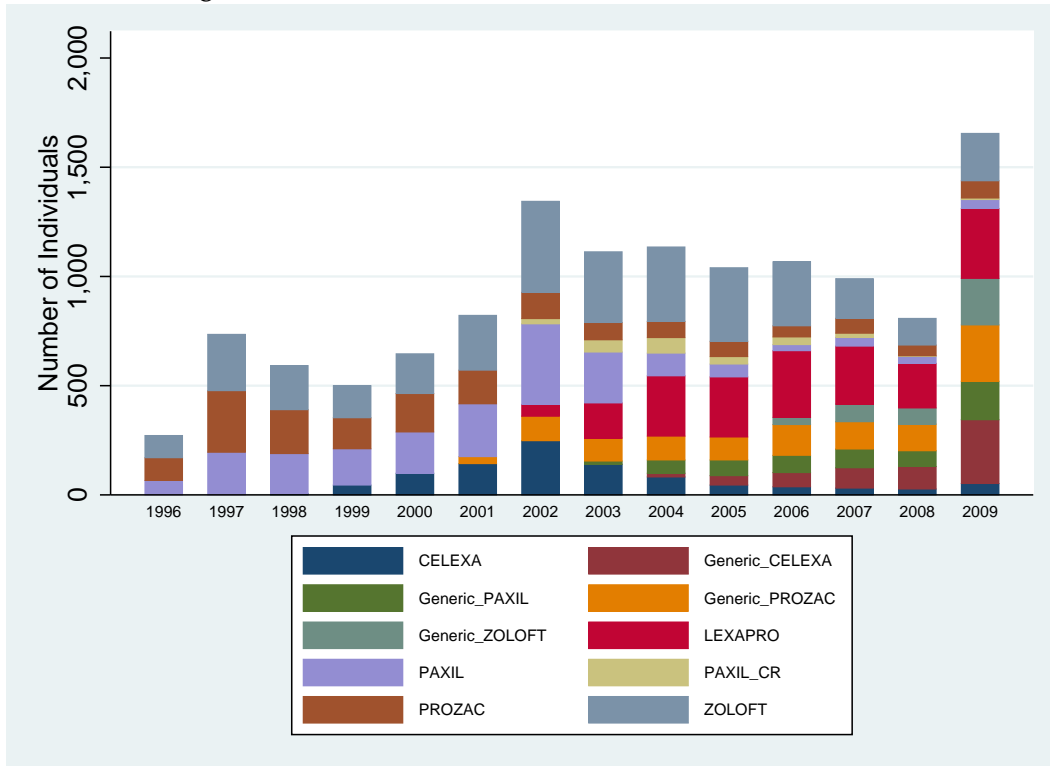
Figure 4: Annual Sales of SSRIs over Brands across Year
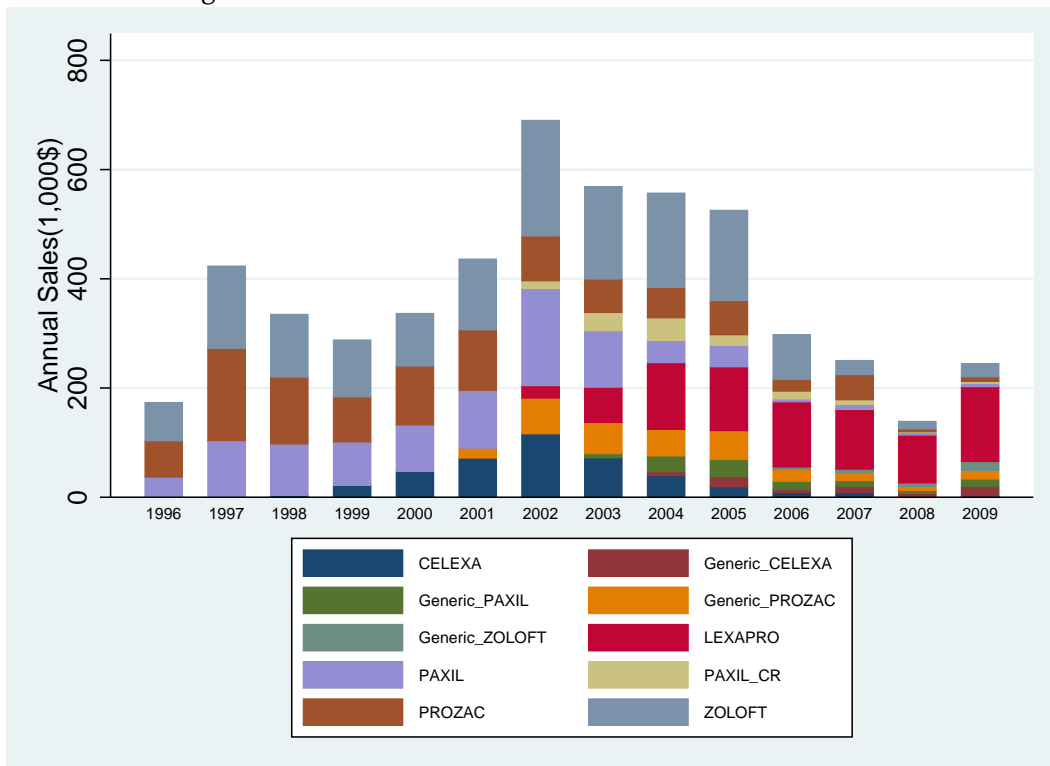
Figure 5: Price Trend with Generic Entry
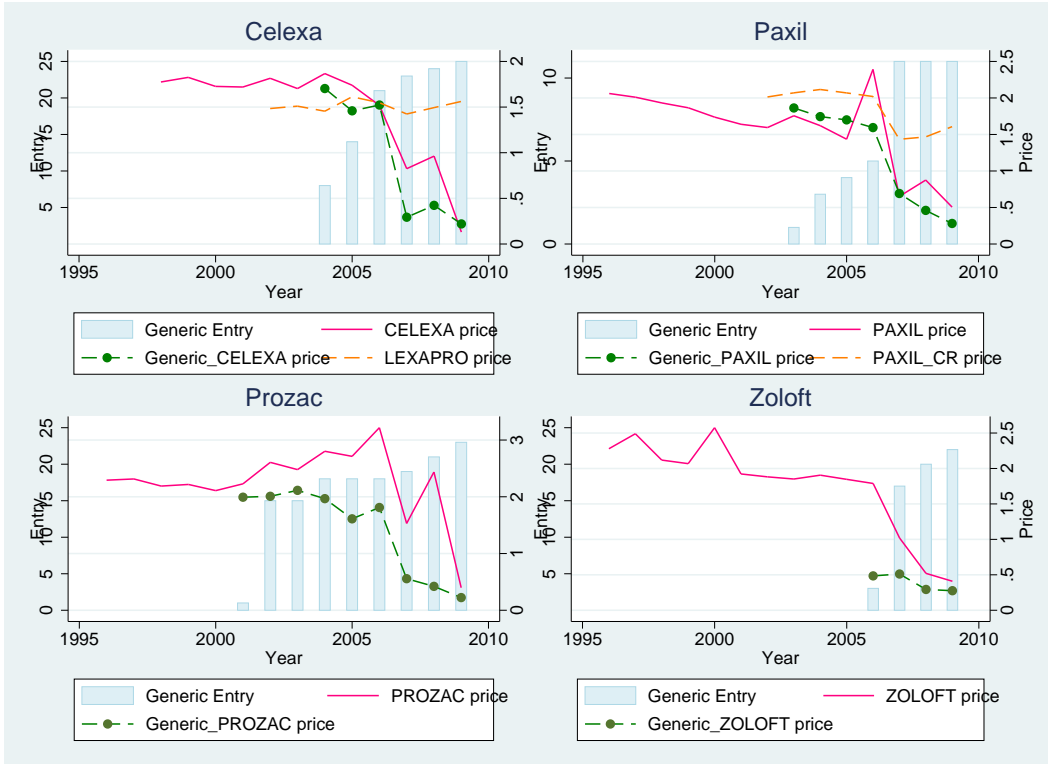
Figure 6: Estimated MC and Margin
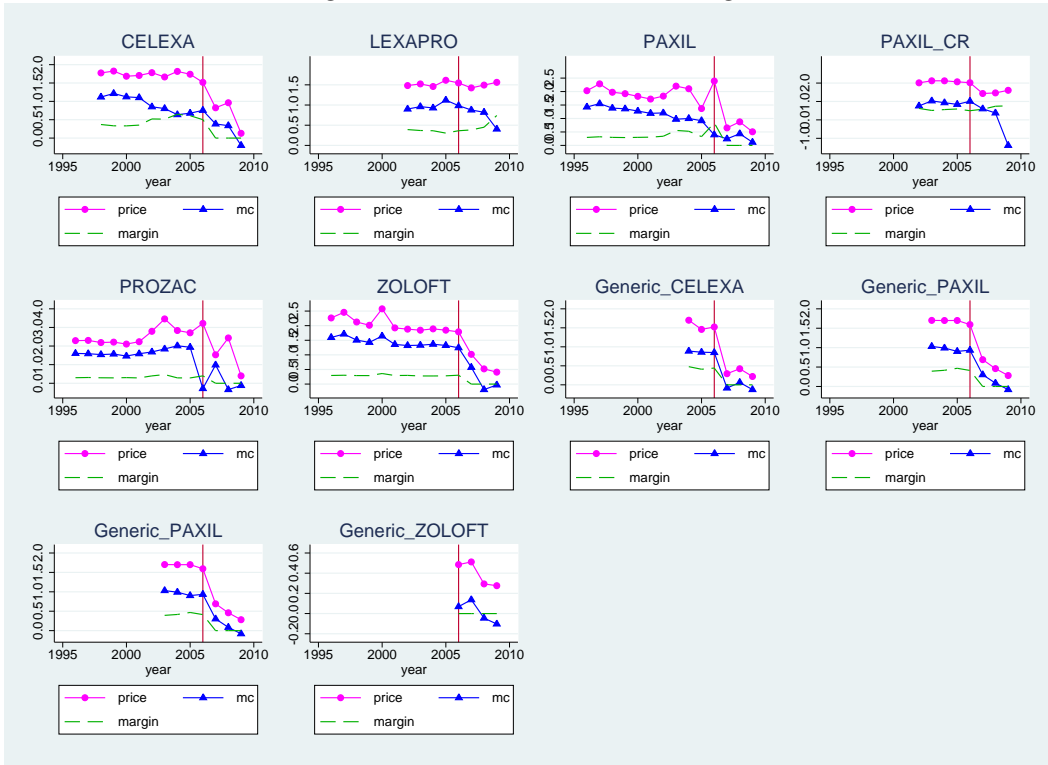
Figure 7: Price Changes from Scenario 1 to Scenario 2
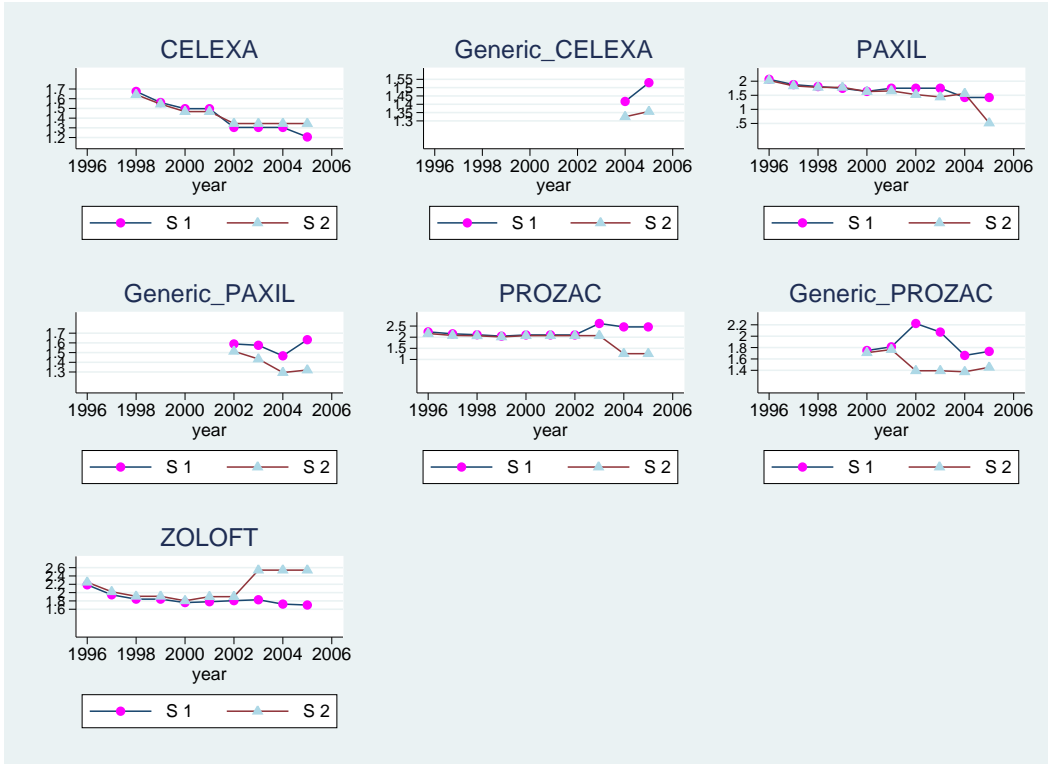
Figure 8: Price Changes from Status Quo to Scenario 2
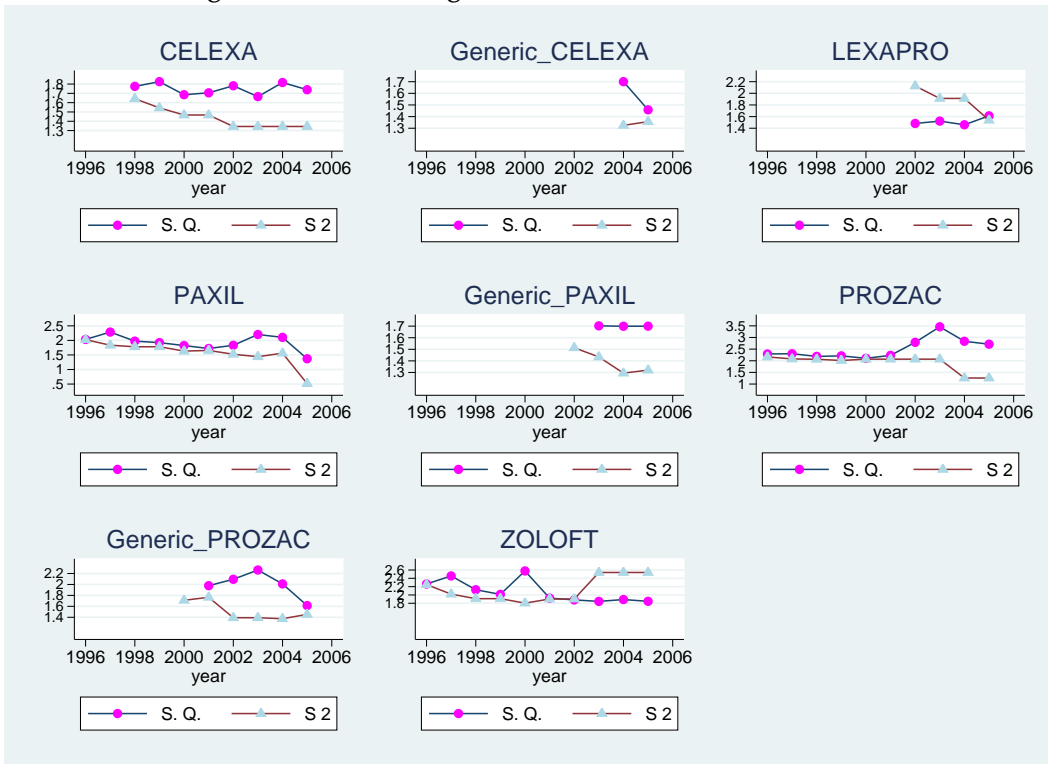
Figure 9: Price Changes from Scenario 3 to Scenario 4

Figure 10: Price Changes from Status Quo to Scenario 4
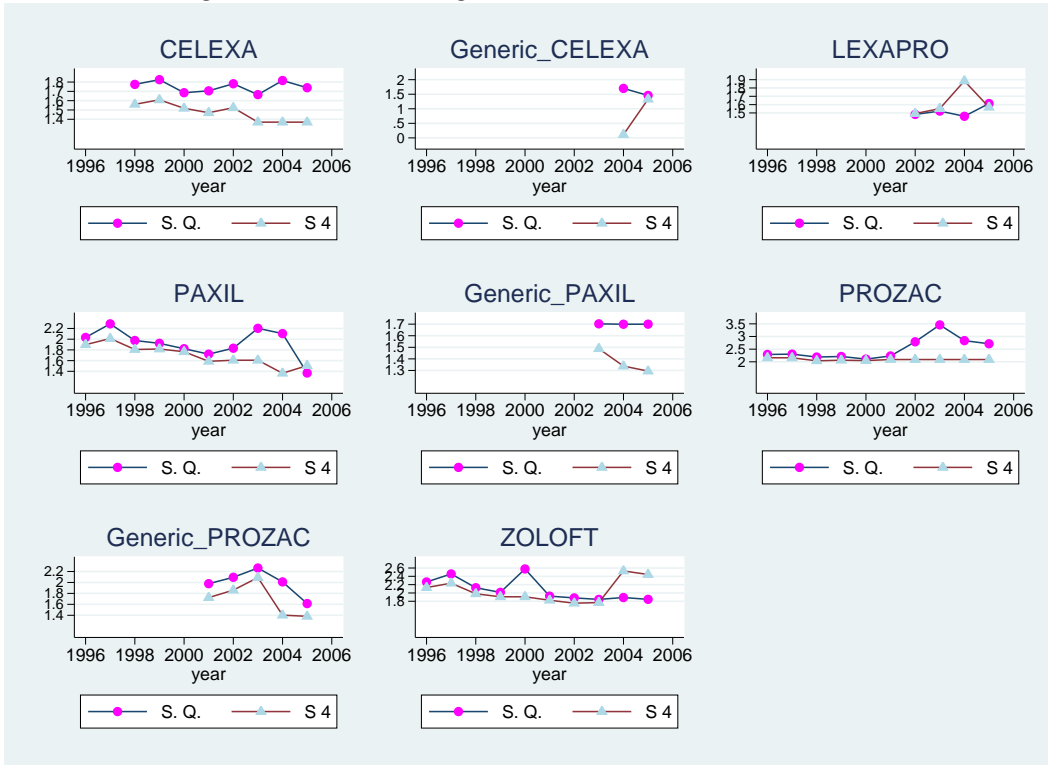
Figure 11: Price Changes from Scenario 5 to Scenario 6
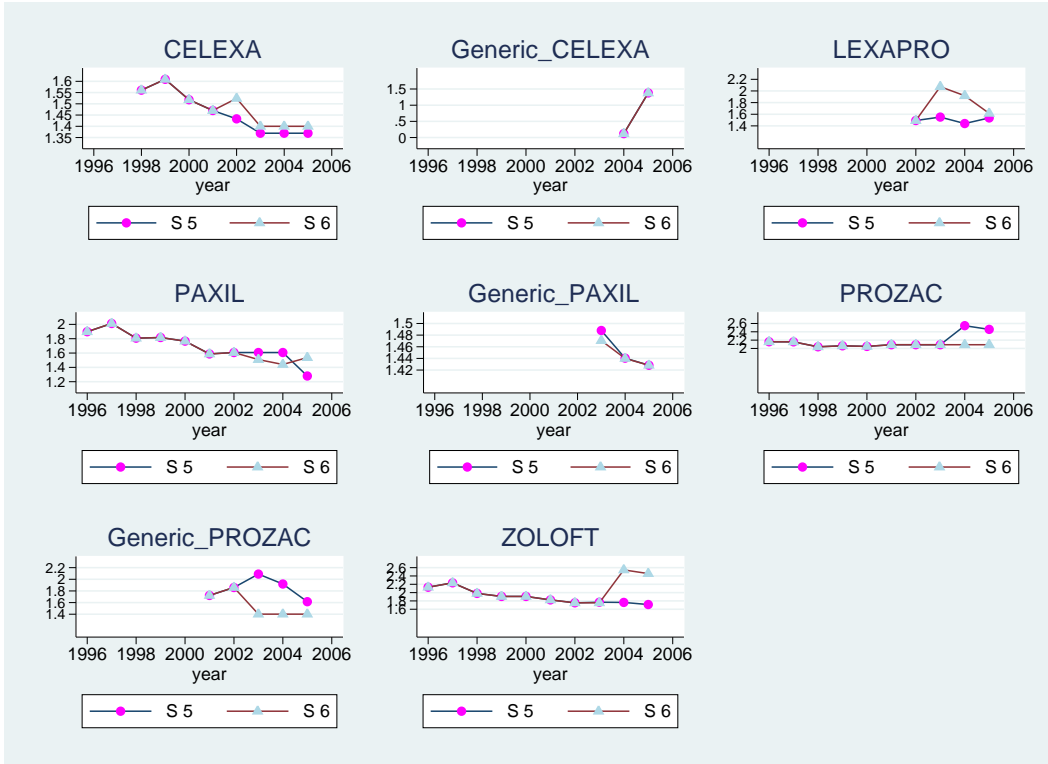
Figure 12: Price Changes from Status Quo to Scenario 6
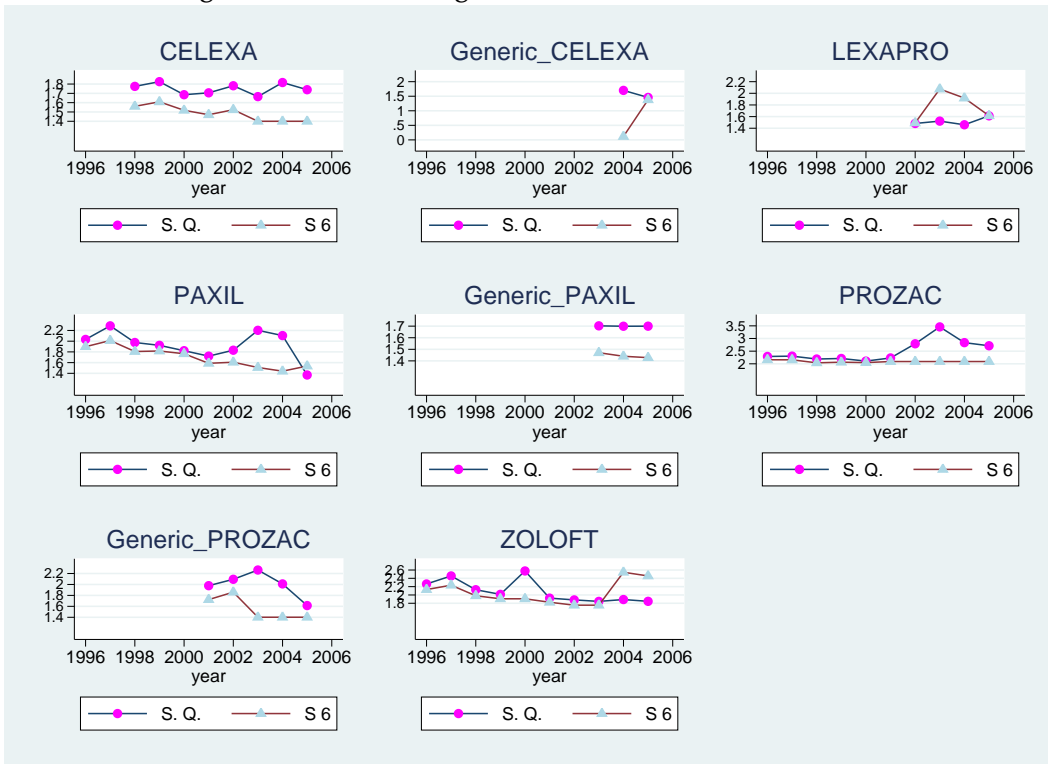
Figure 13: Price Changes from Scenario 7 to Scenario 8
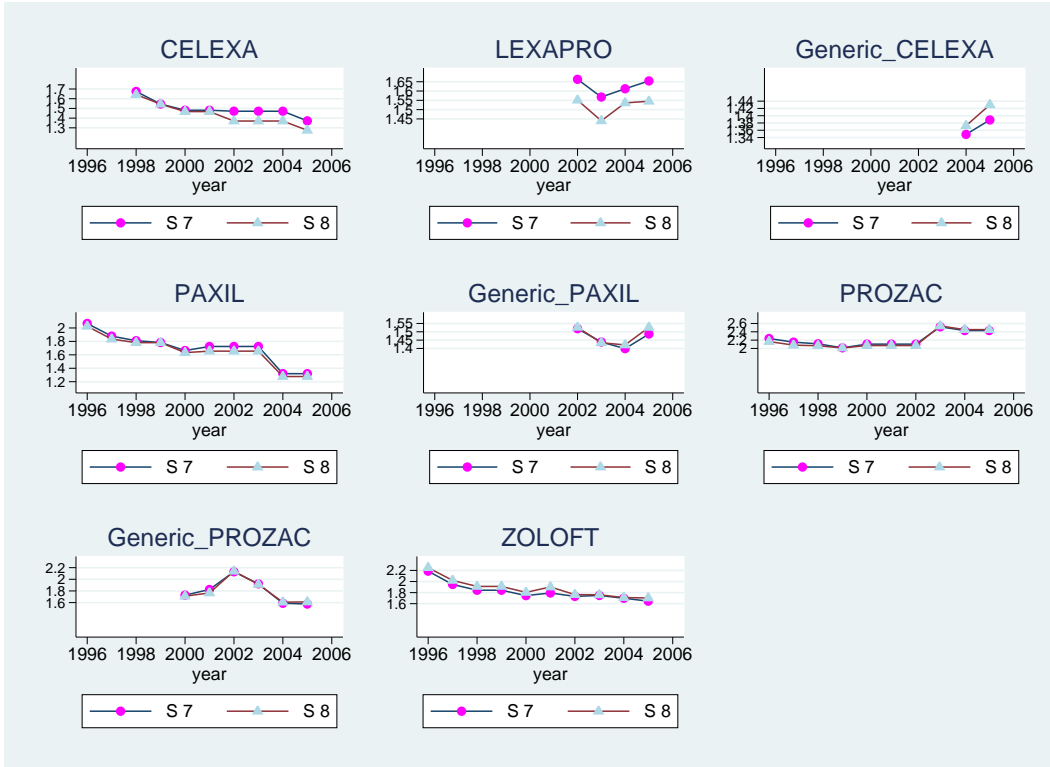
Figure 14: Price Changes from Status Quo to Scenario 8
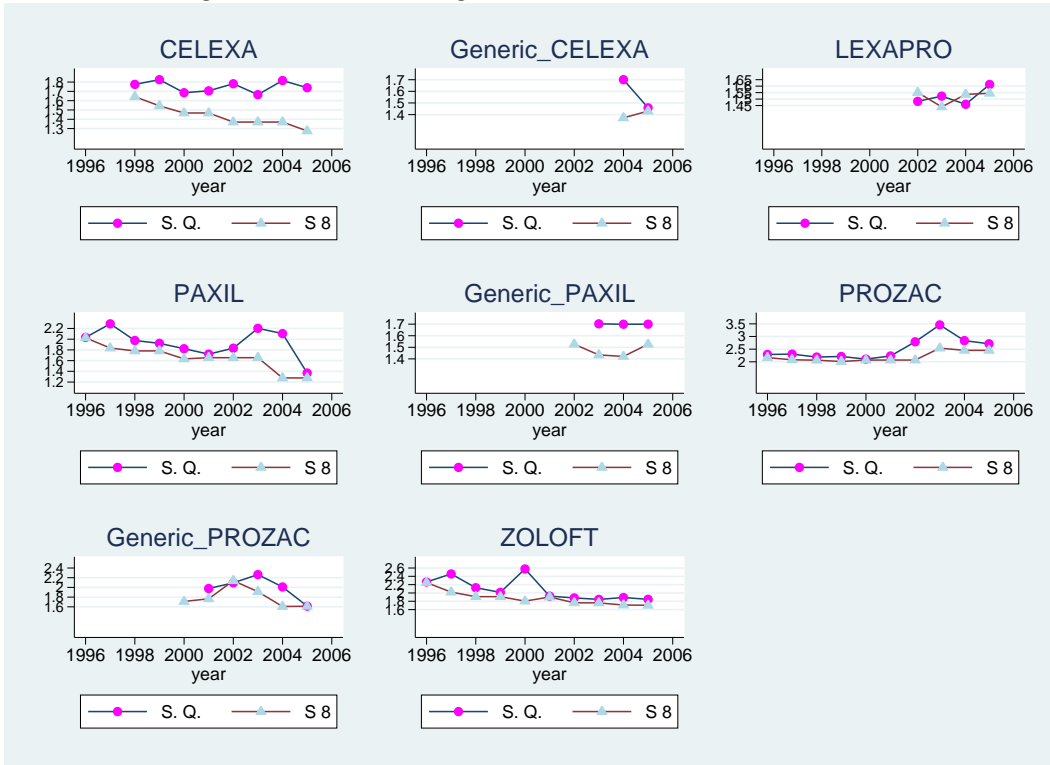
Table 1: Products and Incremental Innovations in SSRI Anti-depressant Drugs

New Molecule	New Formulation	New Indication	Pediatric Usage	Safety	Generics
Celexa 1998	Lexapro 2002	Lexapro 2003 (Form.)			Generic Celexa 2004
Paxil 1992		Paxil 1999		Paxil CR 1999	Generic Paxil 2003
		Paxil 2001			
		Paxil CR 2002 (Safety)			
		Paxil CR 2003 (Safety)			
Prozac 1987		Prozac 2000	Prozac 2003 (Ind.)		Generic Prozac 2001
		Prozac 2006 (Ped.)			Generic Prozac 2003 (Ped.)
					Generic Prozac 2006 (Ped.&Ind.)
Zoloft 1991 (Ped)		Zoloft 2002 (Ped.)			Generic Zoloft 2006 (Ped.)
		Zoloft 2003 (Ped.)			

Note: 1. 4 new molecule entity followed with 12 incrementally innovated drugs and 6 generics(totally 22 products+ outside option); 2. Safety implies less side effects here; 3. The parenthesis includes the already having incremental innovations; 4. Form.– new formulations; Ind.– new indications; Ped.– pediatric usage.

Table 2: Sample Selection

	Conditions			No Conditions; SSRIs
	Conditions; No SSRIs		Conditions; SSRIs	
	No Drugs	Other drugs		
No. of Obs.	7, 298	6, 802	10, 901	1, 914
Percentage	27.10%	25.30%	40.50%	7.10%
Total	26, 915			

Note: (No)Conditions: The respondents reported that they have (no) depressive condition. (No) SSRIs: The respondents purchase (no) SSRI antidepressants. No Drugs: The respondents didn't purchase any antidepressants. Other Drugs: The respondents purchased other class of antidepressants.

Table 3: Individual Demographics

Variables	All MEPS sample (96-09)	Sample Employed in Study	Having Conditions No SSRIs.	Having Cond.; SSRIs	No Cond.; SSRIs
Age	33.62	45.72***	44.03	47.55***	47.78
	[22.55]	[19.04]	[19.58]	[18.04]	[19.47]
Male	0.48	0.32***	0.36	0.28***	0.31***
	[0.50]	[0.47]	[0.48]	[0.45]	[0.46]
Adult (age>18)	0.70	0.92***	0.9	0.95***	0.92***
	[0.46]	[0.27]	[0.30]	[0.22]	[0.27]
Years of Education	9.36	11.75***	11.43	12.15***	11.82***
	[5.60]	[3.64]	[3.89]	[3.26]	[3.62]
Household Income	15.33	16.61***	15.85	17.36***	17.85
Per Capita (1996$)	[15.36]	[16.41]	[16.47]	[16.37]	[15.94]
Household Income	44.6	39.61***	37.77	40.88***	46.00***
(1996$)	[38.40]	[36.61]	[36.17]	[36.52]	[39.26]
Perceived Health	2.21	2.93***	2.86	3.03***	2.85***
Status	[0.95]	[1.04]	[1.04]	[1.04]	[1.05]
Having Medical	0.83	0.88***	0.85	0.92***	0.94***
Insurance	[0.37]	[0.32]	[0.36]	[0.27]	[0.24]
Having Medicare	0.13	0.24***	0.22	0.26***	0.27
	[0.34]	[0.43]	[0.42]	[0.44]	[0.44]
Having Medicaid	0.22	0.25***	0.26	0.24***	0.20***
	[0.42]	[0.43]	[0.44]	[0.42]	[0.40]
Out of Pocket Rate	0.54	0.48***	0.51	0.43***	0.46**
	[0.27]	[0.36]	[0.30]	[0.41]	[0.41]
Having Respiratory	0.04	0.09***	0.08	0.11***	0.08***
Diseases	[0.20]	[0.29]	[0.27]	[0.31]	[0.26]
Having Asthma	0.05	0.09***	0.08	0.10***	0.07***
	[0.22]	[0.29]	[0.28]	[0.31]	[0.26]
Having HIV	0.00	0.00***	0	0	0
	[0.03]	[0.06]	[0.06]	[0.07]	[0.06]
Having Hypertension	0.13	0.28***	0.26	0.31***	0.28***
	[0.34]	[0.45]	[0.44]	[0.46]	[0.45]
Having Cardiovascular	0.08	0.19***	0.17	0.21***	0.2
Heart Diseases	[0.27]	[0.39]	[0.38]	[0.41]	[0.40]
Having Diabetes	0.05	0.12***	0.11	0.14***	0.11***
	[0.23]	[0.33]	[0.31]	[0.35]	[0.32]
Having Depression	0.03	0.93***	1	1	0
	[0.17]	[0.26]	[0.00]	[0.00]	[0.00]
Observations	239720	26915	14100	10901	1914

Note: Standard Deviation is enclosed in the bracket. Income is deflated at 1996 dollar level. The t-test significances are shown by stars: Stars in Column 2 compare Column 1 and 2; Stars in Column 4 compare Column 3 and 4; Stars in Column 5 compare Column 4 and 5. $***p < 0.01$.

Table 4: Manufacturers and Market Share

Products	Analytic Sample		Survey Sample	
	Purchasing Obs.	Market Share	Purchasing Obs.	Market Share
CELEXA	966	7.54	7, 588	7.29
LEXAPRO	1, 869	14.58	14, 591	14.01
PAXIL	1, 961	15.3	15, 632	15.01
PAXIL CR	257	2.01	1, 959	1.88
PROZAC	1, 666	13	14, 099	13.54
ZOLOFT	3, 388	26.44	27, 603	26.5
Generic CELEXA	620	4.84	4, 301	4.13
Generic PAXIL	568	4.43	5, 119	4.92
Generic PROZAC	1, 115	8.7	10, 261	9.85
Generic ZOLOFT	405	3.16	2, 990	2.87
Total	12, 815	100	104, 143	100

Table 5: Summary Statistics of Product Attributes

Variable	Mean	Std. Dev.	Min	Max
Indications				
MDD	1	0	1	1
OCD	0.68	0.48	0	1
PD	0.55	0.51	0	1
PSD	0.23	0.43	0	1
PDD	0.45	0.51	0	1
SAD	0.32	0.48	0	1
BN	0.32	0.48	0	1
Side Effects				
Headache	1.16	0.15	1	1.38
Asthenia	1.80	0.57	1	2.82
Nausea	2.46	0.57	1.5	3.51
Diarrhea	1.85	0.34	1.57	2.57
Anorexia	2.20	1.08	1	3.33
Insomnia	1.94	0.33	1.1	2.33
Anxiety	1.53	0.40	1	2
Somnolence	2.61	0.70	1.8	3.84
Rash	1.49	0.57	1	2.6
Abnormal Ejaculation	13.95	10.48	3.42	29.24
Pediatric	0.36	0.49	0	1
Observation	22			

Note: MDD=Major Depressive Disorder; OCD=Obsessive Compulsive Disorder; PD=Panic Disorder; PSD=Posttraumatic Stress Disorder; PDD=Premenstrual Dysphoric Disorder; SAD=Social Anxiety Disorder; BN=Bulimia Nervosa; Pediatric=The safety and efficacy of the drug for pediatric usage have been established. The values of the side effect variable are calculated as the ratio of hazard rate of the patients who take drugs with respect to the hazard rate of the patients who take placebo.

Table 6: Selected Estimates in SMLE

	Variance	Age	Age2	Medical Insurance	Drug Insurance	Medi-care	Medi-caid	Educ-ation	Log(Inc. Per Cap.)	Perceived Health
Price	0.72***	-7.58***	3.64***	-0.05	0.61***	-0.04	-0.23***	0.16	0.07**	0.04
	(.22)	(2.45)	(1.15)	(.09)	(.1)	(.06)	(.08)	(.14)	(.03)	(.03)
Outside Option		1.35	-0.23	-0.97***	0.31***	-0.55**	0.13	0.14	-0.12	0.03***
		(10.9)	(5.1)	(.31)	(.)	(.23)	(.23)	(70.88)	(.13)	(.)
Agemole		0.93	-0.23	-0.13	-0.67***	-0.23**	-0.02	-0.05	-0.09	-0.18***
		(4.9)	(2.3)	(.12)	(.16)	(.09)	(.09)	(.24)	(.06)	(.05)
Generic	0.29	-4.63	2.41	-0.12	0.73***	0.01	0.03	0.01	0.13***	0
	(.45)	(3.61)	(1.69)	(.12)	(.1)	(.09)	(.09)	(.16)	(.04)	(.03)
Pediatric		-0.2		0.22**	-0.38***	0.19***	0.02	0.05	0.07*	0.05
		(.14)		(.09)	(.13)	(.06)	(.07)	(.32)	(.04)	(.05)

Note: The simulated maximum likelihood estimation includes 109 branded-year fixed effects and 115 explanatory variables (including two random coefficients for price and generic dummy and 113 individual-drug characteristics interaction terms). We listed the parameters we interested here. To see the full picture of the estimation, please check the appendix Table. Standard errors are included in parenthesis. $*p < 0.1$; $**p < 0.05$; $***p < 0.01$.

Table 7: Estimates of Mean Utility on Prices

	OLS	IV: Model I	IV: Model II	IV: Model III
Price	0.388***	-1.443***	-1.680***	-1.304***
	(2.81)	(-2.96)	(-2.94)	(-2.76)
Pediatric	-0.494*	0.166	0.252	0.116
	(-1.87)	(0.46)	(0.65)	(0.33)
Agemole	0.717***	-0.0219	-0.118	0.0341
	(2.78)	(-0.05)	(-0.26)	(0.09)
Constant	-1.125*	2.794**	3.300**	2.497**
	(-1.85)	(2.32)	(2.41)	(2.13)
Brand Dummies	Yes	Yes	Yes	Yes
Indication Dummies	Yes	Yes	Yes	Yes
Observations	96	96	96	96
R-squared	0.67	0.15	0.00	0.23

Note: 1. Dependent variable is the estimated drug-year mean utility; 2. The IVs used in the Column 2 is markup*generic, number of dosage; in column 3 is number of dosage; in column 4 is markup*generic, markup, demand*generic, number of dosage. 5. The Brand Dummies include Generic Celexa, Generic Paxil, Generic Prozac, Generic Zoloft, Lexapro, Paxil, Paxil CR, Prozac, Zoloft and outside option, the excluded one is Celexa. 6. The Indication Dummies include PDD, PSD, SAD, PD. OCD and BN are dropped due to collinearity problem. 7 . t statistics is included in parentheses. 8. $*p < 0.1, **p < 0.05, ***p < 0.01$

Table 8: The Relevance of IV

	Model I	Model II	Model III
Markup			-0.44
			(-0.54)
Markup*Generic	-32.21**		-31.36**
	(-2.1)		(-2.02)
Demand			0
			(-0.04)
No. of Dosage	-0.01**	-0.02**	-0.01**
	(-2.58)	(-2.92)	(-2.55)
Pediatric	0.67***	0.53***	0.66***
	(3.59)	(2.89)	(3.56)
Agemole	-0.35***	-0.35***	-0.37***
	(-2.96)	(-2.97)	(-2.79)
Constant	2.11***	2.12***	2.33***
	12.53	12.64	5.23
Brand Dummies	Yes	Yes	Yes
Indication Dummies	Yes	Yes	Yes
R squared	0.78	0.77	0.78
	96	96	96

Note: 1. Dependent variable is weighted averaged prices at brand-year level. 2. The Brand Dummies include Generic Celexa, Generic Paxil, Generic Prozac, Generic Zoloft, Lexapro, Paxil, Paxil CR, Prozac, Zoloft and outside option, the excluded one is Celexa. 3. The Indication Dummies include PDD, PSD, SAD, PD. OCD and BN are dropped due to collinearity problem.4. t statistics is included in parentheses.5. $*p < 0.1, **p < 0.05, ***p < 0.01$

Table 9: Counterfactual Scenarios

II	W (II, no ME)	W (no II, no ME)
1. All incremental innovations	scenario 2	scenario 1
2. Lexapro as a new formulation of Celexa	scenario 4	scenario 3
3. Paxil CR with improved safety	scenario 6	scenario 5
4. Pediatric use	scenario 8	scenario 7

Table 10: Market Exclusivity Changes across Counterfactuals

II	W (II, no ME) Prices	W (no II, no ME) Prices
1. All incremental innovations	Generic Paxil, Prozac and Zoloft entered one year earlier, Generic Lexapro and Generic Paxil CR entered with Generic Celexa and Generic Paxil	Generic entries for Paxil, Prozac and Zoloft are one year earlier,
2. Lexapro as a new formulation of Celexa	Generic Lexapro entered with Generic Celexa	No Lexapro developed and no generic Lexapro entering
3. Paxil CR with improved safety	Generic Paxil CR entered with Generic Paxil	No Paxil CR developed and no Generic Paxil CR entering
4. Pediatric use	Generic Paxil, Prozac and Zoloft entered one year earlier	Generic Paxil, Prozac and Zoloft entered one year earlier

Note: Prices are calculated in simulation, but are subjected to changes with exclusivity removal. For example, if the exclusivity of Prozac is reduced for one year, competitive market present one year earlier from 2001 to 2000. Then the price curve shift one year earlier.

Table 11: Welfare Changes (Billion Dollars)(for years before 2006)

II	W (II, ME)-W (II, no ME) Consumer	Branded Firm	W (II, no ME)-W (no II, no ME) Consumer	Branded Firm
1. All incremental innovations	-15.7	18	19.5	-20.6
2. Lexapro as a new formulation of Celexa	-7.95	-0.5	-1.27	12.8
3. Paxil CR with improved safety	-7.87	0.3	1.58	-2.07
4. Pediatric use	-11.1	13.6	4.46	-0.6

Table 12: Welfare Changes (Billion Dollars)

II	W (II, ME)-W (II, no ME)		W (II, no ME)-W (no II, no ME)	
	Consumer	Branded Firm	Consumer	Branded Firm
1. All incremental innovations	-27.4	21	29.4	-22.5
2. Lexapro as a new formulation of Celexa	-15.8	4.31	6.32	11.8
3. Paxil CR with improved safety	-12.9	6.35	8.10	-10.1
4. Pediatric use	-16.5	14.3	12.0	-1.27

Table 13: Drug Indications

Ingredient	Brand Name	Entry	MDD	OCD	PD	PSD	PDD	SAD	BN	Ped.
CITALOPRAM HYDROBROMIDE	CELEXA	1998	1	0	0	0	0	0	0	0
	Generic CELEXA	2004	1	0	0	0	0	0	0	0
ESCITALOPRAM OXALATE	LEXAPRO	2002	1	0	0	0	0	0	0	0
	LEXAPRO	2003	1	0	0	0	0	1	0	0
FLUOXETINE HYDROCHLORIDE	PROZAC	1987	1	1	0	0	0	0	1	0
	PROZAC	2000	1	1	0	0	1	0	1	0
	Generic PROZAC	2001	1	1	0	0	1	0	1	0
	PROZAC	2003	1	1	0	0	1	0	1	1
	Generic PROZAC	2003	1	1	0	0	1	0	1	1
	PROZAC	2006	1	1	1	0	1	0	1	1
	Generic PROZAC	2006	1	1	1	0	1	0	1	1
PAROXETINE HYDROCHLORIDE	PAXIL	1992	1	1	1	0	0	0	0	0
	PAXIL	1999	1	1	1	0	0	1	0	0
	PAXIL	2001	1	1	1	1	0	1	0	0
	PAXIL CR	1999	1	0	0	0	0	0	0	0
	PAXIL CR	2002	1	0	1	0	0	0	0	0
	PAXIL CR	2003	1	0	1	0	1	1	0	0
	Generic PAXIL	2003	1	1	1	1	0	1	0	0
SERTRALINE HYDROCHLORIDE	ZOLOFT	1991	1	1	1	0	0	0	0	1
	ZOLOFT	2002	1	1	1	1	1	0	0	1
	ZOLOFT	2003	1	1	1	1	1	1	0	1
	Generic ZOLOFT	2006	1	1	1	1	1	1	0	1

Note: Entry: Approved or Supplemental approved by FDA; MDD=Major Depressive Disorder; OCD=Obsessive Compulsive Disorder; PD=Panic Disorder; PSD=Posttraumatic Stress Disorder; PDD=Premenstrual Dysphoric Disorder; SAD=Social Anxiety Disorder; BN=Bulimia Nervosa; Ped.=The safety and efficacy of the drug for pediatric usage have been established.

Table 14: Side effects of drugs

Ingredient	Brand Name	Headache	Asthenia	Nausea	Diarrhea	Anorexia	Insomnia	Anxiety	Somnolence	Rash	AbnEja
CITALOPRAM HYDROBROMIDE	Celexa	1	1	1.5	1.6	2	1.1	1.33	1.8	1	6
PAROXETINE HYDROCHLORIDE	Paxil	1.38	2.82	3.51	1.89	1	2.33	1.68	3.84	2.6	29.24
FLUOXETINE HYDROCHLORIDE	Prozac	1.1	1.83	2.34	1.57	3.33	1.9	2	2.4	1.33	3.42
SERTRALINE HYDROCHLORIDE	Zoloft	1.08	1.71	2.27	2	3	1.9	1.33	1.86	1.5	14
ESCITALOPRAM OXALATE	Lexapro	1	1	2.14	1.6	1	2.25	1	3	1	10
PAROXETINE HYDROCHLORIDE	Paxil CR	1.35	1.56	2.2	2.57	1	1.89	1	2.75	1	26

Note: The values in this chart are calculated as the ratio of hazard rate of the patients who take drugs with respect to the hazard rate of the patients who take placebo. AbnEja=Abnormal Ejaculation.

Table 15: Estimated Coefficients by SMLE

	Variance	Age	Age2	Medical Insurance	Drug Insurance	Medicare	Medicaid	Education	Log(Income/Per Capita)	Perceived Health	Male	Adult
Price	0.72 (.22)	-7.58 (2.45)	3.64 (1.15)	-0.05 (.09)	0.61 (.1)	-0.04 (.06)	-0.23 (.08)	0.16 (.14)	0.07 (.03)	0.04 (.03)		
Outside Option		1.35 (10.9)	-0.23 (5.1)	-0.97 (.31)	0.31 (.)	-0.55 (.23)	0.13 (.23)	0.14 (70.88)	-0.12 (.13)	0.03 (.)		
Agemole		0.93 (4.9)	-0.23 (2.3)	-0.13 (.12)	-0.67 (.16)	-0.23 (.09)	-0.02 (.09)	-0.05 (.24)	-0.09 (.06)	-0.18 (.05)		
Generic	0.29 (.45)	-4.63 (3.61)	2.41 (1.69)	-0.12 (.12)	0.73 (.1)	0.01 (.09)	0.03 (.09)	0.01 (.16)	0.13 (.04)	0 (.03)		
Pediatric		-0.2 (.14)		0.22 (.09)	-0.38 (.13)	0.19 (.06)	0.02 (.07)	0.05 (.32)	0.07 (.04)	0.05 (.05)		
OCD		0.56 (6.28)	-0.2 (2.95)					-0.17 (.)	0.07 (65.3)		-0.05 (.06)	
PD		2.97 (4.32)	-1.44 (2.03)					-0.01 (.32)	-0.05 (.11)		-0.08 (.04)	
PSD		0.21 (4.68)	-0.12 (2.2)					0.28 (.21)	0.03 (.11)		0.06 (.05)	
PDD		2.83 (3.24)	-1.44 (1.53)					-0.08 (.19)	-0.07 (.09)		0.01 (.04)	
SAD		-1.72 (3.24)	0.83 (1.52)					-0.08 (.2)	-0.02 (.1)		0.05 (.04)	
BN		-1.35 (6.02)	0.43 (2.83)									
Headache					-0.03 (.)			-0.3 (55.82)		-0.02 (52.51)	-0.06 (78.84)	
Asthenia					0.46 (.)			-0.46 (36.)		-0.07 (.)	-0.11 (.)	
Nausea					0.2 (.)			0.05 (19.81)		-0.01 (.)	0.01 (.)	
Diarrhea					0.35 (48.06)			-0.48 (.)		-0.01 (7.54)	-0.22 (34.63)	
Anorexia					0.25 (11.21)			0.3 (.)		0.1 (7.98)	-0.03 (17.25)	
Insomnia					0.37 (.)			-0.05 (7.22)		-0.13 (8.99)	0.1 (22.3)	
Anxiety					-0.2 (87.2)			0.28 (15.92)		0.14 (3.14)	-0.15 (65.65)	
Somnolence					-0.17 (31.52)			0.65 (7.69)		0.17 (8.38)	-0.19 (.)	
Rash					-0.36 (.)			-0.2 (.)		-0.05 (.)	0.34 (56.97)	
Abnormal Ejaculation		-0.02 (.14)			0.03 (35.)			0.01 (6.21)		0.09 (.)	0.13 (65.46)	-0.03 (.04)

Note: Standard errors in parenthesis; The coefficient in"variance" column report the estimated standard errors for random coefficients.

Table 16: Estimated Brand-year Fixed Effects

Brand	Year	Coefficients	St. Dev.	
CELEXA	1999	0.5944	0	***
CELEXA	2000	0.6875	0	***
CELEXA	2001	1.1787	126.5858	
CELEXA	2002	1.6683	0	***
CELEXA	2003	1.1544	0	***
CELEXA	2004	0.8158	0	***
CELEXA	2005	0.2667	204.5615	
CELEXA	2006	0.2525	0	***
CELEXA	2007	0.0014	39.1229	
CELEXA	2008	0.0033	0	***
CELEXA	2009	-0.5079	46.7675	
Generic CELEXA	2004	-1.4079	0	***
Generic CELEXA	2005	-0.5361	204.5532	
Generic CELEXA	2006	0.2513	0	***
Generic CELEXA	2007	-0.1771	38.9684	
Generic CELEXA	2008	0.6432	0	***
Generic CELEXA	2009	0.8733	46.7913	
Generic PAXIL	2003	-2.3003	0	***
Generic PAXIL	2004	-0.6239	0	***
Generic PAXIL	2005	-0.2568	204.587	
Generic PAXIL	2006	0.1326	0	***
Generic PAXIL	2007	-0.133	38.4602	
Generic PAXIL	2008	-0.2701	0	***
Generic PAXIL	2009	0.081	46.7616	
Generic PROZAC	2001	-0.7943	126.7596	
Generic PROZAC	2002	0.3069	0	***
Generic PROZAC	2003	0.4464	0	***
Generic PROZAC	2004	0.5114	0	***
Generic PROZAC	2005	0.3457	204.5877	
Generic PROZAC	2006	0.9155	0	***
Generic PROZAC	2007	0.2055	38.2897	
Generic PROZAC	2008	0.4778	0	***
Generic PROZAC	2009	0.55	46.8321	

Table 15 (Continued)

Generic ZOLOFT	2006	-1.4861	0	***
Generic ZOLOFT	2007	0.094	38.4213	
Generic ZOLOFT	2008	0.1555	0	***
Generic ZOLOFT	2009	0.9183	46.8527	
LEXAPRO	2002	-0.7663	0	***
LEXAPRO	2003	0.7873	0	***
LEXAPRO	2004	1.4238	0	***
LEXAPRO	2005	1.7422	204.629	
LEXAPRO	2006	1.9867	0	***
LEXAPRO	2007	2.2416	0	***
LEXAPRO	2008	2.3089	0	***
LEXAPRO	2009	2.2379	0	***
PAXIL	1996	1.1513	0	***
PAXIL	1997	0.9485	158.4299	
PAXIL	1998	2.3501	0	***
PAXIL	1999	1.4254	0	***
PAXIL	2000	1.1311	0	***
PAXIL	2001	0.9739	126.6269	
PAXIL	2002	1.3784	0	***
PAXIL	2003	1.4426	0	***
PAXIL	2004	0.7399	0	***
PAXIL	2005	-0.282	204.6364	
PAXIL	2006	0.283	0	***
PAXIL	2007	-0.298	0	***
PAXIL	2008	-0.0249	0	***
PAXIL	2009	-0.5776	0	***
PAXIL CR	2002	0.2468	0	***
PAXIL CR	2003	2.155	0	***
PAXIL CR	2004	2.4827	0	***
PAXIL CR	2005	1.9279	204.4874	
PAXIL CR	2006	2.5338	0	***
PAXIL CR	2007	1.7259	0	***
PAXIL CR	2008	0.0901	0	***
PAXIL CR	2009	0.8844	0	***
PROZAC	1996	0.9969	0	***
PROZAC	1997	0.7645	158.4463	
PROZAC	1998	2.059	0	***
PROZAC	1999	0.7415	0	***
PROZAC	2000	0.7803	0	***

Table 15 (Continued)

PROZAC	2001	1.3177	126.7304	
PROZAC	2002	1.2438	0	***
PROZAC	2003	1.1617	0	***
PROZAC	2004	1.0946	0	***
PROZAC	2005	1.1955	204.5415	
PROZAC	2006	1.0298	0	***
PROZAC	2007	0.7707	0	***
PROZAC	2008	1.4179	0	***
PROZAC	2009	0.1152	0	***
ZOLOFT	1996	1.6903	0	***
ZOLOFT	1997	1.5853	158.4378	
ZOLOFT	1998	2.6623	3.0816	
ZOLOFT	1999	1.163	0	***
ZOLOFT	2000	1.4136	0	***
ZOLOFT	2001	1.7355	126.7906	
ZOLOFT	2002	1.6021	0	***
ZOLOFT	2003	1.8479	0	***
ZOLOFT	2004	2.193	0	***
ZOLOFT	2005	2.4159	0	***
ZOLOFT	2006	2.4739	0	***
ZOLOFT	2007	2.0074	38.575	
ZOLOFT	2008	1.4936	0	***
ZOLOFT	2009	1.3749	46.8219	
NO DRUG	1996	0.1615	0	***
NO DRUG	1997	0.7016	158.468	
NO DRUG	1998	2.2866	3.191	
NO DRUG	1999	1.0758	0	***
NO DRUG	2000	0.9876	0	***
NO DRUG	2001	1.5885	126.723	
NO DRUG	2002	2.3198	0	***
NO DRUG	2003	2.3048	0	***
NO DRUG	2004	2.7708	0	
NO DRUG	2005	3.1811	0	***
NO DRUG	2006	3.6272	0	***
NO DRUG	2007	4.5614	38.3853	
NO DRUG	2008	4.7049	0	***
NO DRUG	2009	5.0505	46.8131	

Table 17: The Entry of Generic Manufacturers by year

Trade name	Manufacturers	Entry Year
CELEXA	FOREST LABS	1998
CITALOPRAM HYDROBROMIDE	AUROBINDO	2004
CITALOPRAM HYDROBROMIDE	DR REDDYS LABS LTD	2004
CITALOPRAM HYDROBROMIDE	ACTAVIS ELIZABETH	2004
CITALOPRAM HYDROBROMIDE	COREPHARMA	2004
CITALOPRAM HYDROBROMIDE	SANDOZ	2004
CITALOPRAM HYDROBROMIDE	MYLAN	2004
CITALOPRAM HYDROBROMIDE	WATSON LABS	2004
CITALOPRAM HYDROBROMIDE	ALPHAPHARM	2004
CITALOPRAM HYDROBROMIDE	CARACO	2004
CITALOPRAM HYDROBROMIDE	IVAX SUB TEVA PHARMS	2004
CITALOPRAM HYDROBROMIDE	ROXANE	2004
CITALOPRAM HYDROBROMIDE	APOTEX INC	2004
CITALOPRAM HYDROBROMIDE	EPIC PHARMA	2005
CITALOPRAM HYDROBROMIDE	PLIVA	2005
CITALOPRAM HYDROBROMIDE	BIOVAIL LABS INTL	2005
CITALOPRAM HYDROBROMIDE	TARO	2006
CITALOPRAM HYDROBROMIDE	TEVA PHARMS	2006
CITALOPRAM HYDROBROMIDE	SILARX	2006
CITALOPRAM HYDROBROMIDE	MUTUAL PHARM	2006
CITALOPRAM HYDROBROMIDE	AUROBINDO PHARMA LTD	2006
CITALOPRAM HYDROBROMIDE	INVAGEN PHARMS	2006
CITALOPRAM HYDROBROMIDE	AMNEAL PHARMS NY	2006
CITALOPRAM HYDROBROMIDE	TORRENT PHARMS	2007
CITALOPRAM HYDROBROMIDE	NATCO PHARMA LTD	2008
CITALOPRAM HYDROBROMIDE	GLENMARK GENERICS	2009

Table 16 (Continued)

Trade name	Manufacturers	Entry Year
PAXIL	GLAXOSMITHKLINE	1998
PAROXETINE HYDROCHLORIDE	APOTEX	2003
PAROXETINE HYDROCHLORIDE	ALPHAPHARM	2004
PAROXETINE HYDROCHLORIDE	SANDOZ	2004
PAROXETINE HYDROCHLORIDE	TEVA	2005
PAROXETINE HYDROCHLORIDE	APOTEX INC	2006
PAROXETINE HYDROCHLORIDE	ZYDUS PHARMS USA	2007
PAROXETINE HYDROCHLORIDE	MYLAN	2007
PAROXETINE HYDROCHLORIDE	ROXANE	2007
PAROXETINE HYDROCHLORIDE	CARACO	2007
PAROXETINE HYDROCHLORIDE	TEVA PHARMS	2007
PAROXETINE HYDROCHLORIDE	AUROBINDO PHARMA	2007
PAROXETINE HYDROCHLORIDE	ACTAVIS ELIZABETH	2010
PROZAC	LILLY	1991
PROZAC WEEKLY	LILLY	2001
FLUOXETINE HYDROCHLORIDE	BARR	2001
FLUOXETINE HYDROCHLORIDE	TEVA	2002
FLUOXETINE HYDROCHLORIDE	SANDOZ	2002
FLUOXETINE	WATSON LABS	2002
FLUOXETINE HYDROCHLORIDE	MALLINCKRODT	2002
FLUOXETINE HYDROCHLORIDE	PLIVA	2002
FLUOXETINE HYDROCHLORIDE	ALPHAPHARM	2002
FLUOXETINE	MUTUAL PHARMA	2002
FLUOXETINE HYDROCHLORIDE	MYLAN	2002
FLUOXETINE HYDROCHLORIDE	CARLSBAD	2002
FLUOXETINE HYDROCHLORIDE	DR REDDYS LABS INC	2002

Table 16 (Continued)

Trade name	Manufacturers	Entry Year
FLUOXETINE HYDROCHLORIDE	PHARM ASSOC	2002
FLUOXETINE HYDROCHLORIDE	LANDELA PHARM	2002
FLUOXETINE HYDROCHLORIDE	ACTAVIS MID ATLANTIC	2002
FLUOXETINE HYDROCHLORIDE	IVAX SUB TEVA PHARMS	2002
FLUOXETINE HYDROCHLORIDE	BEIJING DOUBLE CRANE	2002
FLUOXETINE HYDROCHLORIDE	NOVEX	2002
FLUOXETINE HYDROCHLORIDE	HI TECH PHARMA	2002
FLUOXETINE HYDROCHLORIDE	LANNETT	2004
FLUOXETINE HYDROCHLORIDE	RANBAXY	2004
FLUOXETINE HYDROCHLORIDE	PAR PHARM	2004
FLUOXETINE HYDROCHLORIDE	SILARX	2007
FLUOXETINE HYDROCHLORIDE	WOCKHARDT	2008
FLUOXETINE HYDROCHLORIDE	AUROBINDO PHARMA	2008
FLUOXETINE HYDROCHLORIDE	ALEMBIC PHARMS LTD	2009
FLUOXETINE HYDROCHLORIDE	AUROBINDO PHARM	2009
FLUOXETINE HYDROCHLORIDE	DR REDDYS LABS LTD	2010
FLUOXETINE HYDROCHLORIDE	EDGEMONT PHARMS LLC	2011
ZOLOFT	PFIZER	1991
SERTRALINE HYDROCHLORIDE	IVAX SUB TEVA PHARMS	2006
SERTRALINE HYDROCHLORIDE	TEVA	2006
SERTRALINE HYDROCHLORIDE	RANBAXY	2007
SERTRALINE HYDROCHLORIDE	WATSON LABS	2007
SERTRALINE HYDROCHLORIDE	APOTEX INC	2007
SERTRALINE HYDROCHLORIDE	MYLAN	2007
SERTRALINE HYDROCHLORIDE	ACTAVIS ELIZABETH	2007
SERTRALINE HYDROCHLORIDE	SUN PHARM INDS (IN)	2007
SERTRALINE HYDROCHLORIDE	ZYDUS PHARMS USA	2007

Table 16 (Continued)

Trade name	Manufacturers	Entry Year
SERTRALINE HYDROCHLORIDE	MUTUAL PHARM	2007
SERTRALINE HYDROCHLORIDE	SANDOZ	2007
SERTRALINE HYDROCHLORIDE	TORRENT PHARMS	2007
SERTRALINE HYDROCHLORIDE	PLIVA HRVATSKA DOO	2007
SERTRALINE HYDROCHLORIDE	ROXANE	2007
SERTRALINE HYDROCHLORIDE	AUROBINDO PHARMA	2007
SERTRALINE HYDROCHLORIDE	INVAGEN PHARMS	2007
SERTRALINE HYDROCHLORIDE	LUPIN	2007
SERTRALINE HYDROCHLORIDE	DR REDDYS LABS LTD	2007
SERTRALINE HYDROCHLORIDE	WOCKHARDT	2008
SERTRALINE HYDROCHLORIDE	MATRIX LABS LTD	2008
SERTRALINE HYDROCHLORIDE	AUSTARPHARMA LLC	2009
SERTRALINE HYDROCHLORIDE	HIKMA PHARMS	2009
SERTRALINE HYDROCHLORIDE	ACTAVIS TOTOWA	2010
LEXAPRO	FOREST LABS	2002
ESCITALOPRAM OXALATE	ALPHAPHARM	2007

8 Appendix

8.1 Data Construction

8.1.1 Individual-level Data

The individual characteristics are constructed from MEPS Full Year Consolidated files. The Full Year Consolidated file includes demographic and labor market information, sample weights, health status and a rich set of health insurance coverage information. MEPS provides the date of birth for each respondents which can be used to calculate the *Age*. *Years of Education* is collected for each respondents at the first round of interviews. We generate a *Adult* dummy for each individual, *Adult* = 1 if his/her age is greater than or equal to 18 years old. Family Yearly Income is summarized over all household members from three components: person's total income; person's refund income; person's sale income. In MEPS, total person-level income is the sum of all income components with the exception of person's refund income and person's sale income to match as closely as possible the CPS definition of income; For our purpose, we will sum them up to obtain the measure of total individual income. By averaging family income within household members, we obtain Family Income Per Capita. After deflated to 1996 dollars level, we define the income variable as $Log(Family\ Income\ Per\ Capita/1000 + 1)$ to avoid the scale problem in MLE. In the survey, respondents are asked the following question during each round: *"In general, compared to other people of the same age, would you say that your health is excellent, very good, good, fair, or poor?"* Based on this question, the perceived health status of each respondent are evaluated from 1 (excellent) to 5 (poor). The variable *Perceived Health Status* in our study is the mean over rounds. MEPS constructs a medical insurance variable which summarizes health insurance coverage for the person in each year. Our medical insurance variable *Having Medical Insurance* equals to one if the summarized insurance variable indicates the person has either public or private health insurance. Whether the individual participates in *Medicare* or *Medicaid* or not is provided by MEPS. All the purchasing observations for SSRI drugs are precisely recorded in MEPS Prescribed Medicines Component Files. The Prescribed Medicines Component collects information from the actual pharmacies where survey participants obtain their prescriptions. The information obtained from pharmacies includes the national drug code and name of the drug, the strength and quantity obtained, for what condition the drug is prescribed, the total price, as well as the amounts paid by different insurance sources and the patient. Based on the price information provided by MEPS Prescribed Medicines Component Files, we can easily construct *Out of Pocket Rate* by dividing the price paid by patients with the total price. Most of the individuals have purchasing records (not restricted to SSRI drugs) in the data which can be used to generate this variable. Less than 10 % of the individuals have no information of *Out of Pocket Rate*. The mean of *Out of Pocket Rate* in that year is utilized for these observations. A large part of the observations in our study are those who have depression condition. Before we describe the sample construction, the first thing to know is the depression condition dummy. Condition information is provided in Medical Condition Files. The condition can be included in MEPS condition roster only for the following reasons: reported by the household respondent for a particular medical event (hospital stay, outpatient visit, emergency room visit, home health episode, prescribed medication purchase, or medical provider visit); reported as the reason for one or more episodes of disability days; or reported by the household level respondent as a condition "bothering" the person during the reference period. We define a respondent as having depression if the ICD-9-CM code equal to one of the following: 296 for episodic mood disorders, 300 for anxiety, dissociative and somatoform disorders, code 311 for depressive disorder not elsewhere classified. By merging the Medical Condition File with Full Year Consolidated File, we could obtain the sample that has depression. Combining all those who

purchased SSRI anti-depressants with those who have depression conditions gives us the analytic sample.

8.1.2 Drug-level Data

One of the key drug characteristics is price, which we constructed by averaging prices across strengths and dosage forms by sales weight. All prices have been adjusted to unit level, i.e., price per pill; and are deflated to 1996 dollar level by CPI for Managed Care Commodities category (Source: US Bureau of Labor Statistics). The information about drug characteristics is obtained from package insert labels. At the section of Indications and Usage in labels, indications of drugs are enumerated. We generate seven indication dummies for each product, including Major Depressive Disorder (MDD), Obsessive Compulsive Disorder (OCD), Panic Disorder (PD), Post-traumatic Stress Disorder (PSD), Premenstrual Dysphoric Disorder (PDD), Social Anxiety Disorder (SAD), and Bulimia Nervosa (BN). Indications of each product are listed in Table 13. As we see from the table, when a generic drug enters into market, it automatically obtains the new indication of the branded as long as they are therapeutically equivalent, for example Generic Prozac 2001 and Prozac 2000. The reason lies in that the branded firm cannot forbid it without providing new indications within a new strength or a new formulation since physicians could and would prescribe generics for the new indication of the branded one (as long as they are the same). If the safety and efficacy of a drug for pediatric use are provided, then we can regard the drug as having pediatric use. However, the difficulty is that in the label, the safety and efficacy data for pediatric usage are specific to each indication, for example, the efficacy of ZOLOFT for the treatment of OCD was demonstrated in clinical trials. However, safety and efficacy in the pediatric population other than pediatric patients with OCD have not been established. If we consider the pediatric usage for each specific indication will increase the number of dummies several times which brings about an estimation problem, therefore, here as long as the safety and efficacy data for one indication have been established, we will regard this drug with *Pediatric Use* = 1. The side effects information is obtained from the Adverse Reactions Section in the labels. We choose the 10 most common symptoms which bother patients most into our data: Headache, Asthenia, Nausea, Diarrhea, Anorexia, Insomnia, Anxiety, Somnolence, Rash, and Abnormal Ejaculation (these do not need to be capitalized). For each symptom, the side effect ratio is defined as the occurrence rate of the patients taking medicine with respect to the occurrence rate of the patients taking placebo. To illuminating the generating process, the example of Prozac's label is illustrated below: As shown in Figure 15, for symptom nausea, the incidence of nausea is: 21 % of 1728 Major Depressive Disorder patients taking Prozac vs. 9% of 975 subjects feeling nausea who have taken placebo; 26 % of 266 patients taking Prozac to treat OCD felt nausea, while 13 % of 89 OCD patients taking placebo felt nausea; 29% of 450 Bulimia Nervosa patients taking Prozac vs. 11% of 267 BN patients taking placebo; 12 % of 425 Panic Disorder patients taking Prozac vs. 7 % of 342 PD patients taking placebo. Then the hazard rate ratio variable for nausea can be computed as:

$$\frac{\frac{1728*.21+266*.26+450*.29+425*.12}{1728+266+450+425}}{\frac{975*.09+89*.13+267*.11+342*.07}{975+89+267+342}} = 2.34$$

Alternative IVs are constructed in the following way: the number of dosages is the count of strengths and formulations for a molecule produced by one firm is available; years after generic entry is the period length from the generic entry year till the year when purchasing happened; the number of firms (branded and generics) selling the same molecule in the market is specific in each year.

**MOST COMMON TREATMENT-EMERGENT
ADVERSE EVENTS: INCIDENCE IN MAJOR DEPRESSIVE DISORDER,
OCD, BULIMIA AND PANIC DISORDER PLACEBO-CONTROLLED CLINICAL
TRIALS**

	Major Depressive Disorder		OCD Percentage of patients reporting event		Bulimia		Panic	
Body System/ Adverse Event	Prozac (N=1728)	Placebo (N=975)	Prozac (N=266)	Placebo (N=89)	Prozac (N=450)	Placebo (N=267)	Prozac (N=425)	Placebo (N=342)
Body as a Whole								
Asthenia	9	5	15	11	21	9	7	7
Flu syndrome	3	4	10	7	8	3	5	5
Cardiovascular System								
Vasodilatation	3	2	5	--	2	1	1	--
Digestive System								
Nausea	21	9	26	13	29	11	12	7
Diarrhea	12	8	18	13	8	6	9	4
Anorexia	11	2	17	10	8	4	4	1

Figure 15: Part of the Table in Section Adverse Reactions in the label of Prozac

Chapter 2 The Impact of Venture Capital on Innovation

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1   Introduction

Does venture capital foster productive innovation, and if so, how? Is the impact of venture capital on innovation very large? These questions are not only of theoretical interest: answering them correctly is crucial for designing the best public policies on innovation. Although it accounts for a rather low proportion of total entrepreneurial financing, notably compared to bank finance,[1] venture capital is widely regarded as a key factor in the successful performance of the U.S. in terms of innovation, providing a model that has inspired emulation efforts in many other countries. From this perspective too, it is important to understand the model and how it works.

This chapter begins by reviewing the empirical evidence on the impact of venture capital on innovation. We identify some of the key challenges to empirical research in this area and discuss the methods that have been used to address them. Our review is by no means exhaustive, but several findings emerge clearly. First, there is evidence of a substantial impact of venture capital on innovation, measured by patent counts, at the industry level (at least for the United States). Although estimates vary, on average a dollar of venture capital appears to be three to four times more potent in stimulating innovation than a dollar of traditional corporate R&D (Lerner 2002). Second, there is no corresponding evidence of a significant impact of venture capital on innovation at the individual-firm level. We discuss possible explanations for this difference, including the difficulties of adequately controlling for the endogeneity of venture capital investment at the firm level. While valid instruments have been found to address the endogeneity problem at the industry level, this is much harder to achieve at the level of individual firms. Third, there is very little evidence on *how* venture capital affects innovation.

Concerning the second finding, the theoretical literature on venture capital has focused primarily on one source of endogeneity: the ex-ante screening hypothesis. The idea is that venture capitalists have a comparative advantage in evaluating the entrepreneurs who seek funding from them and selecting the "best" ones. As discussed below, this can bias upwards the estimates of the impact of venture capital on innovation, since firms with better entrepreneurs (projects) are more likely to obtain venture funding *and* more likely to produce valuable innovations. We argue, however, that there may be other sources of endogeneity, introducing other biases, possibly going

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[1]For example, Berger and Udell (1998) find that in the US, 3.59% of small business finance comes from angel investors, 1.85% from venture capitalists, and 18.75% from commercial banks. More recently, using UK data, Cosh, Cumming and Hughes (2009) find that 775 out of 952 firms seeking external finance in their sample approached banks, while only 87 approached venture capital funds and 83 approached private individuals. Moreover, rejection rates were much higher among venture capital funds (46%) than among banks (17%).

in the opposite direction, and making it difficult to draw inferences from reduced-form estimates obtained with firm-level data.

Concerning the third finding, the theoretical literature has highlighted two main mechanisms whereby venture capitalists affect the performance of their portfolio firms: monitoring and intervention, on the one hand, which alleviates potential moral hazard problems on the side of the entrepreneur, and the provision of advice and support on the other hand, which helps performance directly.[2] Both mechanisms could, in principle, apply to innovation. However, while there is growing evidence of the role played by venture capitalists in helping to commercialize innovations (Colombo et al. 2006; Gans et al. 2002; Hsu 2006), as well as their role in helping to recruit key personnel and replace founders with new CEOs (Hellmann and Puri 2002), there is very little direct evidence showing that they play an important role in fostering innovation.

There is nevertheless evidence from recent work showing that venture capitalists are highly effective in evaluating the quality of innovations early on, identifying correctly the patent applications that are likely to succeed and lead to the development of valuable new products. Dessí and Yin (2013) build on this observation to develop a theoretical model that highlights some additional ways, beyond monitoring and advising, in which venture capital may influence innovation. We present and analyze a highly simplified model based on Dessí and Yin to show some of the effects at work and the implications for innovation. The model also illustrates a potential source of endogeneity of venture funding that is unrelated to screening. The theoretical analysis therefore suggests that endogeneity can indeed be an important concern in empirical work. On the positive side, the analysis yields a number of potentially testable predictions: investigating predictions of this kind empirically could help to shed new light on the mechanisms whereby venture capital affects innovation.

The remainder of the chapter is organized as follows. We presents a brief overview of the empirical evidence on the link between venture capital and innovation and introduce a simple theoretical model, based on Dessí (2009) and Dessí and Yin (2013). The model is analyzed and the implications are discussed. We conclude by suggesting potential avenues for future research.

2 Venture capital and innovation: a brief overview of the empirical evidence

A large and growing empirical literature examines, in different ways, the link between venture capital and innovation. Our brief overview, summarized in Table 1, is not intended to be exhaustive; it only aims to highlight some of the main contributions and implications. Moreover, it focuses on research that explicitly investigated the impact of venture capital on innovation, rather than more generally the impact of venture capitalists on the firms they finance.

A key challenge in this line of research has been to establish a causal relationship between venture capital funding and different measures of innovative performance, such as patent counts. This issue has been addressed with different methodologies, using data at the industry level and the individual firm level.

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[2]On monitoring and intervention, see Dessí 2005; Holmström and Tirole 1997. On advice and support, see, among others, Bottazzi et al. 2009; Casamatta 2003; Cestone 2002; Cumming et al. 2005; Dessí 2010; Hellmann 1998; Jeng and Wells 2000; Kaplan et al. 2003; Lerner and Schoar 2005; Repullo and Suarez 2000, 2004; Riyanto and Schwienbacher 2006; Schmidt 2003.

2.1 Industry data

The difficulty of establishing causality can be illustrated by reference to the following framework. Consider innovative performance at the industry level, denoted by P_{it}^I, where the subscript i denotes the industry and t denotes time. Suppose that this depends on total R&D expenditure in the industry (R_{it}), on the ratio of venture capital investment to total R&D expenditure (V_{it}/R_{it}), and on unobserved technological opportunities (u_{it}). This suggests estimating the following regression [3],

$$\ln P_{it}^I = a + b \ln R_{it} + c \ln(\frac{V_{it}}{R_{it}}) + u_{it} \tag{1}$$

to see whether venture capital has a significant impact on innovation; i.e. whether the estimated coefficient c is statistically significant. The difficulty here is that the unobserved technological opportunities, captured by the error term u_{it}, are likely to be correlated with the explanatory variables: if there is a positive technology shock that increases technological opportunities in a given industry, venture capital investment in that industry is likely to increase, as is total R&D expenditure. Moreover, there is no reason to believe that they will increase so as to leave the ratio unaffected. To the extent that the explanatory variables are correlated with the error term, OLS estimates of their coefficients will be biased.

The problem can be addressed by estimating an instrumental variable regression, provided appropriate instruments are found. The first paper to do this was Kortum and Lerner (2000). They cleverly exploit the policy shift that occurred in the United States in the late 1970s, when the U.S. Department of Labor clarified the Employee Retirement Income Security Act, freeing pensions to invest in venture capital. This led to a sharp increase in the total funds invested in venture capital, unrelated to changes in technological opportunities. Thus it could be used as an instrument in the estimations.

Kortum and Lerner (2000) found that, even after instrumenting, venture capital has a substantial positive impact on innovation, as measured by the patent count at the industry level. Their results applied to the period 1965-1992. More recently, Ueda and Hirukawa (2008) have replicated these findings with a longer sample period, up to 2001 (i.e. including the period of very high growth of the U.S. venture capital industry in the late 1990s). They show that venture capital continued to have a substantial positive impact on industry patent counts during the boom period of the late 1990s.

Ueda and Hirukawa (2008) then go on to study the impact of venture capital on different measures of innovative performance, including total factor productivity (TFP) growth. They find that, in contrast to the results with patent counts, venture capital does *not* significantly and positively affect TFP growth. It seems therefore that venture capital funding may be particularly important for one measure of innovative performance: patenting success.

2.2 Individual firm data

The findings just discussed at the industry level clearly show the need to understand *how* venture capital funding may affect innovation. This is also crucial in thinking about implications for public policy.

However, the empirical evidence on the mechanisms whereby venture funding impacts on innovation is limited. Hellmann and Puri (2000) examine a sample of high-technology companies

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[3]See Kortum and Lerner (2000) for the theoretical underpinnings of this specification.

in Silicon Valley, both venture-funded and non-venture-funded. They classify companies as "innovators" or "imitators" based on information about their initial strategy. Innovators are either creating a new market, or introducing a radical innovation in an existing market, or developing a technology that will lead to either of the first two outcomes.

Hellmann and Puri (2000) report several interesting results. They find that innovators are more likely to be financed by venture capitalists. This result could be consistent with different possibilities though: it may be that venture capitalists have a comparative advantage in fostering innovation, for example through the provision of valuable advice for example. It may also be that venture capitalists have a comparative advantage in identifying the most promising innovative companies.

Hellmann and Puri (2000) also find evidence that venture-backed companies, especially innovators, are faster in bringing their product to market. Again this could be due to helpful advice by venture capitalists, or to selection of companies with characteristics that are observed by the venture capitalists but not measured in the available data, which make them more likely to bring their product to market in a shorter time.

Some of the more recent studies of the relationship between venture funding and innovation suggest that venture capitalists' ability to evaluate the quality of innovations (patent applications) plays an important role, and that venture capitalists may help to foster growth - but not innovation. Engel and Keilbach (2007) analyze a panel of young German firms. They find that firms with a higher number of patent applications are more likely to receive venture funding. Once the firms are venture-funded, they tend to grow more than comparable nonventure firms, while their innovative performance (in terms of patent applications) does not differ significantly. Caselli et al. (2009) and Peneder (2010) find a similar result using data on Italian and Austrian firms, respectively. These studies carefully estimate propensity scores to match venture-funded firms with otherwise comparable non-venture-funded firms, and thereby minimize the potential selection bias[4]. Nevertheless, the problem remains to the extent that venture-backed firms differ from the non-venture-backed firms they are matched with in terms of unobservable characteristics (observed by the venture capitalists that finance them).

Haeussler et al. (2009) examine data on German and British biotechnology firms. Their results are consistent with those of the studies just cited: firms with a higher number of patent applications obtain venture funding sooner. The authors go on to investigate the quality of patents, measured by received citations, and find that firms with higher patent quality receive venture funding more quickly. Importantly, the citations occur mostly *after* the venture capital investment decision, implying that venture capitalists are highly effective in identifying high-quality innovations (patent applications). This finding will play an important role in the theoretical analysis we develop below.

2.3 Is there a link?

Comparing the evidence from studies using firm-level and industry-level data raises a question: why does venture funding appear to have a positive impact on innovation at the industry level but not at the firm level? The comparison is obviously fraught with difficulties, since different studies use different sample sizes and data from different countries and time periods. This is potentially important given that the venture capital industry has developed quite differently in different countries.

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[4]The propensity score methodology is also employed by Da Rin and Penas (2007). Their paper attempts to address directly the question of how venture capital affects innovation by focusing on the determinants of absorptive capacity. They report that indeed venture capital favors the build-up of absorptive capacity.

There is also a more fundamental difficulty, as suggested in the discussion above: It is very hard to address the selection issue in a completely satisfactory way with firm-level data. This would require an experiment in which start-up firms are *randomly* assigned to receive venture funding or funding from other sources; alternatively, it would require the availability of appropriate instruments, highly correlated with venture capital investment in the firm but uncorrelated with unobservable (to the econometrician) firm characteristics which affect innovative performance.

In the absence of such solutions, can we nevertheless argue that firm-level studies may provide persuasive evidence against the hypothesis of a positive impact of venture capital on innovation? Theoretical analysis can shed light on this claim.

In the existing theoretical literature on venture capital, the main hypothesis concerning selection has been the ex-ante screening hypothesis: Venture capitalists, according to this hypothesis, are highly effective in evaluating the entrepreneurs that seek funding from them, and selecting the "better" ones[5]. Applied to innovation, this hypothesis suggests that venture capitalists will select and fund the entrepreneurs with the greatest potential for innovative success. Since the entrepreneur's potential is not observed by the econometrician, empirical estimates of the impact of venture funding on innovative performance will tend to be biased upward; intuitively some of the estimated effect will be due to the entrepreneur's potential, which makes it more likely that he will be venture-funded *and* that he will be successful in innovating.

If we could be sure that estimates will be biased upward, we might be able to make some inferences concerning the true underlying relationships. However, more recent theoretical work suggests that, at least in some circumstances, other influences may generate a downward bias. We investigate this possibility below. If different and opposing biases are present at the same time, the net effect is not clear. It then becomes difficult to draw inferences from reduced-form estimates obtained with firm-level data. An alternative but complementary approach might be to exploit the full power of theoretical analysis and test a richer set of predictions, as suggested at the end of this chapter.

We can summarize the main findings from our brief overview of the empirical literature as follows. First, there is evidence of a substantial impact of venture capital on innovation, measured by patent counts, at the industry level (at least for the United States). Second, there is no corresponding evidence of a significant impact of venture capital on innovation at the individual-firm level. One possible reason for this difference is the difficulty of adequately controlling for the endogeneity of venture capital investment at the firm level. While valid instruments have been found to address the endogeneity problem at the industry level, this is much harder to achieve at the level of individual firms. Third, there is very little evidence on how venture capital affects innovation. Here theoretical analysis can shed some light, and suggest promising avenues for future empirical work. In what follows, we focus on this possibility.

3   A simple model

This section introduces a very simple model, based on Dessí (2009) and Dessí and Yin (2013). The main purpose of the model is to illustrate some of the ways in which venture capital may affect innovation.

There are two periods and three dates, $t = 0, 1, 2$. At the beginning of the first period ($t = 0$), an entrepreneur with an innovative idea seeks funding to invest in turning the idea into a valuable

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[5]See, for example, Brander et al. 2002; Casamatta and Haritchabalet 2006, 2007; and Garmaise 2007; Ueda 2004. Kaplan and Stromberg (2004) and Lerner (1994) provide evidence of venture capitalists' ex ante screening role.

new product or process. At the end of the first period ($t = 1$), the outcome of this investment is realized. If the investment is successful in producing a valuable innovation, the entrepreneur can apply for a patent. At this stage another entrepreneur may enter the industry and invest in a competing project. During the second period, the patent application succeeds with probability β. The returns from all projects are realized at the end of the second period ($t = 2$). Entrepreneurs possess no capital and need to raise finance from outside investors. For simplicity, there is no discounting. All agents in the model are assumed to be risk neutral and protected by limited liability.

3.1 The incumbent

The first entrepreneur, henceforth also called "the incumbent", requires an initial outlay of value K_I to undertake his project. He succeeds in producing a valuable new product or process at $t = 1$ with probability α: we can think of this as capturing the quality of the entrepreneur and his idea. A valuable innovation can be patented with probability β, which depends on the characteristics of the product. For simplicity, β is assumed to take one of two values, β_G or β_B, with equal probability ($\beta_G > \beta_B > 0$). If the innovation is patented, the incumbent's project yields verifiable returns R at $t = 2$ with probability γ, and 0 otherwise, where $R > K_I > 0$. However, if the innovation is not patented and a potential competitor has entered the industry, the incumbent's probability of success (high returns) is reduced to $\gamma - \mu > 0$.

For simplicity, we assume that in the absence of an innovation, the incumbent's returns are equal to zero.

3.2 The entrant

At $t = 1$, a second entrepreneur (henceforth also called "the entrant" or "the rival") may enter the industry and invest in a competing project. The entrant's project requires an initial outlay of value K_E. It succeeds with probability ρ, unless the incumbent obtains a patent for his innovation: in this case the entrant's probability of success is reduced to zero. Success yields returns Y while failure yields zero; $Y > K_E > 0$.

3.3 Investors

Entrepreneurs may seek financing from a venture capitalist or from other investors. A venture capitalist who funds the incumbent, and interacts closely with him during the first period is assumed to possess enough information, expertise and industry-specific knowledge to be able to evaluate the probability that a patent application by the incumbent will be successful. Other venture capitalists, who have not been involved in the development of the innovation during the first period, will not have sufficient information, and will not be able to evaluate this probability correctly. Nor will other investors, even if they have funded the incumbent at the beginning, because they will not possess the necessary industry-specific knowledge and expertise.

To focus on the implications of this informational difference, we abstract from other differences between venture capitalists and other investors, and assume that they are all competitive.

3.4 Information

Our key informational assumption, as mentioned above, is that the realization of β at $t = 1$ is only observed by the venture capitalist that has funded the incumbent (if external finance is raised from a venture capitalist). The idea is that firm "insiders" possess an informational advantage

Figure 1: Time Line

T=0   T=1   T=2

Incumbent seeks   Innovation?   Project returns
funding.   VC observes β.   realized.
If funded, invests.   Patent application?
                         Entry?
                         Patent granted or
                         not.
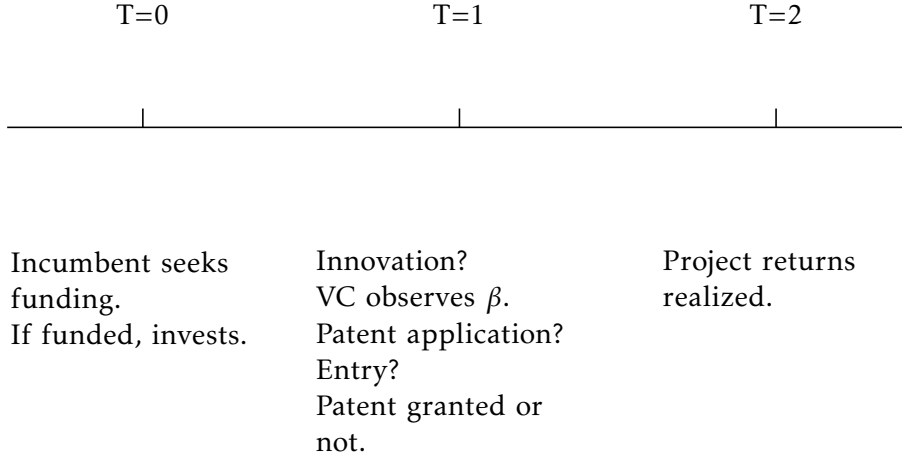
concerning the innovation, which is not fully disclosed in the patent application; moreover venture capitalists have greater expertise and industry-specific knowledge enabling them to assess the likelihood that an innovation will be granted a patent.

This assumption is consistent with the findings by Haeussler et al. (2009), discussed earlier, showing that venture capitalists are highly effective in identifying high-quality patent applications.

3.5 Assumptions

We make the following assumptions throughout the analysis:

$$\frac{1}{2}[(1-\beta_G)+(1-\beta_B)]\rho Y < K_E \qquad (A1)$$

This implies that in the absence of any information concerning the realization of β, the expected return from funding the entrant, is negative once the incumbent applies for patent protection for his innovation.

$$(1-\beta_B)\rho Y > K_E > (1-\beta_G)\rho Y \qquad (A2)$$

The entrant's expected profits are strictly positive when the probability of a patent being granted to the incumbent is low, and strictly negative when the probability of a patent being granted to the incumbent is high.

3.6 Time line

See Figure 1.

4 External finance raised from investors

We begin by examining the case where the incumbent obtains external finance to undertake his project from investors who will not observe the realization of β at the intermediate stage ($t = 1$). These may be "arm's length" investors, who do not interact closely with the entrepreneur while he tries to develop his innovative idea into a valuable new product or process. They may also be investors who do interact repeatedly with the entrepreneur and are involved in a number

of strategic decisions in the course of this relationship, but who do not have the expertise and industry-specific knowledge required to accurately assess the probability that the new product or process will be granted a patent.

In this case there is essentially symmetric information about β between the "insider" investors and other, outside investors. In particular none of them observes the realization of β at the intermediate stage.

By assumption (A1), nobody will be willing to fund the entrant once the incumbent has applied for a patent. Outside investors will be willing to fund the entrant, on the other hand, if the incumbent does not apply for a patent, since $\rho Y > (1 - \beta_B)\rho Y > K_E$. The entrepreneur will therefore apply for a patent when he develops a new product or process, and this will deter entry. Ex ante, the incumbent's expected return from his project is given simply by:

$$U_N = \alpha \gamma R - K_I \tag{2}$$

5   External finance raised from a venture capitalist

In this section we assume that the incumbent obtains the required initial funding for his project from a venture capitalist, who will interact closely with the incumbent during the first period, and have sufficient information as well as the necessary expertise and industry-specific knowledge to assess the probability that the incumbent's patent application will be successful.

At the intermediate stage ($t = 1$), we now have asymmetric information between the venture capitalist who has funded the incumbent and other investors: the former observes the realization of β, while the latter do not.

From assumption (A1), as before, we know that in the absence of any information concerning the realization of β, investors will not be willing to fund the entrant once the incumbent has applied for a patent. Moreover, the incumbent is better off applying for a patent when he develops a new product, because in the absence of a patent application investors will always finance the entrant.

The difference with the previous section is that the venture capitalist who has funded the incumbent now observes the realization of β. When β is low (β_B), the venture capitalist may be willing to fund the entrant. We assume for simplicity that in this case the venture capitalist would extract all the surplus from the transaction, since the entrant could not obtain funding from another source. Denote the surplus by $S \equiv (1 - \beta_B)\rho Y - K_E$. To ensure that the venture capitalist funds the entrant only when this is efficient, the venture capitalist can be given a claim to the final returns from the incumbent's project (i.e. R), in return for a transfer T to the incumbent. This means that the venture capitalist fully internalizes the costs for the incumbent's project when he decides whether to fund the entrant. The venture capitalist will then finance the entrant if, and only if, the following condition holds:

$S > (1 - \beta_B)\mu R.$ 　　　　　($C1$)

Ex ante, the incumbent's expected return from his project is now given by:

$$U_{VC} = \alpha \max[\gamma R, \gamma R + S - (1 - \beta_B)\mu R] - K_I \tag{3}$$

which will be higher than the expected return when financing is raised from other investors if condition ($C1$) holds.

We can define the threshold value α_{VC}^* as the value of α for which $U_{VC} = 0$, and the threshold value α_N^* as the value of α for which $U_N = 0$. These are the threshold values for α below which entrepreneurs will not be able to obtain funding for their projects from venture capitalists and

from other investors, respectively. Clearly if condition $(C1)$ holds, $\alpha_{VC}^* < \alpha_N^*$; otherwise, $\alpha_{VC}^* = \alpha_N^*$.

6 Theory and evidence

In spite of being highly simplified and stylized, the model analyzed above already yields some insights[6].

As we have just seen, venture capitalists, after funding an entrepreneur with an innovative idea, may be able to extract surplus from potential entrants at a subsequent stage, exploiting the informational advantage gained through close interaction with the first entrepreneur. *Ex ante*, this can make it possible to obtain funding for innovative projects that would not be financed by other investors: in the model, this will be the case if $U_{VC} > 0 > U_N$.

There are then two effects on innovation: a direct effect on the number of innovative projects that are undertaken, and an indirect effect on the average quality of funded projects. The first effect is obviously positive; it is analogous to the effect of monitoring by venture capitalists (as in, for example, Holmström and Tirole (1997)), in the sense that it relaxes firms' financing constraint, albeit for a quite different reason.

The second effect can be seen by noting that $\alpha_{VC}^* < \alpha_N^*$. Thus, *ceteris paribus*, the average quality of projects, as measured by the probability of innovation α, will be lower among venture-backed entrepreneurs than among those funded by other investors. Obviously this effect is due to the assumption that α is perfectly observed by venture capitalists and other investors alike. Nevertheless, it illustrates in a simple way the point made earlier, that the endogeneity of venture capital funding can be due to a variety of reasons (not just the screening hypothesis), and the nature of the resulting bias in empirical estimates cannot be predicted with confidence.

The model analyzed in the previous section is very simple in many respects, and further insights can be gained by relaxing some of the assumptions. For example, the probability of developing a valuable new product is assumed to be exogenous: it does not depend on the entrepreneur's effort. One consequence of this is that the projects that are funded when $U_{VC} > 0 > U_N$ would not be worth funding without the possibility of extracting surplus from potential entrants. However, once the model is extended to allow for the need to induce the entrepreneur to provide effort, it will typically be the case that the entrepreneur will earn some rents, reducing the returns that can be earned by outside investors, so that some projects that would be worth funding cannot obtain outside financing. In this case, the venture capitalist's ability to extract surplus (informational rents) from potential entrants may make it possible to undertake projects that would be profitable even on a stand-alone basis, but would be denied funding (Dessí (2009)).

Moreover, and for the same reason, venture funding may make it possible to give more high-powered incentives to the entrepreneur (since the expected surplus from new entrants relaxes the venture capitalist's participation constraint), increasing his effort (Dessí (2009)), and hence the probability of developing a valuable new product or process.

7 Conclusions

The existing empirical literature has shown considerable ingenuity in addressing the challenges of establishing and quantifying a causal relationship between venture capital and innovation. Yet there remains plenty of room for further work shedding light on the precise mechanisms through which venture capital fosters innovation. In this chapter we have argued, using a simple model

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[6]For a richer model and analysis, see Dessí and Yin (2013).

to illustrate our point, that a close interaction between theoretical and empirical analysis offers a promising avenue for future research. For example, our model suggests that the link between venture funding and innovative performance at the level of the individual firm may depend on the potential for surplus extraction from other firms, and hence on industry characteristics and structure. It would be interesting to explore this empirically in future work.

The theoretical analysis could be extended in a number of directions: for example, allowing for exit decisions. The allocation of control rights has been shown to be important for exit decisions (Cumming (2008), Dessí (2005), Hellmann (2006)), and the design of optimal contracts for innovative entrepreneurs in the presence of exit decisions as well as potential entry by competing firms deserves further study. Empirically much work also remains to be done to investigate the relationship between the form of contracts used by venture capitalists (e.g. control rights, staging, syndication) and innovation.

Finally, it is worth emphasizing the limitations of the simple analysis presented in this chapter. For example, we have focused primarily on the role of private, limited partnership venture capital funds, with no strategic or public interest in innovation per se. The role of corporate and government venture capital has been studied elsewhere (see Gompers and Lerner (2004)), and represents an important part of the link between venture capital and innovation.

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Table 1: Summary of Empirical Studies

Author	Sample Description	Data Source	Method of Analysis	Summary of Findings
Kortum and Lerner (2000)	20 U.S. manufacturing industries between 1965 and 1992	Industry patent counts are based on the International Patent Classification assigned to each patent issued by USPTO; Venture funding collected by Venture Economics; Industrial R&D expenditures collected by USF	IV estimation which exploits the policy shift of US freeing pension to invest in venture capital in 1979 ; alternative method is using R&D as controls to disentangle the endogeneity problem.	The impact of venture capital on technological innovation is positive and significant, which is 3 times as potent as the corporate R&D and accounts for 8% of industrial innovations in the decade ending in 1992.
Ueda and Hirukawa (2008)	19 U.S. manufacturing industries from 1965 to 2001	Venture Economics proprietary database(VentureXpert), the NBER productivity Database, the NBER Patent database, and the NSF R&D database.	Similar methods as in Kortum and Lerner (2000)(KL) adopted to re-examine the results of KL in a extended period; Alternatively, utilizing total factor productivity (TFP) growth and labor productivity growth as measures of innovation.	The regressions for patent counts confirm the findings of KL with bigger coefficients. But there is no significant impact of venture capital on TFP growth; Although the impact of VC on labor productivity growth is positive and significant however, it is driven by substitutions of input factors away from labor.

Author	Sample Description	Data Source	Method of Analysis	Summary of Findings
Hellman and Puri (2000)	173 start-up companies that are located in California's Silicon Valley, which is culled from two database and the Silicon Valley business press	A uniquely hand-collected dataset built upon surveys, interviews and commercial databases, as well as any publicly available information	Probit model to examine the likelihood of a company receiving venture capital financing; Cox proportional hazard model to explore whether the product strategy affects the time to receiving VC and whether the VC financing affects the time to market.	Innovators are more likely to be financed by venture capital than are imitators. And innovators obtain venture capital earlier in the life cycle than do imitators. Venture-based companies, especially innovators are faster in bringing their product to market.
Engel and Keilbach (2007)	All German firms starts-up between1995 and 1998, including 50754 non venture funded firms and 274 venture funded firms.	A dataset which merged ZEW-Foundation panels provided by Creditreform (the largest German credit rating agency) with information from other sources, including DPA patent application data.	Propensity score matching procedure to alleviate selection bias which arises from the extensive pre-investment screening process of VC.	Firms with higher patent applications and higher educated management have a larger probability of being venture funed. And venture-based firms display a higher growth rate than the comparable non venture-funded firms, however, their innovative performance doesn't show significant difference.

Author	Sample Description	Data Source	Method of Analysis	Summary of Findings
Caselli, Gatti and Perrini (2008)	153 Italian IPOs firms between1995 and 2004, including 37 venture-funded firms and 116 non venture-funded firms.	A self-collected dataset based on the information provided by Italian Association of VC and PE operators, VC-funded companies and the Italian Trademark and Patents Office.	Similar methods as in Engel and Keilbach (2007).	The entry of venture capital into the company does not promote continued innovation, but mainly develops the sales.
Peneder (2010)	250,000 Austrian companies including 166 venture funded companies.	Database collected by Austrian Private Equity and Venture Capital Organization (AVCO) combined with firm database provided by the leading Austrian credit rating agency and a comprehensive enterprise survey.	A two-stage propensity score matching.	VC-backed firms are constrained to obtain financing through traditional channels. VC-backed firms are more innovative which is prove to be a pure selection effects. And they grow faster in term of turnover and employment which encompass both causal effects and selection effects.

Author	Sample Description	Data Source	Method of Analysis	Summary of Findings
Haeussler, Harhoff and Muller (2009)	190 German and British biotechnology companies founded after 1989; 87 of them are VC-financed and 103 of them are non VC-financed.	Questionare surveys; face-to-face interviews with companies; and official patent reports from European Patent Office(EPO).	Cox proportional hazard model to investigate how patent related variables influence the hazard of obtaining VC financing.	Signals generated in patenting process increase VC financing and attract VC faster. Companies with higher quality of patent (measured in citation) receive VC faster, while patent indicators generated by patent examiner has weak effects on VC financing which indicates that VCs are capable of detecting high-quality patent applications at the early stage.
Da Rin and Penas (2007)	7808 Netherland portfolio companies;91 of them are VC-financed; 7717 of them are non VC-financed.	CIS survey data covering 1998-2004; VentureXpert; PATSTAT database developed by OECD and EPO.	Probit model to examine the relationship between VC and innovation strategies; furthermore, propensity score method to distinguish treatment effect from selection effect.	Venture capital favors the build-up of absorptive capacity and results in a more permanent in-house R&D efforts. While the public funding relaxes the financial constraints, but does not lead to a build-up absorptive capacity.

Chapter 3 Intellectual Property and Cumulative Innovation

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1   Introduction

Economists generally accept that intellectual property rights may promote innovation, but may also impede subsequent research. Patents, in particular, allow innovators to appropriate returns by blocking others from using their ideas. If research is cumulative, patents potentially prevent scientists from "standing on the shoulders of giants" to build on prior work. Theoretical work includes Bessen and Maskin [2009], who illustrates that patents may not be efficient when innovation is sequential and complementary; and Heller and Eisenberg [1998], who suggest the possibility of a scientific "anticommons" when too many patentholders use their property rights to exclude others. Recent empirical work confirms the validity of these concerns (Murray and Stern [2007], Williams [2013], and Galasso and Schankerman [2013]). The explosion of patent activity, including by universities (Schacht [2009]), suggests that the negative consequences of IPRs on cumulative innovation may grow in importance.

Patent policy in many countries addresses the possible impediments by exempting some research from infringement concerns. These exemptions take different forms (statutory vs. case law) and apply to different types of organizations or research. For example, most European countries restrict the use of patents to block research for noncommercial purposes. In the United States, no such statutory exemption exists. However, the US and other countries allow generic drug firms to use patented materials to prepare applications for regulatory approval. There is little empirical work on the use and importance of these exemptions. Survey evidence in Walsh et al. [2007] suggests that academic scientists are unaware of or insensitive to their potential infringement, although those working in biomedical fields report more issues related to intellectual property rights.

We investigate the potential effects of intellectual property and research exemptions on cumulative innovation in drug development. Cumulative innovation in this context may be finding new

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uses for existing treatments, or using existing treatments to establish the benefits of a new compound. In the absence of a license from the patentholder, use of a patented drug in experiments may constitute infringement. The cost of obtaining a license and the risk of litigation increase the costs of cumulative innovation and may impede follow-on work.

Patent protection at the drug level varies over time and across countries; policies such as patent terms, patent exhaustion and research exemptions also vary across time and countries. We exploit this variation to identify the effect of patents on cumulative innovation. If research can be costlessly relocated, the total effect of patent rights on cumulative innovation may be insignificant; however, patents may be an important determinant of where research occurs, and therefore still of interest for local policy. If relocation of research is difficult, then the policies of countries with higher innovative capacities may have global importance.

We use new clinical trials as a measure of innovative effort. Data come from the major clinical trial registries around the world, including those of the US, the European Union, Japan, China, India, and others. We combine this with patent information at the drug and country level. Due to variation of statutory provisions about research exemption across countries, our study is capable of investigating the effect of research exemption and how it interacts with patent protection. As the vast list of countries provide idiosyncratic political and economical environments that might promote or hurdle innovation, we propose to utilize the innovative capacity index of countries to capture the competitiveness in research across countries. We also distinguish the innovative efforts that conducted before the drug launch and after as the marketed drug facilitates the experiments even under patent protection. Our results show that the overall effect of patent protection tends to promote the innovative activities; post launch drugs facilitate the clinical trial conducted on them. Research exemption turns out to be associated with lower level of follow-on innovation activities. Clinical trials tend to conducted in higher ICI countries and the ICI index promotes more innovative activities in patent protection and post launch case.

The remainder of the paper is as follows. The next section discusses the background of drug development and IP law; Section 3 discusses the literature and theoretical motivation; Section 4 describes the data employed; Section 5 develops the empirical framework and predictions of hypothesis; Section 6 presents the summary statistics and empirical findings. We conclude in Section 7 by discussing the broader implications for science and IP policy.

2   Theoretical motivation

Of particular interest in recent years is the relationship between intellectual property and cumulative innovation. The choice of patent breadth, for example, is impossible to assess without also considering the treatment of cooperation between firms and collusive licensing (Scotchmer [1991]). Shapiro [2000] and others highlight the potential costs associated with fragmented IP rights, or patent thickets, for follow-on innovation. A license may be required from many different IP owners, who may be difficult to find and who fail to account for the effect of their own license prices on demand for others. Heller and Eisenberg [1998] asks whether there is an anti-

commons in biomedical research. They note that the inefficiency is greatest when patent rights to fundamental innovations are fragmented.

Empirical work on patent law and cumulative innovation is limited, and has focused primarily on the possibility of an anticommons. In discussing results from a survey of academic scientists, Walsh et al. [2007] are generally skeptical of the idea of a research anticommons: scientists did not report that IP hindered their work. However, drugs were an important exception. Researchers' requests for drugs to use in their work were less likely to be fulfilled, especially from industry. Drugs were also seen as more limited by patents than other inputs to research. In contrast, Hansen et al. [2005] report that 40% of the scientists responding to a different survey said that difficulties in obtaining permission to use patented materials had adversely affected their work.

Several recent papers suggest that there is some cause for worry about the negative effects of patent protection and cumulative innovation. Murray and Stern [2007] study "patent-paper" pairs, in which the same idea diffuses under two different IP regimes. They find that following a patent grant, citations in the scientific literatire to an idea modestly lower than to comparable ideas. Williams [2013] compares genes with and without IP during a 2 year period, and finds that scientists used the genes protected by patents less than those without. Like Murray and Stern [2007], she measures use with citations in scientific papers, as well as the development of a genetic test that uses the gene; she also finds significant effects of IP on the use of patented materials. Galasso and Schankerman [2013] apply a different empirical approach and examine a broader set of industries. They examine citations to a patent before and after its invalidation, using a clever instrumental variable derived from the random assignment of judges to patent cases. Their study shows interesting heterogeneity across technologies/industries: the effect of invalidation is largest in computers, electronics, and medical technology.

Most work in this area, in legal scholarship as well as in the economics literature, has focused on the United States. This reflects the importance of patent activity (and litigation), which has grown substantially over the last several decades. The definition of patentable subject matter is broader in the US than in many other countries, currently encompassing aspects of genetics, research tools, software, and business methods. With multilateral and bilateral trade agreements that include amendments to patent laws, the discussion of these issues now extends to other places, especially emerging markets. The most notable of the multilateral agreements is that adopted in 1994, when the World Trade Organization was established. The Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement requires WTO members to grant patents of at least 20 years, including on pharmaceutical products. But the TRIPS Agreement also allows a number of exceptions to rights conferred by intellectual property, partly in response to concerns raised by developing countries; compulsory licensing of patents, for example, is permitted under some circumstances. Individual countries may include these exceptions without violating the TRIPS Agreement, but are not obligated to do so, and there is variation in their use across countries.

In this paper, we focus on exceptions for the use of patented material in "acts done for experimental purposes" or "acts done privately and for non-commercial purposes," or a research

exception more generally. In general, patent law allows the owner of patents to prevent the use of their inventions by unauthorized third parties. These exceptions stem from the view that innovators should be rewarded with monopoly power over commercial activity, but that patents should allow innovators to should not provide a monopoly over non-commercial activity. In particular, it has long been held that patent rights should not restrict scientific research. However, considerable debate exists both between and within countries over the definition of "non-commercial" or "experimental" use. Should experimentation for the purpose of designing around a patent be exempted from infringement? Should such experimentation be exempted only when there is no commercial aspect? Distinguishing between commercial and non-commercial use is not always straightforward. In some countries, the activities of non-profit organizations or state institutions considered non-commercial.

Of particular relevance to pharmaceutical research is the so-called "Bolar" exception[1] used by many countries, including the US. This exception allows generic firms to conduct research on a molecule still under patent protection if that research is conducted for purposes of winning regulatory approval following the patent's expiration. However, this exception is less important for cumulative product innovation, since generic drug firms using the Bolar exception are usually manufacturing a version that is as close as possible to the originator's product.

Unlike many other countries, the US has no statutory exception for research or experimental use. Case law in the US has established an experimental use exception, but also taken a broad view of commercial activity. In the well-known Madey vs. Duke case, the Court of Appeals of the Federal Circuit noted that university research often has commercial elements, and does not necessarily qualify for the experimental use exception. Following recent court decisions in the US, DeFranco [2006] states "[i]t is clear that under most practical circumstances neither industrial nor academic researchers can successfully invoke the experimental use exception to charges of patent infringement. Instead, the exception remains unavailable for uses of patented inventions in pursuit of any business interests, including both design-around attempts and at least some uses in a university research setting." However, US courts have taken a broad view of the Bolar exception (as in the Merck KGaA v Integra Lifesciences I Limited decision), permitting the use of a patented drug in clinical research without infringement if the research might ultimately result in data relevant for regulatory approval.

As noted by Dent et al. [2006], there is only limited evidence on the importance of patents and the research exception for cumulative innovation, despite its relevance in current policy discussions. As the US negotiates "TRIPS-plus" trade agreements with partners in the developing world, conformity with US-style IP laws is likely to increase. Some developed countries have also recently made adjustments to their research exceptions. In early 2013, for exmaple, the UK changed its patent law to expand the research exception to clinical trials, and the Minister for

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[1]So named because of Roche Products v. Bolar Pharmaceutical, 733 F.2d 858 (Fed. Cir. 1984), in which the Court of Appeals for the Federal Circuit determined that the experimental use exception did not extend to the activities of generic drug firms. Soon after, the 1984 Hatch-Waxman Act changed the law to permit generic firms to conduct research prior to patent expiration.

Universities and Science David Willetts said this "marks an important step forward by removing the risks of patent infringement when testing new drugs and treatments. This will make the UK a more attractive location for research and development, supporting growth and innovation."[2]

Overall, we expect a patent on a drug to raise the costs of research for non-originators, and consequently for fewer clinical trials to be conducted on that drug in countries where it is patented. This may be moderated by the presence of a research exception for researchers in the non-commercial sector (particularly academic and non-governmental organizations). In addition, both patents and a research exception are likely to be more important in countries with high innovative capacities; conversely, patents are probably not the more important impediment to cumulative research efforts in countries with low innovative capacity. A product patent on a drug may also affect the nature of cumulative research efforts by non-originators. Discovery of a new use would be commercially valuable only with permission to produce from the holder of a product patent, for example.

At the same time, there are many reasons to expect that patents have only a small effect, if any, on cumulative innovation in pharmaceuticals. Galasso and Schankerman [2013] find that patents had no statistically significant effect on citations in some sectors, including drugs. Licensing is widespread in pharmaceuticals, which suggests that transaction costs in contracting may not pose a large barrier to cumulative innovation. So-called patent thickets, where a large number of patent owners hold overlapping IP rights, are more typical in other sectors such as semiconductors. In addition, academic researchers may be unaware of IP barriers, or may see the risk of litigation as too low to affect their behavior (Walsh et al. [2007]). Even if they are sensitive to infringement concerns, it may be possible for researchers to shift the location of their activities to countries where IP barriers are lower instead of (or in addition to) adjusting the level of those activities in response to intellectual property policies. For example, DeRouen et al. [2012] find that US policies limiting stem cell research are associated with a reduction in the output of US-based scientists relative to those located outside the US. The total welfare effect depends on whether the decline in US research was fully offset by an increase elsewhere. In addition to shifting research across space, researchers may shift across time: they may simply wait for key patents to expire. The welfare effects of any delay are also difficult to assess.

3   Description of drug development and IP law

In order to win regulatory approval for sale, innovators must demonstrate the safety and efficacy of a new drug for a specific use through evidence from human clinical trials. These trials often take years to complete, are expensive, and have high failure rates.[3] Because imitation of drug is relatively easy once its quality has been established, patents play a more important role in the pharmaceutical sector than in most others (Cohen et al. [2000]). It is generally (though not universally) agreed that patent protection for pharmaceuticals induces more innovative ef-

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[2] https://www.gov.uk/government/news/cutting-of-red-tape-to-benefit-research-and-d evelopment-of-new-drugs
[3] For an overview of the process, see the FDA website.

fort, though the elasticity of R&D with respect to patent protection varies by country (Kyle and McGahan [2012]).

The number of patents granted to a drug depends on several factors. First, the drug's originator may apply for a product patent on the molecule itself; this is usually considered the "strongest" patent in that it is difficult for others to invent around it. While most countries are now required to grant product patents on pharmaceuticals, many changed their patent laws after 1995 in order to comply with the TRIPS Agreement.[4] Often, innovators apply for subsequent patents covering new uses of the molecule, manufacturing processes, or similar chemical forms such as salts or isomers. Patent offices in different countries may use different criteria in determining the eligibility for protection, which results in varying degrees of IP for the same drug across countries. These follow-on patents may come years after the initial product patent, so the number of patents on a drug within a country also varies over time.

Cumulative innovation in pharmaceuticals can take several forms. These include process innovations, such as refinements to manufacturing or compounding that lower the cost of production. In this paper, we focus on cumulative product innovations. For example, new uses for a drug can be found, and sometimes patented. Decades after its discovery as a pain reliever, aspirin was shown to have value as a preventative treatment for heart attacks. More recently, a new use (growing thicker eyelashes) for the glaucoma treatment bimatoprost was discovered. Additional uses for the cancer drug Avastin are currently being explored. Other incremental innovations include the development of better dosing formulations, such as extended-release pills or pediatric liquids that improve compliance. Finally, existing pharmaceuticals are often the comparator treatments in clinical trials of other molecules. That is, they are an input in the research conducted in the development of other treatments.

"Inventing around" a patent might also be considered a form of cumulative innovation. Particularly when no product patent exists (but other types of patents do), imitators may find ways to produce the same molecule without infringement. In many countries, including the US, an abbreviated approval process exists for generic drugs. Rather than requiring the same long and expensive clinical trials to demonstrate safety and efficacy again, regulators allow generic firms to reference that data and submit less onerous testing to demonstrate bioequivalence.[5] Such tests still take some time and potentially delay generic entry.

For drugs already on the market, patentholders may not be able to control how the product is used in research if the first sale doctrine applies. Once the product has been sold, intellectual property rights may be considered exhausted, and researchers able to purchase the drug for use in their studies through standard channels. In this scenario, investigators may face high acquisition cost of the patented materials due to monopoly pricing, but do not require a license. In our empirical analysis, we distinguish between research performed prior to a drug's launch and that done

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[4]Countries that are members of the World Trade Organization must comply with the Trade-Related Aspects of Intellectual Property (TRIPS) Agreement, which includes a number of requirements for pharmaceutical patents. Least-developed countries have a 2016 deadline for compliance.

[5]However, in many countries the firm that conducted the initial trials that generic applications reference enjoys a period of data exclusivity, during which no other firm may rely on that data; see Liu and LaCroix [2013].

afterwards. Prior to launch, the research exception may be relevant, because the only means of obtaining the material would be to manufacture it (normally an act of infringement) or to request it directly from the patentholder. After launch, the research exemption may not be necessary.

The existence of patent protection has implications for the extent and location of cumulative innovation activity. As discussed above, patent law can influence the incentive to develop a new use for a molecule as well as the cost of incremental or follow-on work performed by firms other than the patentholder. Since we are looking at patents on molecules rather than on genes or research tools, an anticommons that stems fragmentation of patent rights may be less of a concern. Without a research exception, cumulative innovation on a patented drug must be undertaken by the owner of the patent or those with a license from the patentholder. The cost of obtaining patented materials or permission to use them may be nontrivial, even when no "thicket" of patent rights exists.

The research exception adopted by many countries specifically recognizes the benefits associated with the use of patented materials in subsequent research. With a research exception that applies only to noncommercial activities, academic or government scientists may attempt cumulative innovation, but commercial firms may not do so without permission. The specific implementation of experimental or research use exceptions and the scope of activities that are defined as noncommercial may affect the share of cumulative research performed in the academic or public sector. Even when the research exception is narrow or does not exist, the cost of enforcement may shield academic researchers from lawsuits by patentholders.

We study three types of exemption in the regression: experimental exemption, non-commercial exemption, and Bolar exemption. The exemption dummies are recorded as one if and only if the countries have a statutory exemption. (We are refining this to include case law exemptions.) An experimental/non-commercial exemption states that any use of the compound in experiments/non-commercial research is exempt from infringement. The Bolar exemption assures that all use of compound that are reasonably related to submission of information to the government under any law regulating the manufacture, use or distribution of drugs.

This paper examines the extent to which either IP protection or the research exception matter for cumulative innovation involving pharmaceuticals. We exploit variation in the extent of IP protection on a specific drug across countries, and within countries over time, to test whether patents are associated with lower levels of research activities directed at cumulative innovation. We test also whether the effect of patents on cumulative innovation is lower in the presence of a research exception, and whether the effects of patent protection and the research exception vary with a country's level of innovation. Finally, since research exemptions and incentives to litigate vary across organization types, we explore differences between research activity conducted by patentholders, for-profit competitors, and the public and academic sector.

4 Methods

Our theoretical motivation suggests that the level of follow-on research depends not only on the proprietary rights of the experimental products but also on any statutory research exception. To test this idea, we examine how the number of clinical trials is related to the patent status of each drug, which varies across countries and time, and the research exception provisions in each country, which varies across countries and on the types of organizations to which they apply.

4.1 Identification

Ideally, to test the effect of a patent on subsequent clinical trials, we would randomly assign patents to drugs and research exceptions to countries. In practice, this is of course infeasible. Instead, we exploit variation in patent laws across countries and variation over time and across countries in the patent status of a drug, and employ a differences-in-differences (DID) approach. Essentially, we want to compare the use of patented knowledge (or a drug) with use of unpatented drugs in clinical trials. Obviously, patented drugs are likely to be systematically different from unpatented drugs, and this simple comparison will yield a biased estimate of the effect of a patent. However, we are able to compare the *same* drug in environments with patent protection to environments without patent protection. In general, this comparison will also be biased due if we fail to account for differences between those environments.

The validity of DID depends on the conditional independence assumption (CIA). That is, conditional on the controls we include, there is no systematic difference in research effort across countries, drugs and years for which patent protection is and isn't in effect. Section 5 provides a detailed explanation of the control variables used. We believe these are sufficient for CIA to hold for the following reasons.

Aside from the intellectual property environment, an investigator's decision to initiate a trial and where to do so depends on several other considerations. Some countries may be more attractive locations for research because of the quality of their science base is high. The importance of a country as a potential market for future products may also play a role, as clinical trials may serve as a form of advertising. The prevalence of the disease of interest is also salient, since it affects the costs of enrolling trial subjects. The number of trials may vary over time in response to disease shocks (a flu pandemic, for example) or following the development of new research tools.

We control for these factors by including country, drug and year fixed effects in our analysis. While patent policies are not randomly assigned across countries, we argue that first, most developed countries did not make large changes to their patent laws during our sample period (2002-2012). Developing countries have generally increased patent protection, but these changes were largely forced upon them by the TRIPS Agreement.[6] Usually, if inventors want protection in multiple countries, they must apply within 24 months of their first application. However, there is some variation in patent expiration dates across countries associated with differences in patent

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[6]See Hamdan-Livramento [2009] and Kyle and McGahan [2012].

term extensions. Our primary worry is the existence of an omitted variable that drives both adoption of particular patent policies as well as the location of clinical trials, which is why we include a measure of a country's innovative capacity. At the drug level, molecules with many patents are likely to be systematically different from those with very few: originators invest in obtaining more patents for more valuable drugs. However, by including drug fixed effects, we are able to sweep out these differences in quality or value.

Our empirical approach is similar in many ways to those adopted by Murray and Stern [2007], Williams [2013] and Galasso and Schankerman [2013]. These papers examine how the addition or subtraction of patent rights changes citations (in other patents, or in scientific papers) to an idea; that is, they rely on within-idea changes in IP status over time. We use an additional source of variation in patent rights, that across countries. We also employ an outcome measure appropriate for the specific context of our study, that of pharmaceutical innovation.

4.2 Empirical model

Before the comprehensive analysis, we will first have a look at a baseline model by considering the response of the global trials to the patent status in the US and other countries. To be specific, the model is expressed in this form:

$$
\begin{aligned}
No.\ of\ Trials_{it} \quad = \quad & \alpha \\
+ \quad & \beta_1 Any\ product\ patent\ in\ the\ US_{it} \\
+ \quad & \beta_2 No.\ of\ other\ country\ with\ product\ patents_{it} \\
+ \quad & \beta_3 Prior\ to\ drug's\ global\ launch_{it} \\
+ \quad & \beta_4 Prelaunch_{it} * Any\ product\ patent\ in\ the\ US_{it} \\
+ \quad & \beta_5 Prelaunch_{it} * No.\ of\ other\ country\ with\ product\ patents_{it} \\
+ \quad & \gamma_1 Drug\ Age_{it} + \gamma_2 Drug\ Age_{it}^2 \\
+ \quad & \gamma_3 Years\ since\ first\ patent\ application_{it} \\
+ \quad & Year\ FE + Drug\ FE + \epsilon_{it},
\end{aligned}
$$

The unit of observation in this model is at drug-year level. We are curious about how global innovation activities that conducted on each drug in each year varies with the drug's product patent status in the US and other countries, with the timing of drug launch and other controls (drug age, years after patent application, etc.).

Here, our dependent variable $No.\ of\ Trials_{it}$ measures the total number of interventional trials conducted globally on the drug i in year t. The explanatory variables include,

- *Any product patent in the US$_{it}$*, equals to one if there is any product patent for the drug i in the US in year t;

- *No. of other country with product patents$_{it}$*, denotes the number of countries except the US

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that have product patent on drug i in year t;

- *Prior to drug's global launch$_{it}$*, equals to one if drug i hasn't been launched globally yet at year t;

- Interaction terms among the above three variables.

Besides the explanatory variables, we also control the $Drug\,age_{it}$, and $Years\,since\,first\,patent$ $application_{it}$, which is the number of year since the drug's first patent application has been filed.

After get a flavor of this question, we then turned to a more delicate model below:

$$
\begin{aligned}
No.\,of\,Trials_{ijt} \;=\; & \alpha \\
& + \;\beta_1 Patent_{ijt} \\
& + \;\beta_2 Prior\,to\,drug's\,launch\,in\,country_{ijt} \\
& + \;\beta_3 Patent_{ijt} * Prelaunch_{ijt} \\
& + \;\beta_4 Patent_{ijt} * Research\,Exemption_j \\
& + \;\beta_5 Prelaunch_{ijt} * Research\,Exemption_j \\
& + \;\beta_6 Prelaunch_{ijt} * Patent_{ijt} * Research\,Exemption_j \\
& + \;\beta_7 Patent_{ijt} * Innovative\,Capacity\,Index_j \\
& + \;\beta_8 Prelaunch_{ijt} * Innovative\,Capacity\,Index_j \\
& + \;\beta_9 Patent_{ijt} * Prelaunch_{ijt} * Innovative\,Capacity\,Index_j \\
& + \;\beta_{10} Patent_{ijt} * Research\,Exemption_j * Innovative\,Capacity\,Index_j \\
& + \;\beta_{11} Prelaunch_{ijt} * Research\,Exemption_j * Innovative\,Capacity\,Index_j \\
& + \;\beta_{12} Prelaunch_{ijt} * Patent_{ijt} * Research\,Exemption_j \\
& \quad * \;Innovative\,Capacity\,Index_j \\
& + \;\beta_{13} Prelaunch_{ijt} * Patent_{ijt} * Innovative\,Capacity\,Index_j \\
& + \;\theta_1 No.\,of\,other\,countries\,with\,product\,patent_{ijt} \\
& + \;\theta_2 No\,product\,patent * Log\,of\,No.\,of\,other\,countries \\
& \quad\; with\,product\,patent_{ijt} \\
& + \;\gamma_1 Drug\,Age_{it} + \gamma_2 Drug\,Age_{it}^2 + \gamma_3 DALY_{ij} \\
& + \;\gamma_4 Years\,since\,first\,patent\,application_{ijt} \\
& + \;Year\,FE + Country\,FE + Drug\,FE + \epsilon_{ijt},
\end{aligned}
$$

Our dependent variable is $No.\,of\,Trials_{ijt}$, defined as the number of trials conducted on the drug i in country j at year t. $Patent_{ijt}$ is the treatment variable, equal to one if drug i has patent protection in country j in year t. We use several measures of patent protection to verify robustness, including the existence of any patent, the existence of a product patent, and the number of patents

on drug i in country j in year t.

The effect of a patent should be smaller for some types of organizations (mainly those with nonprofit status or engaged in noncommercial research) if a country has a research exception, since this removes the threat of litigation and the need for a license.[7]

Therefore, we interact the patent dummy with a dummy for whether a country has a statutory research exemption, $Research\ Exemption_j$. We also want to check whether the importance of patents and research exemptions varies across countries: these are likely to be irrelevant in countries with almost no research activities, and most salient in places with high innovative capacities. Therefore, a triple interaction effect is included, i.e., $Patent_{ijt} * Research\ Exemption_j * Innovative\ Capacity\ Index_j$.

After a drug's launch, experimenters may simply buy the drug and use it as they want under the doctine of first sale, which means that patent protection should have little impact on follow-on research. Prior to launch, however, researchers need to acquire the product from the patentholder; if this is difficult or expensive, cumulative research efforts may be affected. We include a dummy variable indicating whether the clinical trial began prior to drug i's launch in country j, as well as its interaction with the patent, research exemption, and innovative capacity variables.

Additionally, we also include the $No.\ of\ other\ countries\ with\ product\ patent_{ijt}$ and the interaction terms of $Product\ Patent_{ijt}$ and $No.\ of\ other\ countries\ with\ product\ patent_{ijt}$ to check whether the investigators tend to relocate the clinical trials across countries to avoid patent protection in home countries.

Finally, we control for other drug-year covariates, such as years since the first patent application for a drug, the age of a drug (years since its first global launch) and its square, and a measure of the disease burden (measured as disability-adjusted life years) associated with the condition a drug treats ($DALY_{ij}$). Drug fixed effects, country fixed effects and year fixed effects are included in all the regressions. These fixed effects account for the heterogeneity across drugs and countries, as well time-varying shocks in demand or in clinical trial practices.

The dependent variable is a count variable, which suggests using a Poisson or negative binomial model rather than OLS. The large number of fixed effects, however, makes estimation of non-linear models more difficult. In addition, the dependent variable ranges from 0 to 126, so its distribution resembles that of a highly skewed continuous variable. We therefore log $No.\ of\ Trials_{ijt}$ and all continuous explanatory variables ($Disability\ Adjusted\ Life\ Year_{ij}$, $Innovative\ Capacity\ Index_j$, $No.\ of\ other\ countries\ with\ product\ patent_{ijt}$).

We repeat this exercise for the trials conducted by the public sector, originators and non-originators (i.e., organizations that are neither public sector nor an originators or co-developer of the focal drug). We also estimate this specification for subsets of countries: those ranked in the top 10 of ICI, those ranked in the top 50 of ICI, and those above the median total trial count.

Future work will include information available for trials registered in the US or EU on drug

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[7]A Bolar exemption is relevant only for generic manufacturers (commercially oriented non-originators). However, we don't expect to observe many clinical trials performed for the purpose of obtaining regulatory approval for a generic drug, as generic firms need only to demonstrate bioequivalence of their products in the US and Europe.

i's role in a trial, to distinguish between trials that test for a new use of drug *i* and trials that use drug *i* as a comparator in testing a different compound.

5 Data

5.1 Drug-level data

We focus on drugs first brought to market between 1950 and 2012 for which we can obtain patent information across countries. Our assumption is that the bulk of the R&D costs required to develop the drug have been sunk by the time the drug is approved for launch in at least one market. Our interest is in the *use* of this drug in subsequent research. We determine launch dates of new products using IMS R&D Focus, and match the sample of drugs to country-level patent information provided by IMS Patent Focus. This results in a sample of 1158 drugs.

Table 1 presents a summary of patent status of our drug-level data. The earliest patent on a drug in our sample was granted in 1950, and the last in 2012. The earliest patent application is a bit earlier and dates back to 1945 and the last in 2011. On average, these drugs have some patent protection in 48 countries. The mean number of patents per country is 1571, and with 20.4% of all the 74,054 patents across countries and drugs expiring by 2012. 21% of drugs over the 1,158 drugs will lose all their patents by 2012. On average, the drug's launch year is in 1998 and expiry year is in 2017. The latest patent expiration of the drugs will be in 2031.

5.2 Clinical trial data

Over the last 15 years, regulatory authorities around the world have established registries of clinical trials conducted on pharmaceuticals. For example, the United States created clinicaltrials.gov in 2000, following the passage of the Food and Drug Administration Modernization Act of 1997. Section 113 of this act required clinical trials testing drugs for their effectiveness in treating "serious or life-threatening" to be registered. Coverage of this registry was very incomplete until 2005, at which point the International Committee of Medical Journal Editors (ICMJE) announced a policy of requiring registration of any clinical trial described in manuscripts submitted for publication in major medical journals. Retrospective registration of trials initiated prior to this policy was permitted, which significantly improved the registry's coverage. Registration requirements were expanded by the Food and Drug Administration Amendments Act of 2007 to include a broader set of trials (beyond "serious and life-threatening" diseases) and trial results, and introduced non-compliance penalties.

National authorities in the European Union began providing information to the EudraCT database starting in 2004. The clinicaltrialsregister.eu database includes information on phase II-IV adult clinical trials with investigator sites in the European Economic Area and all pediatric clinical trials (conducted anywhere) that form part of an application for regulatory approval. The World Health Organization established a clinical trial registration policy in 2006, and maintains the International Clinical Trials Registry Platform (ICTRP) to aggregate information from the US,

EU, Australia, Brazil, China, Korea, India, Cuba, Iran, Japan, Sri Lanka, and the Pan African Clinical Trials Registry.[8] Figure 1 graphs the distribution of trials conducted all over the world during 2002-2012. Consistent with registration requirements in the US and Europe, we observe a large increase in the number of trials registered between 2002 and 2005. Since then, the number of trials keep above 4500.

Clearly, not every clinical trial conducted around the world is registered. While publicizing the existence of a clinical trial might facilitate recruitment of participants, trial sponsors often cite some risks of disclosure, such as interference with patent applications. Zarin et al. [2007], Prayle et al. [2012] and others have noted problems of incomplete compliance. With these limitations in mind, this is nevertheless a useful source for information on cumulative innovation. Trials conducted with public funds are more likely to be registered (this is now a condition of funding from many agencies), and disclosure of trials conducted by organizations with non-commercial interests is probably more likely. Academic scientists wishing to publish their work also have strong incentives to register trials they help to run. We believe the data is most reliable for this set of organizations.

An alternative is to examine scientific publications that are based on research using patent-protected materials, such as Murray and Stern [2007] and Williams [2013]. Since this paper focuses on a broader set of innovations, it is more challenging to identify them in papers than in clinical trial registries, which include a data element for intervention names. In addition, "failed" research producing statistically insignificant or unfavorable results might not be published. Because clinical trials should be registered prospectively, these registries also include unsuccessful research efforts. Future work should examine both the change in research effort as well as the change in successful outputs.

We downloaded data on all registered trials on clinicaltrials.gov and the ICTRP in February 2013. We exclude duplicate registrations of the same trial in multiple registries. For each registered trial, information is available on its sponsors, its start and end dates, its countries of recruitment, and the condition studied. If the trial is an interventional study, i.e. if a drug is being tested, then the name of the intervention is also provided. Information on the placebo or control treatment is included for controlled trials.

We focus on interventional trials that involve one of our sample drugs, either as the intervention or as a control. This requires us to search for each drug name and all of its synonyms in the intervention fields of the trial data, since interventions may be listed using a drug's generic (INN) name or country-specific brand name. Where possible, we distinguish between trials that are conducted on the drug itself (to find a new use or test a new dosage, for example) and trials that use the drug as a comparator when testing a different treatment.

We classify academic institutions, government agencies, foundations, and other non-profit organizations are as "public sector" research institutions. Depending on a country's definition of non-commercial, this set is most likely to avail themselves of the research exception where it ex-

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[8]The ICMJE now considers registration on the ICTRP compliant with its policy.

ists. We define all other sponsors as commercial. This set is more likely to risk infringement if they use a patented substance without a license, which may be costly to obtain. We also distinguish between trials conducted by the original patent applicant, the firms listed as co-developers on a drug project, and all other firms. This allows us to explore how patents affect the research efforts of different organization types.

The initial download included 202,171 trials, of which 76,459 study a drug intervention. We identified 65,180 trials that used at least one of our sample drugs. We restrict our analysis to trials that started from 2002 to 2012, resulting in 58,463 trials; though trials with earlier start dates exist in some registries, we felt the coverage was too thin prior to this point. Our final sample of trials recruited patients in 151 countries.

Figure 2 and 3 shows the distribution of trials across country income groups from 2002 to 2012. Countries are classified using the World Bank's definition as high income OECD, high income non OECD, upper middle income, lower middle income, and low income. Countries without income group definition are categorized in the missing income group. Most trials (far above 70% of our sample) are conducted in High income OECD countries. The share of these countries has declined in recent years. To see the trend of other countries, in Figure 3, we exclude the High OECD countries. It becomes obvious that the lower middle income and upper middle income groups have experienced a significant increase. The share of trials conducted in the upper income group grew from 9% in 2002 to 18% in 2012, which is consistent with the finding of Thiers et al. [2008] that clinical trials are shifting from developed countries to emerging countries.

5.3 Patent data

IMS Patent Focus data provides us detailed information on all the patents associated with each drug, including their type (product, process or method, etc.), application date, and grant date at the country level. Patent expiration is generally 20 years after the initial application date, although some countries grant additional patent terms to compensate for regulatory delays and others granted shorter patent terms at the time of application.

We match the patent data to the clinical trial data by searching for a drug's generic name and any other information on brand names or synonyms in the title, abstract, or intervention fields of the trial. Grant dates and expiration dates determine whether a drug was under patent protection at the time a clinical trial began.

Figure 4 illustrates the distribution of drugs losing product patent protection over time. This figure includes the drugs whose product patents expired globally during 2002-2012, since this is the period of clinical trials we examine.[9]. From 2002-2011, on average, there are 30 drugs' product patent expire each year. As time goes by, there are more and more drugs facing product patent expiration. To 2012, the trend achieves its peak: around 98 drugs lose their product patents globally.

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[9] In this figure, we only consider the drugs whose product patent expires during 2002-2012, while for the regressions, we will include all drugs

We only focus on the last product patent expiration for each drug globally in Figure 4. To see the variation of expiry year for each drug, Figure 5 shows us the distribution of the expiry year lag across countries by drug. Although the largest portion of drugs lose all of their product patents in the same year across countries (which are around 202 drugs and are excluded in the figure), there are still quite a few drugs which have more than 2 years of lag between the earliest patent expiration and the latest (48 drugs have 1 year lag, 30 drugs have 2 year-lag, and 72 drugs have more than 2 year lag with maximum lag at 10 years), which provides the opportunity for the investigators to relocate their clinical trials globally.

Figure 6 plots the each country's share of drug trials by the proportion of drug-year[10] observations on patent. We exclude the United States from this chart for scaling purposes. The association between the share of trials and propotion of drug-years on patent is non-linear: low income country observations are concentrated around the origin, with a very small share of trials and a low proportion of drug-years with patent protection; high income countries have the highest fraction of drug-years with patent protection and higher share of trials. This pattern suggests that the importance of innovative capacity may overwhelm any negative effect of patent protection in the location of research activities.

5.4 Country-level data

The most challenging component of country-level information concerns the existence and breadth of the research exemption in patent law. Our primary sources for this information are reports from the Standing Committee on Patents of the World Intellectual Property Organization (WIPO). We code the existence of a statutory research exemption using Annex 2 of Patent Related Flexibilities in the Multilateral Legal Framework and their Legislative Implementation at the National and Regional Levels. We also code whether each country's patent law mentioned an exception for experimental use and/or noncommercial use according to the WIPO's Report on the International Patent System[11].

Case law may establish a research exemption even in countries without a statute to that effect. In addition, while the language of various patent statutes may be similar, the interpretations can vary. For example, the application of a research exemption to the activities of not-for-profit organizations is not necessarily uniform. In the Madey vs. Duke decision in the US, the court noted that universities may have commercial interests in their research, but courts in other countries may reach different conclusions. We are in the process of defining whether each country's research exemption is "narrow" or "broad," relying primarily on Correa [2004], Garrison [2006], O'Connor [2009], and others.

Porter and Stern [2001] provide an index of "national innovative capacity" for most countries. This index is derived from data on patent applicants, the number of scientists and engineers, and

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[10]We use drug-year level rather than drug level because patent protection changes over time, as patents expire.

[11]We code the experimental exemption, non-commercial exemption and bolar exemption literally based on the legal statements from each countries. And then define research exemption equals to one if the countries either holds experimental exemption or non-commercial exemption.

other factors. In our empirical analysis, we use this index or a country's corresponding rank in this index as a measure of the relevance of the research exemption and an explanatory variable for the location of clinical trial activity.

We use several standard sources for other country-level information. Data on disease burden comes from the World Health Organization (WHO) Global Burden of Disease project; we use 2004 age-standardized disability-adjusted life years (DALYs), revised in 2009. Due to the difficulty matching specific disease conditions listed for each clinical trial to the disease codes from the WHO, we match the WHO disease codes to the broad therapeutic class assigned to each drug in our sample, as described in **??**. The World Development Indicators from the World Bank provide the other country variables. We exclude countries that had no clinical trial activity at any point during 2002-2012. In the end, our analysis focuses on 159 countries.

Table 2 provides an overview for country-specific characteristics. For the 151 countries included in our study, 53% of the countries have experimental exemption, and 46.4% of which have non-commercial exemption. Only 19.9% of the countries have bolar exemption[12]. The information of innovative capacity index is limited: only 54.3% of countries have the Innovative Capacity Index (ICI). Overall, the country level information is quite incomplete. Therefore, we will try different specifications by varying the countries sample. One alternative is to focus on those countries which have highest ICI rank (the top 50 ICI rank countries, in the following, we refer them as ICI 50 countries). Table 3 illustrates the summary statistics for the ICI 50 countries. Within this group, 80% of which have experimental exemption and 74% of which have non-commercial exemption, while only 38% of them have bolar exemption. The innovative capacity index ranges from 16.8 to 30.3 with an average at 22.4. Missing values are greatly reduced in this sample.

Figure 7 shows the number of countries in each income group with exemption (experimental exemption, non-commercial exemption and bolar exemption). In each group, the first bar denotes the number of countries for which we have information on any statutory research exemption. The second-fourth bar denote experimental, non-commercial exemptions, and bolar exemption respectively. Overall, the experimental exemption is more prevalent among countries than non-commercial exemption and bolar exemption. Bolar exemption is much rarely than other types of exemptions. And research exemptions are more common in high income countries. Lower income countries have historically had lower levels of patent protection (making exemptions less meaningful), but we are also missing data for many of them. In robustness checks, we exclude these countries from our analysis, since the recent introduction of patent rights and low initial levels of research capacity complicates the interpretation of effects. [13]

5.5 Final data

Ultimately, we create a rectangular dataset of drug-country-year observations. Our dependent variables are the number of clinical trials performed on drug i in country j in year t and the share

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[12]For the case that doesn't provide exemption, we code it as zero. Therefore, the missing exemption dummies denotes those which have no statutory exemptions.

[13]The detailed country information is provided in Appendix Table 1.

of clinical trials performed on drug i in country j in year t. This yields a fully rectangular[14] dataset of 1,539,747 drug-country-year observations on 1158 drugs and 151 countries from 2002-2012.

Tables 4 and 5 provide summary statistics for all the dependent and explanatory variables used in our regressions. Table 4 presents the overall information for our main specification (See Model 1). For each drug-country-year, there are on average 0.075 trials started, in which 43% (=0.032/0.075) are from public investigators, 36% (=0.027/0.075) are from originators, and 21% (=0.016/0.075) are from non-originators. 15.9% of the drug-country-year are in patent protection, and around half of them (0.078/0.159) are in product patent protection. 86.1% of the studies are conducted prior to the drug's launch in that country. And 55.6% of the studies are subjected to the research exemption. The average drug age in our sample is 1.335 years old. The mean years since first patent application is 2.353 years.

Table 5 provides the summary statistics of the regression data in drug-year level. Overall, there are 52.5 trials conducted for the drug-year. 35.4% are from public innovators, and 39.1% are from the originators, and 25.7% are from non-originators. Comparing with the distribution of trials by organization in drug-country-year level data, we can find that public investigators tend to conduct clinical trials in more countries than private investigators. In this sample, there are 63.6% of the drugs in the year have product patent in the US. The average number of other countries in product patent protection is only 2.1. 98.2% of the drug-year are prior to the drug's global launch. While the mean years since the first patent application is only 14 years.

6 Results

Table 6 presents the OLS regression for the baseline model. The trials conducted all over the world tends to be less responsive to the product patent protection in the US, as the insignificant coefficients suggests. As the global trials sum up the innovative activities that take place inside of the US and outsides, both effects might work in the opposite direction and therefore, makes our estimation difficult to evaluate. Although the number of other country with product patents has significantly positive effects on the global trials number, but we still can't distinguish patent effects which are from home country and those from neighborhood country from this aggregate level of regression. Intuitively the patent protection from the home country or the neighborhood country has distinct effects on the sponsor's location decision. Therefore, more thorough way to disentangle this question is to consider the innovative activities in drug-country-year level, while taking into account the country specific characteristics.

Table 8 – 12 investigate the problem as we suggested above in drug-country-year level, changing the specification in terms of varying fixed effects, interactions, trial sponsors, country samples, drug samples and patent measures. In Table 8, we address the question by regressing the Log number of all trials conducted in each country-drug-year on the product patent dummy, pre-launch dummy, Log of ICI index, research exemption dummy and gradually added fixed effects

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[14]Our dataset is not the usual panel, as panel has two dimensions such as x_{it}, while in our data, each observation has three dimensions as y_{ijt}.

(Year FE, Drug FE, and Country FE) and interaction terms. Including additional fixed effects and interaction terms doesn't alter coefficients much in terms of the sign and significance, except that the country specific variables become no longer identified.

From Table 9 – 11, we keep the same specification as the last column at Table 8 but vary the estimation samples. Table 12 replace the important explanatory variable with other two alternatives. Year fixed effects (FE), drug FE, and country FE are all included in these tables. And variance is clustered at drug level. As see from Figure 2 and Table 13, over 90% of the trials are conducted in Top ICI 50 countries, and there is quite a few missing country specific information for the lower ranked country (See Table 2 and 3) , therefore, from Table 9 on, our analysis focuses on Top 50 ICI ranked countries.

To investigate how innovative behaviors from the public, the originators and the competitors vary with the patent status of the experimental drugs, in Table 9, we regress the trials conducted by all sponsors, public sponsors, originators and non-originators separately on the explanatory variables and controls. Since the country's idiosyncratic characteristics might also affect the innovative activities and the effects might be most salient for public sponsors, therefore in Table 10, we focus on public sponsored trials and varys the country range from Top 50 ICI-ranked countries to top 11th-50th ICI-ranked countries, Top 10 and Top 10 excluding US countries.

Additionally we do another two robustness checks: Table 11 narrows the sample to the trials conducted on those drugs which have ever been on product patent protection, those drugs which have ever expired its product patent, or those which have experienced the intellectual property change (experiencing both the patent on and off process) during the year window we observed (2002-2012); Table 12 replaces the product patent dummy with other two patent measures: any patent protection dummy and log of number of patents.

6.1 The main effect of patent protection

Our primary interests lie in the effect of patent on the clinical trial activities. Not surprisingly, almost all the results from our regression show that the coefficients of patent protection is negative and statistically significant, even with the different patent measures (Product patent dummy, any patent dummy, log of number of patent) (See Table 12). However, the total patent effects depend on many other factors, including the country's innovative capacity, whether the trial is prior to the drug's launch in the country, whether there is statutory research exemption, etc..

Therefore, the interaction terms of patent dummy with other research environment variables are included and the significance of the coefficients verifies our expectation: the effect of patent protection interwines with other effects. For example, without taking into account research exemption, Figure 8 shows the conditional means of clinical trials by the specific value of patent dummy, ICI index and pre-launch dummy, which is predicted by the regression in Table 8 column 3. In the figure, the green line denotes the predicted log of number of trials by ICI index on drugs with patent protection and post launch. In contrast with the blue line, the clinical trials for drugs in patent protection are more than twice of those trials on drugs without patent protection

and post launch.

After introducing research exemption (in Figure 9 for Table 8 column 4), the overall effect of patent conditional on other explanatory variables remains the same pattern as in Figure 8: the patent effects is positive, no matter for pre-launch or post-launch, with research exemption or not. The partial effects of patent protection given other variables (at the means) generated with margins command in stata confirms that it's significantly positive. Drugs with patent protection would increase the number of trials 1.8% on average.

Note that we also include log of number of other countries with product patent, no product patent * log of number of other countries with product patent in the main specification. In all the regression with product patent dummy as the major patent measure, the coefficients for these two variables are insignificant except the robustness check with alternative patent measures (any patent dummy and log of number of patent), in which case, the more number of other countries with product patent, the large number of trials are conducted in the home country.

6.2 The effects of research exemption

Most of the evidence shows that the research exemption matters most for the post-launch phase. Coefficients for the triple interaction terms of patent, pre-launch, and research exemption are always significantly negative, see Table 10 and 12. The results from the regression over all the countries are less clear see Table 8 and 18. But from the Figure 9 (corresponding to column 4 in Table 8), we can see it more clearly that the provision of research exemption lowers down the overall innovative activities, the scale is the largest for the drugs in patent and post-launch. The overall partial effects of research exemption on number of trials are also significantly negative: the presence of research exemption tends to reduces the number of trials by 3.2% on average. The results are striking and count-intuitive since we might expect that research exemption facilitates the uses of drugs in the clinical trials therefore foster the trial numbers. The potential reason might be that research exemption coincides with other countries effects which turn out to be a barrier to the innovation. For example, the US and the Australia don't have research exemption, but they may provides other research friendly environment for investigators.

We try to investigate deeply about this issue by seeing the public sector activities by different country group in Table 10. [15] As shown in the Fig 10 and 11, for the group of country with ICI ranked between 11 to 50, research exemption promote the innovative activities done by public sponsors, especially on the drugs which have patent protection and are post-launch. But for the top 10 countries which locates in the high range of ICI interval, there is no much variation of research exemption in those countries, therefore, we didn't see much of the effects from it. If we take a close look at the top 10 countries except the US, (see Figure 13), almost all the countries (except Australia) do provide research exemption, then we doesn't have variation and can't identify the effect of research exemption.

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[15]The reason we only focus on the public sectors is that public sectors tends to be affected by research exemption more than other sponsors.

6.3 Timing of the drug launch

We are curious about whether the timing of drug launch matters and the direction of the drug launch on the innovation. As we discussed before, before drug launch, drug products is unavailable on market which creates a great barrier for the investigators, which presents more difficult than patent protection. The results confirm our conjecture: as shown in Figure 8, no matter for the drugs in patent protection or not, post-launch always leads to a higher level of research activities. (green line v.s. orange line and blue line v.s. pink line). Additionally, the innovation gap due to the patent protection (the difference between green line and blue line) is smaller that those due to prelaunch (the difference between green line and the orange line). After introducing the effect of research exemption (see Figure 9), the above results still hold, although it's not easy to read because the lines are overlapped. The partial effect of prelaunch dummy indicates on average the drug before launch could lower down the number of clinical trials by 4.3%.

6.4 The overall effect of ICI index

Overall, we can see that ICI associates positively with the predicted trial number. From the basic model in Table 8 column 1-2, we can see that the coefficient of ICI index is significantly positive. After including country FE, the effect of ICI index is fully captured by country FE and therefore, we can't identify it. However, we still can learn more about the ICI index from its interaction with other variables. Also we can see from the predicted dependent variable by ICI that the slope of predicted line are almost positive, i.e., investigators are more likely to conduct clinical trials in countries with higher innovative capacity index. The partial effect of log of ICI index on the log of number of trials is 4.9% for all the countries on average. That's to say, when the ICI index increases every 1%, the number of trials increase on average about 4.9%.

Also note that the slope of ICI with predicted number of trials is the highest for the case with patent and post-launch (as evidenced by Figure 8- 11), which implies that the innovation friendly environment matters most in the post launch and patent protected case. The countries with higher ICI provides important institutional infrastructures or policies that facilitate the investigators overcome the patent barrier in the post launch phase. The fact that the slope of ICI with predicted number of trials remains constant across different cases (patent protection/prelaunch/research exemption) in ICI 10 countries results from the smaller variation of ICI across these countries (See Figure 12-13).

6.5 The innovative behavior among different sponsors

We wonder that different sponsors might behave quite differently due to its research objective and subjects to the different exemption. As public sponsors tend to be more influenced by the institutional and policy differences across countries than the global private innovators. Therefore, in Table 18, we explore the trials conducted by different type of lead-sponsors (all sponsors, public sponsors, originators, and non-originators), corresponding to column 1-4 respectively. We inves-

tigate the sponsor's innovation strategy within the ICI 50 countries because most of the developed countries and newly emerging markets are covered in ICI 50 countries.[16]

From Table 9, it's easy to see that the patent effects together with research exemption, ICI and prelaunch dummy have similar pattern (The sign and the significance are almost the same) to the trials conducted by different sponsors. But the effects on different sponsors have quite different scale effects. In comparison with originators and non-originators, public sponsors are more sensitive to the country-specific research environments and patent protection: the coefficients of all these explanatory variables and their interaction terms are at least doubled (in some case, five times) for the public investigators than other innovators.

Public investigators tends to innovate much less with the presence of patent protection than the originators and the non-originators (-4.027 v.s. -2.311/-1.532). However, research exemption promotes the innovation of public sponsors most in case of patent protection (3.186 v.s. 1.896 /1.266). Drug prelaunch reduced the research exemption effect on public innovation than on private innovation (-1.605 v.s. -0.297/-0.634). And drug prelaunch also reduced the research exemption effect in case of patent protection on public innovation than on private innovation (-2.784 v.s. -1.000/1.147). Similarly, the national innovative capacity affect most the public investigators than private investigators, evidenced by all the coefficients of the interaction terms with ICI index. In one word, public innovative activities are more geographically dependent comparing to their private counterparts.

6.6 Does country make the difference?

From Table 13, we can find that clinical trials are highly concentrated and unbalanced over the countries. Over 30% of the trials are conducted in the US. Around 80% trials have ever been conducted in the top 10 ICI-ranked countries. Observations from the US constitute outliers for our study. Table 10 focuses on the trials conducted by the public sponsors and restricts the sample to the trials conducted in those countries which is ranked in the top 50 (top 11-50, top 10, or the top 10 excluding the US) by innovative capacity index (See column 1-4 respectively). Our aim is to see whether the public sponsors' behavior varies across countries, especially inside/outside the US. The reason of focusing on the public investigators lies in that, as we believe, the private innovators are the more global ones in contrast to the public sectors and are less subjected to the geographical restriction.

Table 10 tells us that the US, the other top 10 countries, the top 11-50 countries are all quite different from each other (as shown in column 2-4). [17] Column 2 and 3 in Table 10 illustrate the regression results in two distinct subgroups: the countries which is ranked in top 11th-50th and which is ranked in top 10. The distinction is so salient that: Top 10 countries observations are

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[16] As we know from appendix Table 1, most of the clinical trials are conducted in these countries. Therefore, we focus on the sub-sample (ICI 50 countries) for the regression, which provides intensively informative data. But we also include the trials from all the countries as a robustness check in the appendix.(See Table 18)

[17] For top 10 countries without the US, due to lack of variations in the country specific variables, there are three interaction terms are omitted in the regression because of collinearity.

highly responsive to most of the explanatory variables. Excluding the US changes the coefficients significantly and in some cases it even shifts the sign, evidenced by the regression exclusive to the US (See column 4). For example, patent protection has negative effects on the follow on research with coefficient -9.217, while after excluding the US, the effect from patent protection becomes significantly positive, as 1.539. It implies that most of the negative effects are driven by the observation from the US. Prelaunch has negative effects on the number of trials of other top 10 countries with coefficient -1.739 and it further inhibit the innovative activity in case of patent protection with coefficient at -0.902; while including the US, the coefficient becomes 10.721 and 5.295. Top 11-50 countries seem to have the similar patterns as the US but with smaller effects.

6.7 Other robostness check

Up to now, we only use product patent dummy as the measure of patent protection as product patent is the most strong patent that claims exclusivity over the infringement. However, firms also try to apply for as many as possible patent around their products to protect their exclusivity. Therefore, the other patent might also play the role in prohibiting the use of the drugs. Therefore, we also use any patent dummy and log of the number of patents as alternative measures of patent protection and results are presented in Table 12. For the country in ICI 50, we found that these three patent measures have similar patterns in the interactions and the single effect. The sign and significance of the coefficients across the measures are almost the same. Consistent with our expectation, product patent has stronger effects than other two measures in term of coefficients size.

Our study so far is devoted to explore all the variations of the patent status across drug, country and year. Now specifically, we are interested in the drugs which are subjected to patent status change, that's to say, it provides us perfect experiments to explore the variations across year for drugs. In Table 11, by restricting our study on those drugs which have ever been on/off patent or losing patent protection during 2002-2012 for countries within ICI 50, our sample is largely reduced, from 499,653 to 124,223 for ever on patent drug, 448,041 for ever off patent drug, and 72,611 for losing patent drug. The coefficients of patent protection are still significantly negative but with smaller size(-2.002 v.s. -4.027).

6.8 The controls

Besides the patent dummy and its interaction term with other exlanatory variables(research exemption dummy, prelaunch dummy, and ICI index), the controls we take into account include drug age, drug age squared, year since first patent application, log of DALY and fixed effects of year/country/drugs.

The results on the control variables reveal that the younger the drug is, the more clinical trials are conducted on. The result is quite intuitive as the younger the drug is, the less research attention that ever been focused on and the more research opportunities the drug possesses. There is almost no non-linear effect on drug age as the square of drug age is insignificant and non sizable.

Year since first patent application has significantly positive effect on the innovative activities, however the scale is quite small and negligible. *Log of DALY* has significantly positive effect on the clinical trial activities as DALY indicates the potential market value for the specific diseases and it provides an important incentive for the R&D investment.

7 Conclusion

In this paper, we investigate how the following-on innovation efforts are determined by patent status of the original products by exploring the number of clinical trials that conducted on patented drugs as opposed to the un-patented ones. Because of the regulation on the registration of clinical trial globally, fortunately we are able to collects most of the clinical trial activities across countries, which provides a perfect playground to investigate the follow-on innovation built upon the previous patented innovation and the potential effects of intellectual property system in the modern continuous innovative process.

Due to variation of statutory provisions about research exemption across countries, our study is capable of investigating the effect of research exemption and how it interacts with patent protection. As the vast list of countries provide idiosyncratic political and economical environments that might promote or hurdle innovation, we propose to utilize the innovative capacity index of countries to capture the competitiveness in research across countries. We also distinguish the innovative efforts that conducted before the drug launch and after as the marketed drug facilitates the experiments even under patent protection.

Our results reach consistent conclusions across different specifications with varied sample or alternative patent measures. Our results show that the overall effect of patent protection tends to promote the innovative activities; post launch drugs facilitate the clinical trial conducted on them. Research exemption turns out to be associated with lower level of follow-on innovation activities. Clinical trials tend to conducted in higher ICI countries and the ICI index promotes more innovative activities in patent protection and post launch case.

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Figure 1: Distribution of Trials across Year
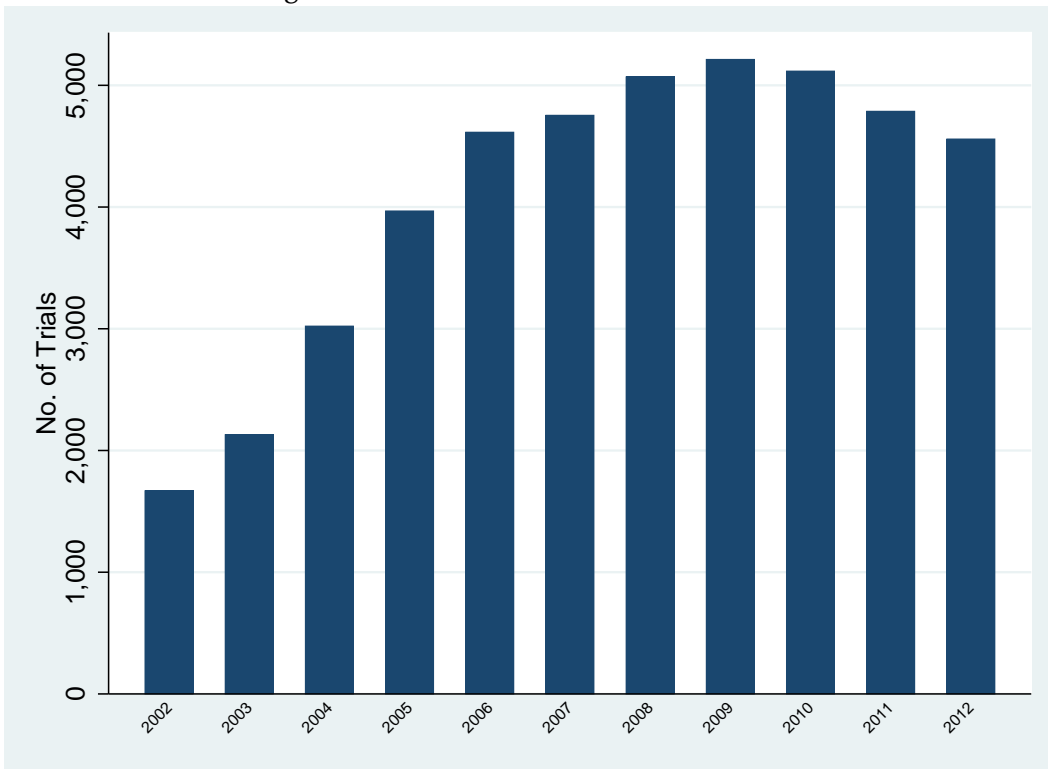
Figure 2: Share of trials by income group
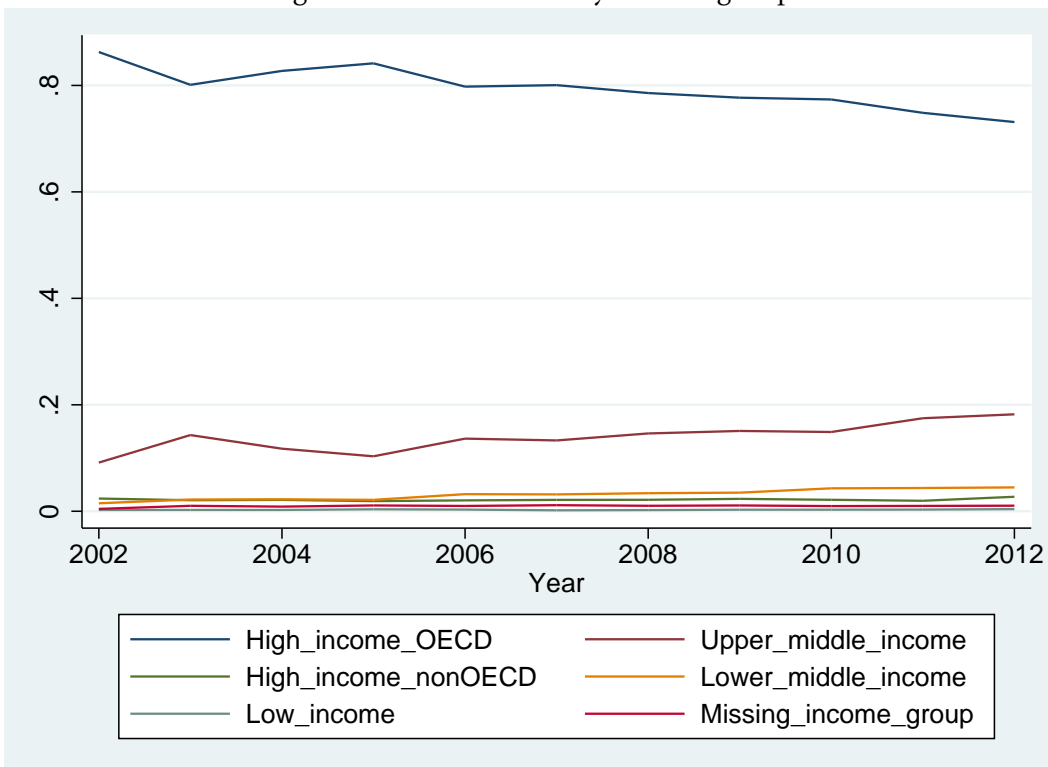
Figure 3: Share of trials by income group (excluding High-income)
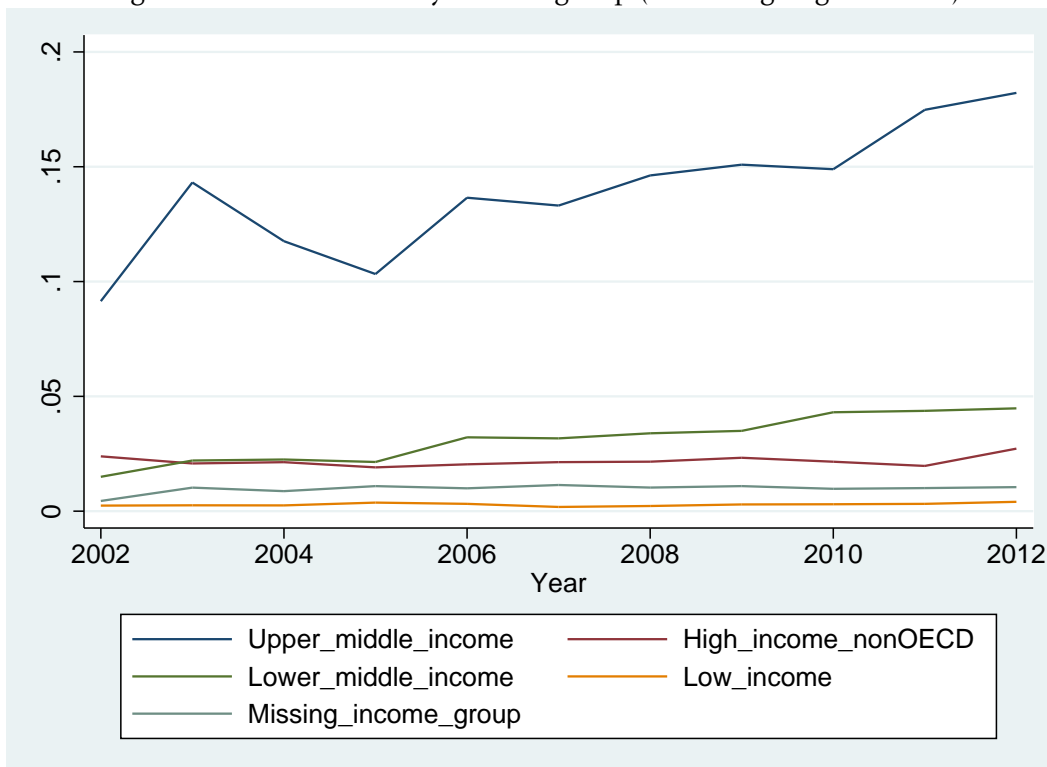
Figure 4: Distribution of drugs losing its product patent globally across year
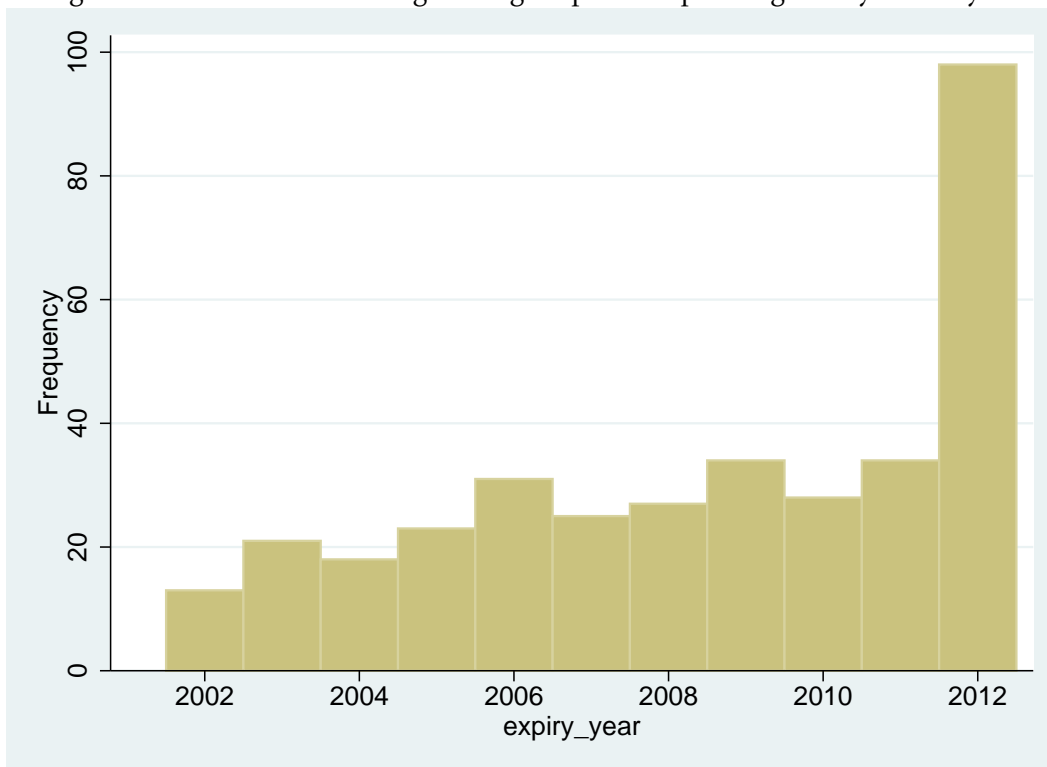
Figure 5: Distribution of lag of expiry year across countries by drug
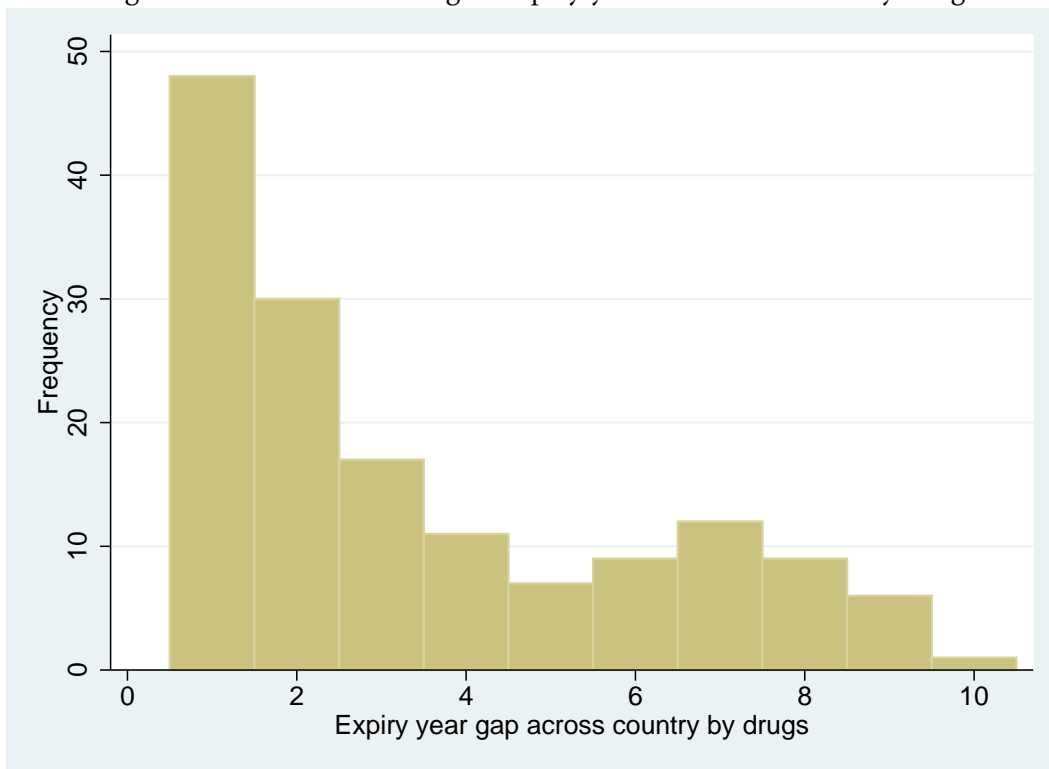
Figure 6: Share of trials and fraction of patented drugs
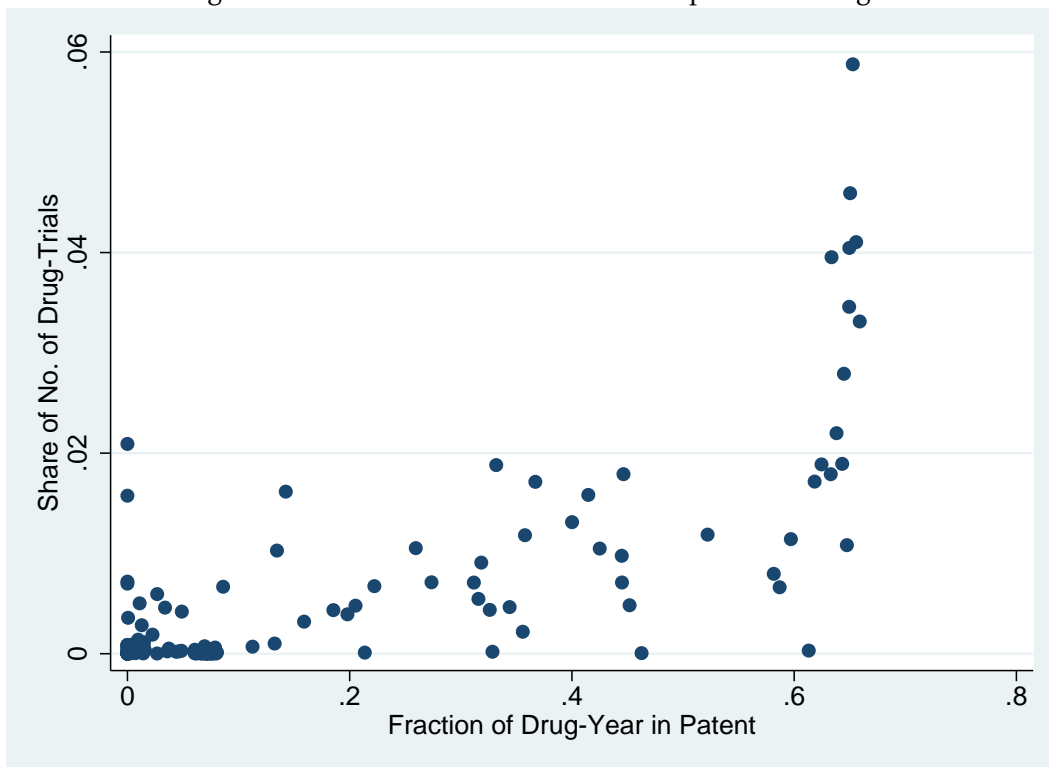
Figure 7: Research exemption by income group
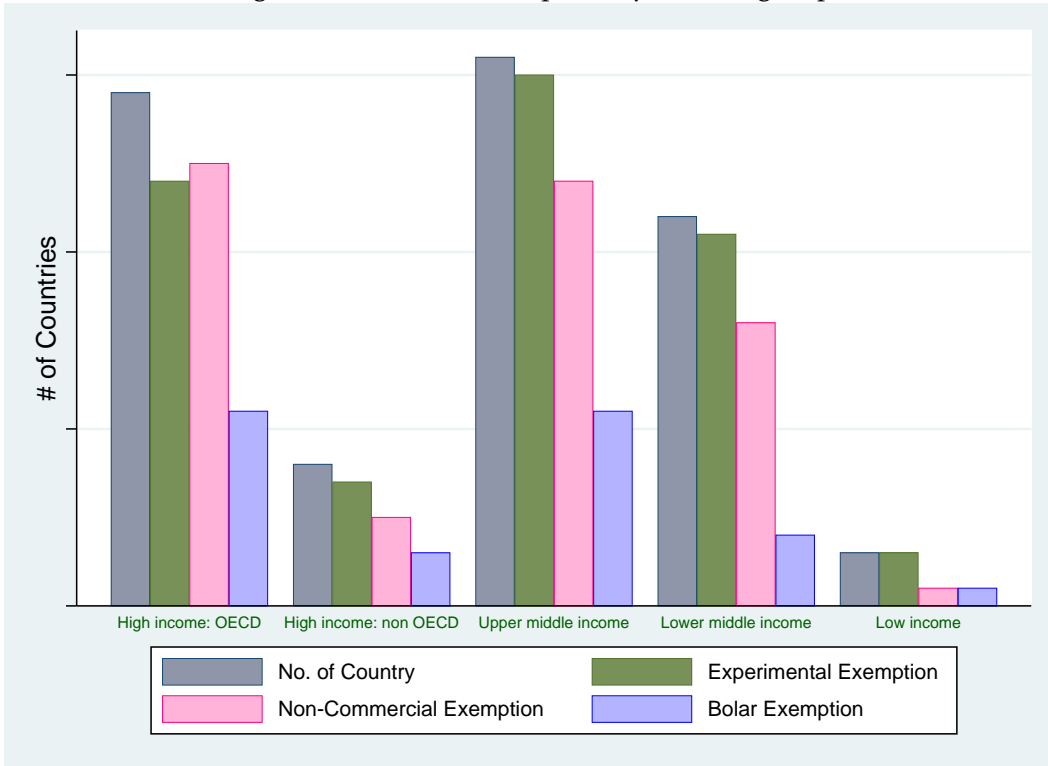
Figure 8: Predicted innovative activities by group(FE2 model)
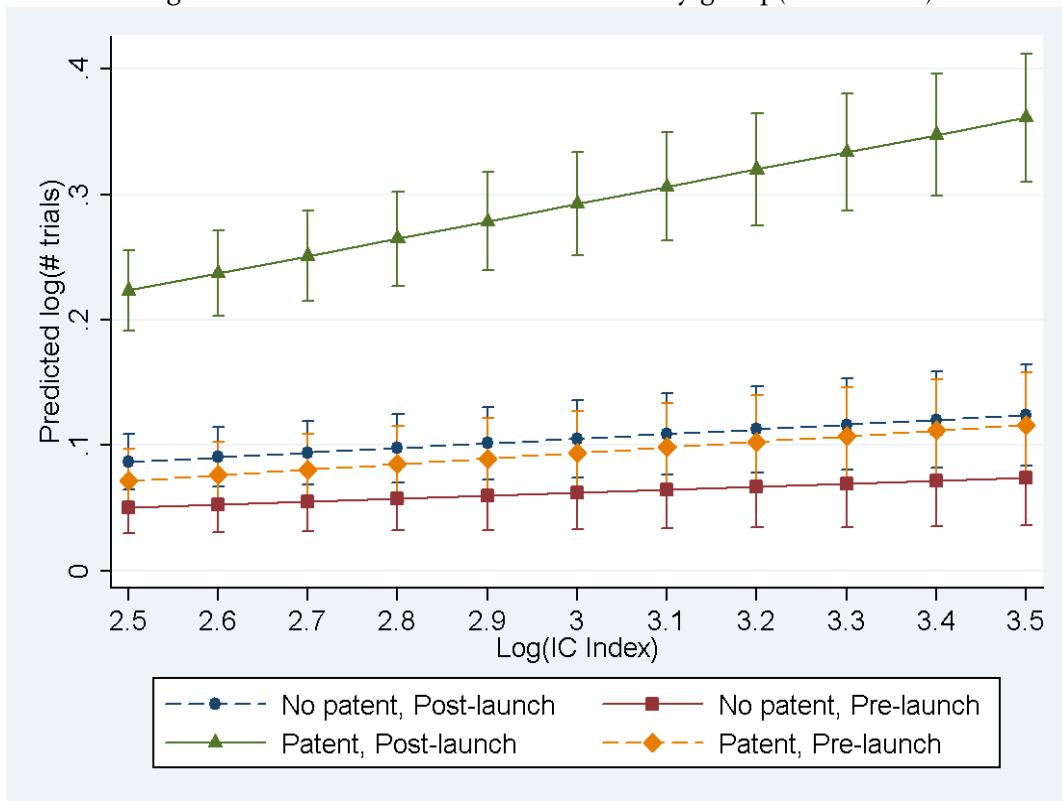
Figure 9: Predicted innovative activities by group(Full model)
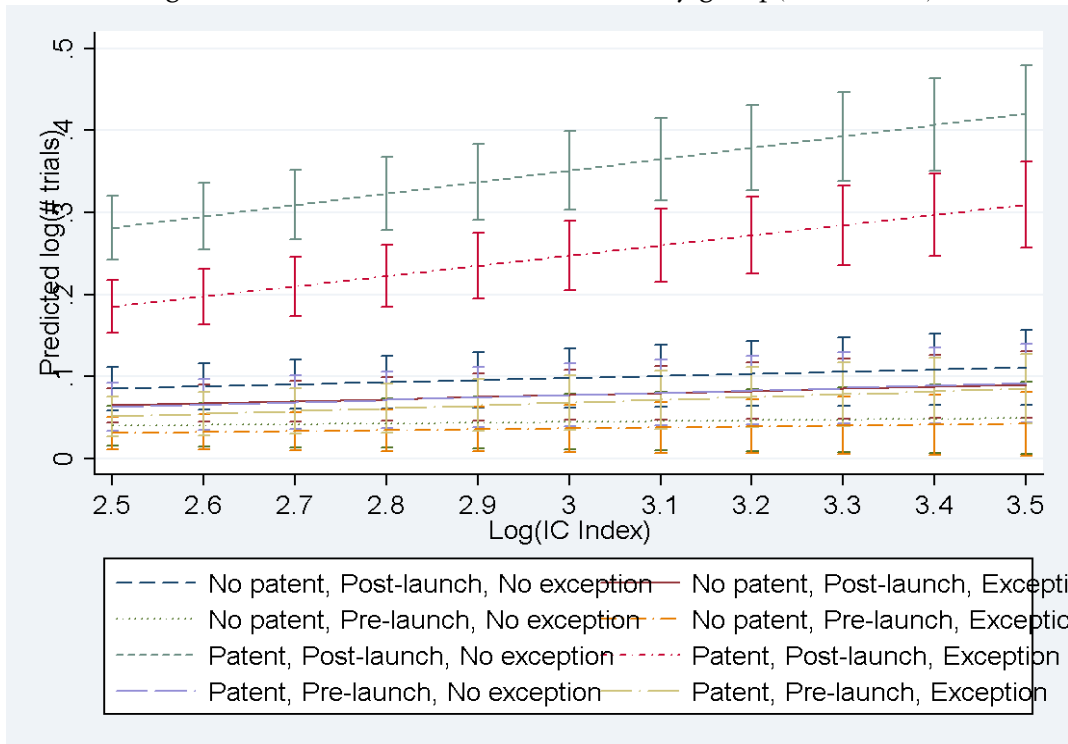
Figure 10: Predicted innovative activities by group(Full model (Public)ICI 50)
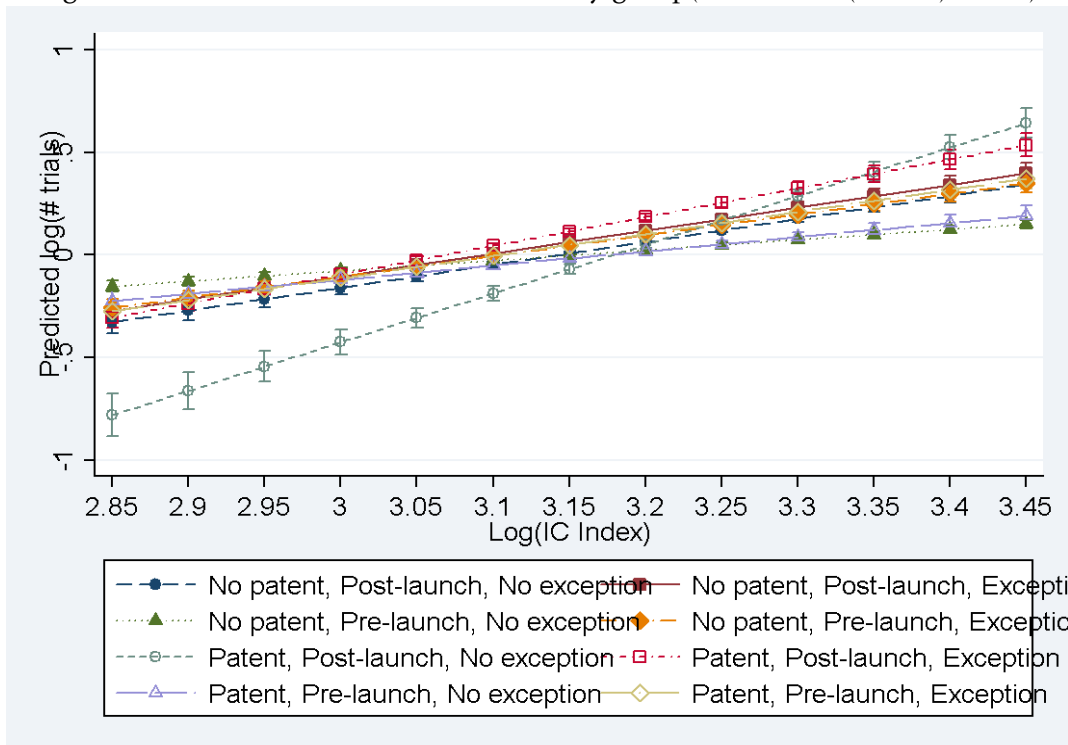
Figure 11: Predicted innovative activities by group(Full model, Public, ICI 11 50)
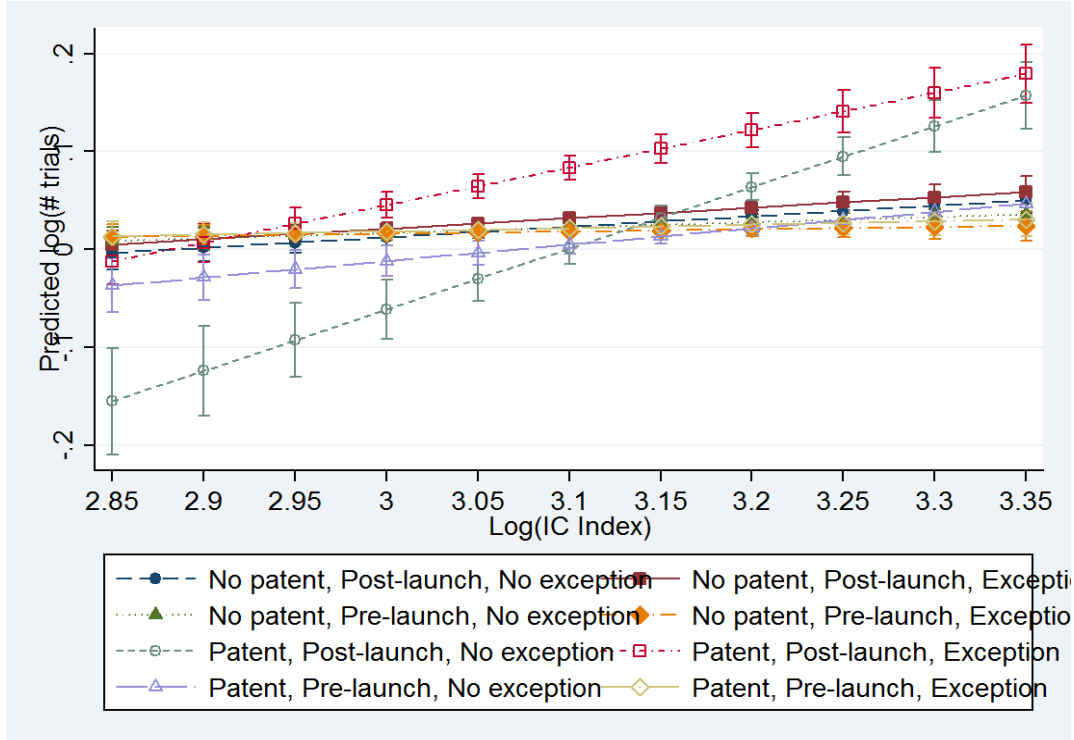
Figure 12: Predicted innovative activities by group(Full model, Public, ICI 10)
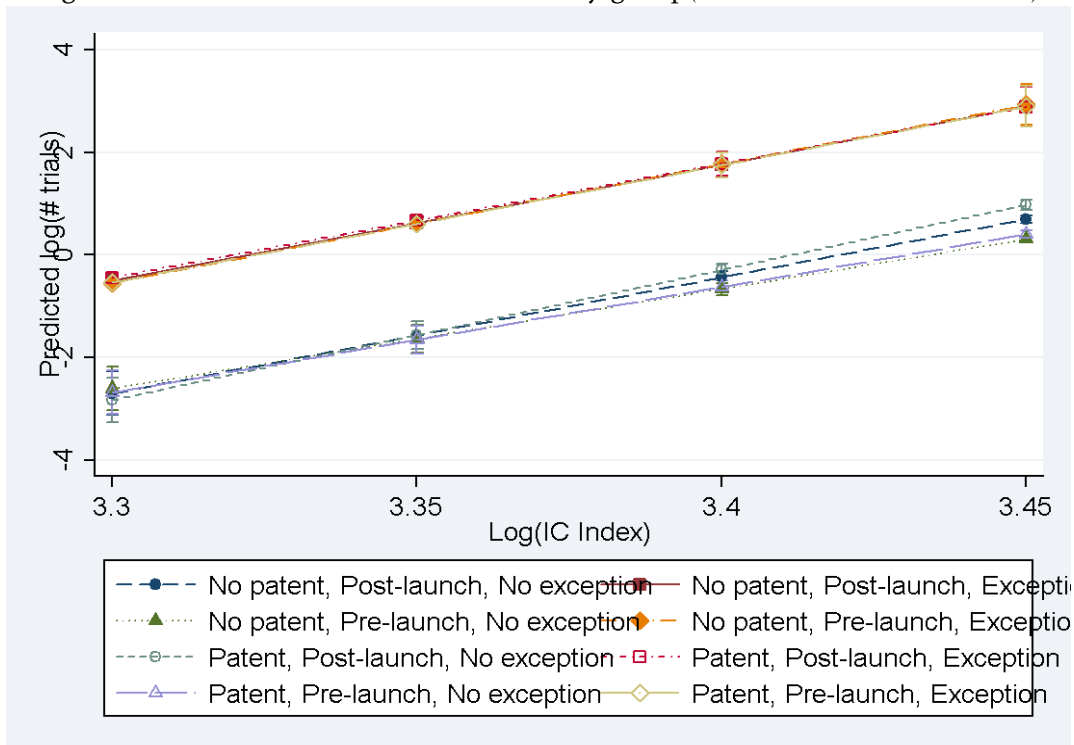
Figure 13: Predicted innovative activities by group(Full model, Public, ICI 10 ex US)
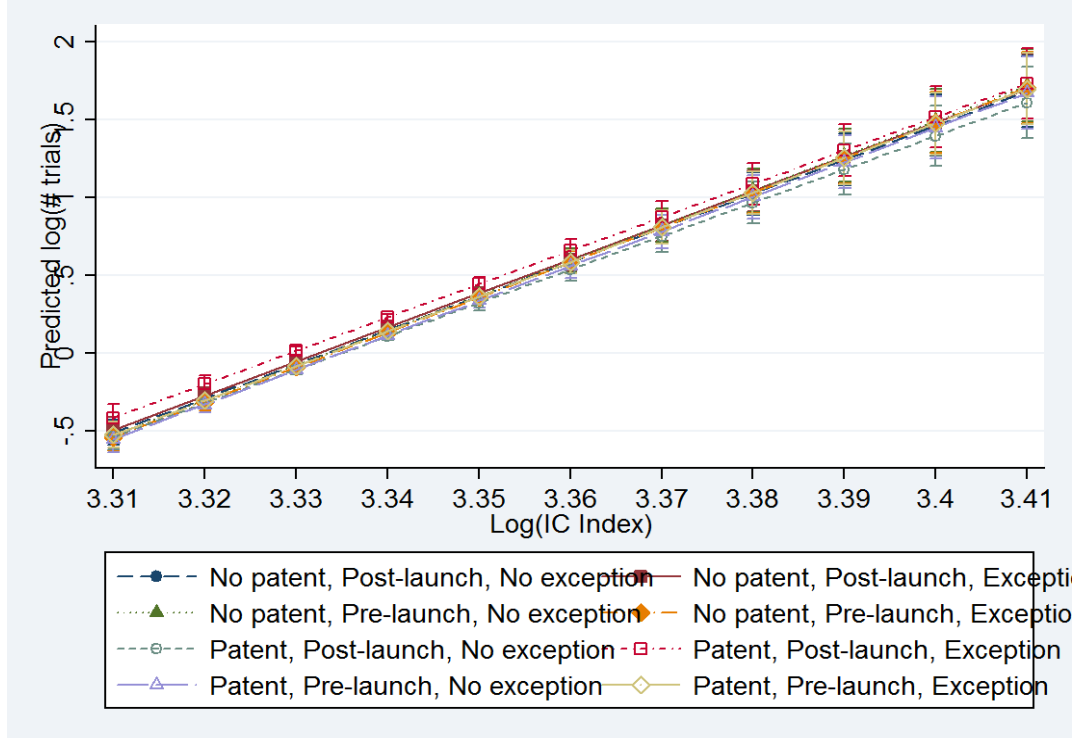
Table 1: Summary Statistics at patent-drug level

Variable	Mean	(Std. Dev.)	Min.	Max.	N
Drug ID	588.377	(333.819)	1	1158	74054
First patent application year	1990.894	(8.282)	1945	2010	73524
Last patent application year	1997.299	(7.726)	1948	2011	73524
First patent grant year	1995.614	(8.907)	1950	2012	69026
Last patent grant year	2002.03	(8.174)	1950	2012	69026
Number of patent in each country	1571.834	(765.968)	1	2911	74054
Number of country in patent protection per drug	48.121	(20.282)	1	107	74054
Patent expires after 2012	0.204	(0.403)	0	1	74054
Drug's patent expired	0.212	(0.409)	0	1	1158
Launch Year	1998.435	(8.305)	1950	2012	73980
Expiry Year	2017.299	(7.726)	1968	2031	73524

Table 2: Summary Statistics in Country Level

Variable	Mean	(Std. Dev.)	Min.	Max.	N
Experimental Exemption	0.53	(0.501)	0	1	151
Non Commercial Exemption	0.464	(0.5)	0	1	151
Research Exemption	0.556	(0.498)	0	1	151
Bolar Exemption	0.199	(0.4)	0	1	151
Innovative Capacity Index	20.128	(5.023)	11.6	30.3	69
Missing Experimental Exemption	0.47	(0.501)	0	1	151
Missing Non Commercial Exemption	0.536	(0.5)	0	1	151
Missing Research Exemption	0.444	(0.498)	0	1	151
Missing Bolar Exemption	0.801	(0.4)	0	1	151
Missing Innovative Capacity Index	0.543	(0.5)	0	1	151

Table 3: Summary Statistics in Country Level for ICI 50

Variable	Mean	(Std. Dev.)	Min.	Max.	N
Experimental Exemption	0.8	(0.404)	0	1	50
Non Commercial Exemption	0.74	(0.443)	0	1	50
Research Exemption	0.86	(0.351)	0	1	50
Bolar Exemption	0.38	(0.49)	0	1	50
Innovative Capacity Index	22.408	(3.81)	16.8	30.3	50
Missing Experimental Exemption	0.2	(0.404)	0	1	50
Missing Non Commercial Exemption	0.26	(0.443)	0	1	50
Missing Research Exemption	0.14	(0.351)	0	1	50
Missing Bolar Exemption	0.62	(0.49)	0	1	50
Missing Innovative Capacity Index	0	(0)	0	0	50

Table 4: Summary Statistics for Dependent Var. and Explanatory Var.

Variable	Mean	(Std. Dev.)	Min.	Max.	N
Trials	0.075	(0.690)	0	125	1539747
Public sector trials	0.032	(0.481)	0	104	1539747
Originator trials	0.027	(0.246)	0	21	1539747
Nonoriginator trials	0.016	(0.202)	0	25	1539747
Log(Trials)	0.035	(0.201)	0	4.836	1539747
Log(Public sector trials)	0.015	(0.131)	0	4.654	1539747
Log(originator trials)	0.015	(0.121)	0	3.091	1539747
Log(nonoriginator trials)	0.009	(0.094)	0	3.258	1539747
Patent	0.159	(0.366)	0	1	1539747
Product Patent	0.078	(0.268)	0	1	1539747
Log(Patents)	0.202	(0.526)	0	5.176	1539747
IC Index	1.381	(1.514)	0	3.444	1539747
Prior to drug's launch in country	0.861	(0.346)	0	1	1539747
Research exemption	0.556	(0.497)	0	1	1539747
Log(# other countries with product patent)	0.067	(0.445)	0	4.357	1539747
No product patent*Log(# other countries with product patent)	0.028	(0.259)	0	4.357	1539747
Drug age	1.335	(4.251)	0	62	1539747
Drug age^2	19.858	(95.97)	0	3844	1539747
Years since first patent application	2.353	(6.082)	0	67	1539747
Log(DALYs)	2.488	(1.654)	0	7.772	1539747

Table 5: Summary Statistics for Dependent Var. and Explanatory Var. for Global Specification

Variable	Mean	(Std. Dev.)	Min.	Max.	N
Trials	52.521	(61.592)	0	453	58380
Public sector trials	18.614	(27.549)	0	246	58380
Originator trials	20.558	(30.721)	0	297	58380
Nonoriginator trials	13.5	(28.685)	0	277	58380
Log(Trials)	3.256	(1.418)	0	6.118	58380
Log(Public sector trials)	2.194	(1.336)	0	5.509	58380
Log(originator trials)	1.954	(1.646)	0	5.697	58380
Log(nonoriginator trials)	1.346	(1.566)	0	5.628	58380
Any product patent in the US	0.636	(0.481)	0	1	58380
Log(# other country with product patents)	2.142	(1.644)	0	4.673	58380
Prior to drug's global launch	0.982	(0.131)	0	1	58380
Drug age	0.16	(1.63)	0	54	58380
Drug age^2	2.684	(45.471)	0	2916	58380
Years since first patent application	13.992	(8.164)	0	60	58380

Table 6: OLS Regression of count of global trials over product patent status

	(1) Total b/se	(2) Public b/se	(3) Originators b/se	(4) Non-originators b/se
Any product patent in the US	−0.053	0.038	0.136	0.140
	(0.071)	(0.070)	(0.103)	(0.092)
Log(# other country with product patents)	0.108***	0.125***	0.162***	0.072***
	(0.022)	(0.021)	(0.031)	(0.028)
Prior to drug's global launch	−0.365***	−0.303***	−0.178*	0.202**
	(0.064)	(0.063)	(0.093)	(0.083)
Prelaunch*Any product patent in US	0.148**	0.112	0.004	−0.089
	(0.070)	(0.069)	(0.102)	(0.090)
Prelaunch*Log(# other country with product patents)	0.020	0.023	0.006	−0.021
	(0.021)	(0.021)	(0.030)	(0.027)
Drug age	−0.010	−0.014**	−0.013	0.018**
	(0.006)	(0.006)	(0.009)	(0.008)
Drug age^2	0.000	0.000	0.000	−0.000
	(0.000)	(0.000)	(0.000)	(0.000)
Years since first patent application	−0.002***	0.001*	−0.009***	0.005***
	(0.001)	(0.001)	(0.001)	(0.001)
Intercept	0.707***	−0.608***	0.836***	−0.750***
	(0.165)	(0.161)	(0.239)	(0.212)
N	58380	58380	58380	58380
Adjusted R^2	.771	.754	.644	.691
Fixed effects		Year Drug		

* p<0.10, ** p<0.05, *** p< .01.

Table 7: Notation for Interaction Variables in the Following Regression

Variables	Labels
1.Product Patent	Product Patent Dummy
1.Prior to drug's launch in country	Prior to drug's launch in country
1.pp_dcy#1.prelaunch	Product Patent * Prelaunch
1.pp_dcy#c.log_ici_index	Product Patent * Log (ICI Index)
1.prelaunch#c.log_ici_index	Prelaunch * Log (ICI Index)
1.pp_dcy#1.prelaunch#c.log_ici_index	Product Patent * Prelaunch * Log (ICI Index)
1.pp_dcy#1.research	Product Patent * Research Exemption Dummy
1.prelaunch#1.research	Prelaunch * Research Exemption Dummy
1.pp_dcy#1.prelaunch#1.research	Product Patent * Prelaunch * Research Exemption Dummy
1.pp_dcy#1.research#c.log_ici_index	Product Patent * Research Exemption Dummy * Log (ICI Index)
1.prelaunch#1.research#c.log_ici_index	Prelaunch * Research Exemption Dummy * Log (ICI Index)
1.pp_dcy#1.prelaunch#1.research#c.log_ici_index	Product Patent * Prelaunch * Research Exemption Dummy * Log (ICI Index)

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8 Appendix

Table 8: OLS Regression of count of trials, varying fixed effects and interactions

	1	2	3	4
	b/se	b/se	b/se	b/se
1.Product Patent	−0.079***	−0.141***	−0.115***	−0.089***
	(0.020)	(0.016)	(0.015)	(0.021)
1.Prior to drug's launch in country	−0.001	−0.009	−0.003	−0.005
	(0.002)	(0.008)	(0.008)	(0.008)
1.pp_dcy#1.prelaunch	0.062***	0.114***	0.084***	0.063***
	(0.017)	(0.015)	(0.013)	(0.020)
IC Index	0.118***	0.126***		
	(0.007)	(0.007)		
1.pp_dcy#c.log_ici_index	0.105***	0.116***	0.101***	0.114***
	(0.008)	(0.008)	(0.007)	(0.010)
1.prelaunch#c.log_ici_index	−0.019***	−0.016***	−0.013***	−0.016***
	(0.002)	(0.003)	(0.003)	(0.003)
1.pp_dcy#1.prelaunch#c.log_ici_index	−0.082***	−0.093***	−0.080***	−0.095***
	(0.007)	(0.007)	(0.007)	(0.010)
Research exemption	−0.005***	−0.006***		
	(0.001)	(0.001)		
Log(# other countries with product patent)	−0.001	−0.001	0.009	0.009
	(0.008)	(0.007)	(0.007)	(0.008)
No product patent*Log(# other countries with product patent)	0.010	0.007	0.002	0.002
	(0.007)	(0.007)	(0.007)	(0.007)
Drug age	−0.005**	−0.004***	−0.003**	−0.003**
	(0.002)	(0.001)	(0.001)	(0.001)
Drug age^2	0.000*	0.000**	0.000	0.000
	(0.000)	(0.000)	(0.000)	(0.000)
Years since first patent application	0.003***	0.003***	0.002***	0.002***
	(0.001)	(0.000)	(0.001)	(0.001)
Log(DALYs)	0.004***	0.003***	0.018***	0.018***
	(0.001)	(0.001)	(0.003)	(0.003)
Missing ICI index	0.267***	0.297***	0.045*	0.007
	(0.018)	(0.017)	(0.026)	(0.027)
Missing DALY	0.010***	0.009***	0.025**	0.025**
	(0.004)	(0.003)	(0.012)	(0.012)
1.pp_dcy#1.research				−0.037
				(0.023)
1.prelaunch#1.research				0.007***
				(0.002)
1.pp_dcy#1.prelaunch#1.research				0.027
				(0.023)
1.pp_dcy#1.research#c.log_ici_index				−0.015*
				(0.009)
1.prelaunch#1.research#c.log_ici_index				0.002
				(0.002)
1.pp_dcy#1.prelaunch#1.research#c.log_ici_index				0.018**
				(0.009)
Intercept	−0.274***	−0.312***	−0.115***	−0.076***
	(0.019)	(0.020)	(0.025)	(0.027)
N	1539747	1539747	1539747	1539747
Adjusted R^2	.132	.195	.239	.24
Fixed effects	Year	Year Drug	Year Drug Country	Year Drug Country

* p<0.10, ** p<0.05, *** p< .01.

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Table 9: OLS Regression of count of trials, by trial sponsor in ICI50

	Total b/se	Public b/se	Originators b/se	Non-originato b/se
1.Product Patent	−5.285***	−4.027***	−2.311***	−1.532***
	(0.508)	(0.502)	(0.220)	(0.235)
1.Prior to drug's launch in country	2.276***	1.922***	0.329***	0.676***
	(0.224)	(0.202)	(0.090)	(0.097)
1.pp_dcy#1.prelaunch	3.784***	3.422***	1.221***	1.364***
	(0.523)	(0.512)	(0.223)	(0.243)
1.pp_dcy#1.research	4.203***	3.186***	1.896***	1.266***
	(0.483)	(0.472)	(0.214)	(0.233)
1.prelaunch#1.research	−1.957***	−1.605***	−0.297***	−0.634***
	(0.210)	(0.191)	(0.088)	(0.094)
1.pp_dcy#1.prelaunch#1.research	−3.038***	−2.784***	−1.000***	−1.147***
	(0.516)	(0.497)	(0.225)	(0.248)
1.pp_dcy#c.log_ici_index	1.654***	1.254***	0.727***	0.479***
	(0.159)	(0.157)	(0.069)	(0.073)
1.prelaunch#c.log_ici_index	−0.729***	−0.614***	−0.107***	−0.216***
	(0.071)	(0.064)	(0.028)	(0.031)
1.pp_dcy#1.prelaunch#c.log_ici_index	−1.183***	−1.066***	−0.384***	−0.426***
	(0.163)	(0.160)	(0.070)	(0.076)
1.pp_dcy#1.research#c.log_ici_index	−1.280***	−0.970***	−0.580***	−0.390***
	(0.150)	(0.147)	(0.066)	(0.072)
1.prelaunch#1.research#c.log_ici_index	0.618***	0.508***	0.094***	0.201***
	(0.066)	(0.061)	(0.028)	(0.030)
1.pp_dcy#1.prelaunch#1.research#c.log_ici_index	0.917***	0.848***	0.300***	0.351***
	(0.160)	(0.155)	(0.070)	(0.077)
Log(# other countries with product patent)	0.009	0.004	0.007	0.001
	(0.007)	(0.004)	(0.005)	(0.003)
No product patent*Log(# other countries with product patent)	0.002	0.001	−0.000	0.003*
	(0.006)	(0.004)	(0.005)	(0.002)
Drug age	−0.004***	−0.002**	−0.003***	0.001
	(0.001)	(0.001)	(0.001)	(0.001)
Drug age^2	0.000*	0.000	0.000**	−0.000
	(0.000)	(0.000)	(0.000)	(0.000)
Years since first patent application	0.001***	0.001**	0.001***	−0.000
	(0.000)	(0.000)	(0.000)	(0.000)
Log(DALYs)	0.015***	0.011***	0.006***	0.002***
	(0.002)	(0.002)	(0.001)	(0.001)
Missing DALY	0.022**	0.011	0.017***	−0.003
	(0.011)	(0.007)	(0.006)	(0.005)
Intercept	−4.459***	−3.512***	−0.977***	−1.169***
	(0.267)	(0.249)	(0.105)	(0.113)
N	499653	499653	499653	499653
Adjusted R^2	.33	.222	.215	.235
			Year	
Fixed effects			Country	
			Drug	

* p<0.10, ** p<0.05, *** p< .01.

Table 10: OLS Regression of count of trials, varying country samples for public sponsors

	Top 50 b/se	11-50 b/se	Top 10 b/se	Top 10 exUS b/se
1.Product Patent	−4.027***	−1.625***	−9.217***	1.539**
	(0.502)	(0.262)	(1.468)	(0.653)
1.Prior to drug's launch in country	1.922***	0.162**	10.721***	−1.739***
	(0.202)	(0.063)	(0.958)	(0.352)
1.pp_dcy#1.prelaunch	3.422***	1.259***	5.295***	−0.902
	(0.512)	(0.279)	(1.653)	(0.681)
1.pp_dcy#1.research	3.186***	0.823***	10.877***	0.103***
	(0.472)	(0.264)	(1.735)	(0.015)
1.prelaunch#1.research	−1.605***	0.085	−12.460***	−0.032***
	(0.191)	(0.060)	(1.095)	(0.007)
1.pp_dcy#1.prelaunch#1.research	−2.784***	−0.489*	−6.002***	−0.062***
	(0.497)	(0.291)	(1.840)	(0.017)
1.pp_dcy#c.log_ici_index	1.254***	0.517***	2.753***	−0.472**
	(0.157)	(0.083)	(0.439)	(0.196)
1.prelaunch#c.log_ici_index	−0.614***	−0.053***	−3.220***	0.521***
	(0.064)	(0.020)	(0.287)	(0.106)
1.pp_dcy#1.prelaunch#c.log_ici_index	−1.066***	−0.405***	−1.588***	0.272
	(0.160)	(0.088)	(0.495)	(0.204)
1.pp_dcy#1.research#c.log_ici_index	−0.970***	−0.242***	−3.236***	
	(0.147)	(0.083)	(0.519)	
1.prelaunch#1.research#c.log_ici_index	0.508***	−0.032	3.734***	
	(0.061)	(0.020)	(0.328)	
1.pp_dcy#1.prelaunch#1.research#c.log_ici_index	0.848***	0.141	1.785***	
	(0.155)	(0.092)	(0.551)	
Log(# other countries with product patent)	0.004	0.004	0.001	−0.005
	(0.004)	(0.003)	(0.007)	(0.005)
No product patent*Log(# other countries with product patent)	0.001	−0.002	0.004	0.003
	(0.004)	(0.003)	(0.012)	(0.006)
Drug age	−0.002**	−0.001***	0.001	0.000
	(0.001)	(0.000)	(0.001)	(0.001)
Drug age^2	0.000	0.000	−0.000	−0.000
	(0.000)	(0.000)	(0.000)	(0.000)
Years since first patent application	0.001**	0.001***	−0.000	0.000
	(0.000)	(0.000)	(0.001)	(0.000)
Log(DALYs)	0.011***	0.007***	0.007**	0.016***
	(0.002)	(0.001)	(0.003)	(0.002)
Missing DALY	0.011	0.007	−0.017	0.026**
	(0.007)	(0.005)	(0.018)	(0.012)
Intercept	−3.512***	−0.355***	−77.549***	−72.987***
	(0.249)	(0.093)	(5.518)	(5.215)
N	499653	397683	101970	91773
Adjusted R^2	.222	.131	.361	.275
Fixed effects		Year Country Drug		

* p<0.10, ** p<0.05, *** p< .01.

Table 11: OLS Regression of count of trials, varying drug samples in ICI 50

	Ever on b/se	Ever off b/se	IP change b/se
1.Product Patent	−2.002∗∗∗	−2.531∗∗∗	−0.585
	(0.611)	(0.668)	(0.501)
1.Prior to drug's launch in country	3.798∗∗∗	2.033∗∗∗	4.033∗∗∗
	(0.644)	(0.196)	(0.653)
1.pp_dcy#1.prelaunch	1.101∗	2.376∗∗∗	0.210
	(0.647)	(0.681)	(0.518)
1.pp_dcy#1.research	1.596∗∗∗	2.130∗∗∗	0.588
	(0.577)	(0.656)	(0.521)
1.prelaunch#1.research	−2.944∗∗∗	−1.727∗∗∗	−3.229∗∗∗
	(0.615)	(0.185)	(0.614)
1.pp_dcy#1.prelaunch#1.research	−0.971	−2.103∗∗∗	−0.452
	(0.633)	(0.671)	(0.543)
1.pp_dcy#c.log_ici_index	0.619∗∗∗	0.791∗∗∗	0.185
	(0.191)	(0.209)	(0.156)
1.prelaunch#c.log_ici_index	−1.198∗∗∗	−0.650∗∗∗	−1.272∗∗∗
	(0.202)	(0.062)	(0.205)
1.pp_dcy#1.prelaunch#c.log_ici_index	−0.338∗	−0.744∗∗∗	−0.067
	(0.202)	(0.213)	(0.162)
1.pp_dcy#1.research#c.log_ici_index	−0.482∗∗∗	−0.649∗∗∗	−0.174
	(0.180)	(0.205)	(0.163)
1.prelaunch#1.research#c.log_ici_index	0.923∗∗∗	0.546∗∗∗	1.011∗∗∗
	(0.193)	(0.059)	(0.192)
1.pp_dcy#1.prelaunch#1.research#c.log_ici_index	0.289	0.643∗∗∗	0.135
	(0.198)	(0.209)	(0.169)
Log(# other countries with product patent)	−0.006	0.005	−0.011
	(0.006)	(0.004)	(0.007)
No product patent*Log(# other countries with product patent)	−0.005	−0.001	−0.004
	(0.005)	(0.004)	(0.005)
Drug age	0.002	−0.002∗∗∗	0.000
	(0.002)	(0.001)	(0.002)
Drug age^2	−0.000∗∗	0.000∗	−0.000
	(0.000)	(0.000)	(0.000)
Years since first patent application	0.001	0.001∗∗∗	0.001
	(0.001)	(0.000)	(0.001)
Log(DALYs)	0.010∗∗∗	0.008∗∗∗	0.007∗∗∗
	(0.002)	(0.001)	(0.003)
Missing DALY	0.027	0.008	0.041∗
	(0.021)	(0.007)	(0.023)
Intercept	−5.537∗∗∗	−3.421∗∗∗	−5.420∗∗∗
	(0.643)	(0.250)	(0.677)
N	124223	448041	72611
Adjusted R^2	.304	.174	.286
Fixed effects		Year Country Drug	

* p<0.10, ** p<0.05, *** p< .01.

Table 12: OLS Regression of count of trials for all observations, varying patent measure in ICI 50

	Product patent b/se	Any patent b/se	Log(# patents) b/se
1.Product Patent	−5.285∗∗∗	−4.904∗∗∗	−3.019∗∗∗
	(0.508)	(0.427)	(0.224)
1.Prior to drug's launch in country	2.276∗∗∗	1.302∗∗∗	1.363∗∗∗
	(0.224)	(0.240)	(0.244)
1.pp_dcy#1.prelaunch	3.784∗∗∗	3.862∗∗∗	1.912∗∗∗
	(0.523)	(0.412)	(0.306)
1.pp_dcy#1.research	4.203∗∗∗	3.967∗∗∗	2.488∗∗∗
	(0.483)	(0.398)	(0.209)
1.prelaunch#1.research	−1.957∗∗∗	−1.131∗∗∗	−1.134∗∗∗
	(0.210)	(0.225)	(0.228)
1.pp_dcy#1.prelaunch#1.research	−3.038∗∗∗	−3.203∗∗∗	−1.601∗∗∗
	(0.516)	(0.398)	(0.305)
1.pp_dcy#c.log_ici_index	1.654∗∗∗	1.536∗∗∗	0.949∗∗∗
	(0.159)	(0.134)	(0.070)
1.prelaunch#c.log_ici_index	−0.729∗∗∗	−0.421∗∗∗	−0.442∗∗∗
	(0.071)	(0.077)	(0.078)
1.pp_dcy#1.prelaunch#c.log_ici_index	−1.183∗∗∗	−1.209∗∗∗	−0.595∗∗∗
	(0.163)	(0.129)	(0.095)
1.pp_dcy#1.research#c.log_ici_index	−1.280∗∗∗	−1.219∗∗∗	−0.759∗∗∗
	(0.150)	(0.124)	(0.065)
1.prelaunch#1.research#c.log_ici_index	0.618∗∗∗	0.359∗∗∗	0.360∗∗∗
	(0.066)	(0.072)	(0.073)
1.pp_dcy#1.prelaunch#1.research#c.log_ici_index	0.917∗∗∗	0.981∗∗∗	0.485∗∗∗
	(0.160)	(0.125)	(0.095)
Log(# other countries with product patent)	0.009	0.025∗∗∗	0.017∗∗
	(0.007)	(0.007)	(0.006)
No product patent*Log(# other countries with product patent)	0.002	−0.011∗	−0.005
	(0.006)	(0.006)	(0.006)
Drug age	−0.004∗∗∗	−0.003∗∗∗	−0.003∗∗∗
	(0.001)	(0.001)	(0.001)
Drug age^2	0.000∗	0.000	0.000
	(0.000)	(0.000)	(0.000)
Years since first patent application	0.001∗∗∗	0.001	−0.001∗
	(0.000)	(0.000)	(0.000)
Log(DALYs)	0.015∗∗∗	0.016∗∗∗	0.016∗∗∗
	(0.002)	(0.002)	(0.002)
Missing DALY	0.022∗∗	0.006	0.008
	(0.011)	(0.011)	(0.010)
Intercept	−4.459∗∗∗	−3.293∗∗∗	−2.911∗∗∗
	(0.267)	(0.283)	(0.291)
N	499653	499653	499653
Adjusted R^2	.33	.325	.334
Fixed effects		Year Country Drug	

* p<0.10, ** p<0.05, *** p< .01.

Table 13: List of Countries with Characteristics and Trial Distribution

country name	total trial	share	interven-tional trial	experi-mental	noncom-mercial	bolar	ici rank	ici index	income group
United States	69237	.3466547	28505	1		1	1	30.3	HighOECD
United Kingdom	19864	.0994548	5811	1	1	1	4	27	HighOECD
Germany	18801	.0941326	7232	1	1	1	3	27.2	HighOECD
Japan	13277	.0664751	3893	1	1		12	26.4	HighOECD
France	12516	.0626649	5103	1	1		9	26.8	HighOECD
Canada	12294	.0615534	4672	1	1	1	10	26.5	HighOECD
Netherlands	12062	.0603918	3502	1	1		6	26.9	HighOECD
Italy	11366	.0569071	5008	1	1		22	23.3	HighOECD
Spain	10361	.0518753	4800	1	1		21	23.4	HighOECD
Belgium	6547	.0327794	2791	1	1		15	25.4	HighOECD
Australia	6513	.0326092	2451	1	1		7	26.9	HighOECD
India	6004	.0300607	1917	1		1	38	18.9	Low middle
Sweden	5678	.0284285	2322	1	1		8	26.9	HighOECD
Denmark	5555	.0278127	2127	1	1		19	25.2	HighOECD
China	5508	.0275774	1892	1		1	43	18.1	Upper middle
Korea, Republic of	5125	.0256598	2490	1	1		23	22.9	HighOECD
Austria	4987	.0249688	2231		1		17	25.3	HighOECD
Czech Republic	4616	.0231113	2074		1	1	26	21.3	HighOECD
Poland	4609	.0230763	2297	1			36	19.6	HighOECD
Israel	4558	.0228209	1321	1	1	1	11	26.5	HighOECD
Hungary	4425	.022155	2160	1	1		28	21.1	HighOECD
Brazil	4389	.0219748	1640	1	1		33	20.1	Upper middle
Iran, Islamic Republic of	4153	.0207932	816	1					Upper middle
Switzerland	3596	.0180044	1489	1	1	1	5	26.9	HighOECD
Taiwan, Province of China	3391	.016978	1281	1	1		14	26	HighOECD
Finland	3387	.016958	1454	1	1		2	29.1	HighOECD
Russian Federation	3353	.0167877	1884	1	1		30	20.6	Upper middle
Mexico	2522	.0126271	1442	1	1		53	16.8	Upper middle
Norway	2468	.0123567	919	1	1		18	25.3	HighOECD
South Africa	2382	.0119262	1280	1	1	1	29	21	Upper middle
Greece	2371	.0118711	1386	1	1		42	18.4	HighOECD
Argentina	2211	.01107	1269	1	1		49	17	Upper middle
Romania	1920	.009613	1083	1	1		55	16.3	Upper middle
Portugal	1837	.0091975	1021		1	1	25	21.6	HighOECD
Bulgaria	1770	.008862	798	1	1		50	16.9	Upper middle
Turkey	1638	.0082011	881	1	1	1	44	17.8	Upper middle
Thailand	1611	.0080659	742		1	1	46	17.4	Upper middle
New Zealand	1607	.0080459	634	1		1	24	22.1	HighOECD

Table 14: List of Countries with Characteristics and Trial Distribution (Cont'd)

country name	total trial	share	interven -tional trial	experi -mental	noncom -mercial	bolar	ici rank	ici index	income group
Ireland	1598	.0080008	821	1	1		16	25.4	HighOECD
Slovakia	1528	.0076504	872	1	1		34	20	HighOECD
Ukraine	1513	.0075753	792	1	1	1	32	20.3	Low middle
Puerto Rico	1437	.0071947	1303						HighnonOECD
Singapore	1343	.0067241	596	1	1		13	26	HighnonOECD
Lithuania	1334	.0066791	653	1	1		37	19.2	Upper middle
Estonia	1213	.0060732	525	1	1		27	21.2	HighOECD
Chile	1186	.005938	567				35	19.7	Upper middle
Latvia	1155	.0057828	529	1	1		41	18.5	Upper middle
Hong Kong	1077	.0053923	576						HighnonOECD
Peru	1009	.0050518	617	1	1		60	14.3	Upper middle
Colombia	975	.0048816	497	1	1		59	15.1	Upper middle
Philippines	829	.0041506	466	1	1		56	15.8	Low middle
Malaysia	803	.0040204	433	1	1	1	52	16.8	Upper middle
Serbia	784	.0039253	334	1	1				Upper middle
Croatia	774	.0038753	419	1	1	1			HighnonOECD
Egypt	551	.0027587	240	1	1	1	48	17.2	Low middle
Slovenia	546	.0027337	277	1	1		31	20.4	HighOECD
Saudi Arabia	318	.0015922	130	1	1				HighnonOECD
Uganda	277	.0013869	92						Low
Guatemala	277	.0013869	172	1	1	1	63	13.2	Low middle
Pakistan	275	.0013769	103	1	1				Low middle
Indonesia	252	.0012617	120	1	1		54	16.4	Low middle
Kenya	236	.0011816	47	1	1	1			Low
Lebanon	231	.0011566	108						Upper middle
Viet Nam	212	.0010614	75				61	13.8	Low middle
Panama	207	.0010364	148	1	1		45	17.4	Upper middle
Tanzania, United Republic of	199	.0009964	59						Low
Tunisia	191	.0009563	105	1	1	1			Upper middle
Cuba	188	.0009413	29						Upper middle
Iceland	188	.0009413	96	1	1		20	24.8	HighOECD
Belarus	176	.0008812	72	1	1				Upper middle
Bangladesh	175	.0008762	28				70	11.6	Low
Venezuela, Bolivarian Republic of	153	.000766	127				58	15.2	Upper middle
Costa Rica	148	.000741	113	1	1	1	39	18.8	Upper middle
Georgia	138	.0006909	47						Low middle
Malawi	136	.0006809	58						Low
Bosnia and Herzegovina	134	.0006709	79	1	1				Upper middle

Table 15: List of Countries with Characteristics and Trial Distribution (Cont'd)

country name	total trial	share	interven-tional trial	experi-mental	noncom-mercial	bolar	ici rank	ici index	income group
Sri Lanka	127	.0006359	22	1	1		57	15.5	Low middle
Zambia	118	.0005908	35						Low middle
Dominican Republic	116	.0005808	41	1	1	1	62	13.6	Upper middle
Ecuador	112	.0005608	62	1	1		69	11.9	Upper middle
United Arab Emirates	110	.0005507	57						HighnonOECD
Ghana	110	.0005507	6	1	1				Low middle
Macedonia, the former Yugoslav Republic of	109	.0005457	86	1	1	1			Upper middle
Burkina Faso	93	.0004656	14						Low
Jordan	91	.0004556	47	1		1			Upper middle
Korea, Democratic People's Republic of	88	.0004406	11						Low
Morocco	88	.0004406	50	1	1				Low middle
Mali	86	.0004306	8						Low
Luxembourg	79	.0003955	44	1	1				HighOECD
Nigeria	73	.0003655	19		1				Low middle
Zimbabwe	63	.0003154	41				65	13	Low
Nepal	58	.0002904	9						Low
Gambia	58	.0002904							Low
Moldova, Republic of	55	.0002754	20	1	1				Low middle
Ethiopia	54	.0002704	9						Low
Algeria	52	.0002604	27	1	1				Upper middle
Uruguay	49	.0002453	28	1	1	1	51	16.8	Upper middle
Kuwait	49	.0002453	28						HighnonOECD
Malta	47	.0002353	27	1	1				HighnonOECD
Botswana	47	.0002353	30						Upper middle
Cameroon	45	.0002253	17						Low middle
Cyprus	43	.0002153	25	1	1				HighnonOECD
Senegal	42	.0002103	18						Low middle
Qatar	41	.0002053	14						HighnonOECD
Guinea-Bissau	41	.0002053	3						Low
Mozambique	38	.0001903	4	1					Low
El Salvador	38	.0001903	23	1	1		67	12.5	Low middle
Cambodia	37	.0001853	10						Low
Kazakhstan	36	.0001802	15						Upper middle
Rwanda	36	.0001802	2						Low
Honduras	32	.0001602	4				68	11.9	Low middle
Benin	31	.0001552	3						Low
Albania	30	.0001502	13	1	1				Low middle
Armenia	30	.0001502	8	1	1				Low middle

Table 16: List of Countries with Characteristics and Trial Distribution (Cont'd)

country name	total trial	share	interven-tional trial	experi-mental	noncom-mercial	bolar	ici rank	ici index	income group
Gabon	29	.0001452	6						Upper middle
Bolivia, Plurinational State of	29	.0001452	8	1	1		71	11.6	Low middle
Jamaica	27	.0001352	2						Upper middle
Congo	27	.0001352	5						Low middle
Cte d'Ivoire	23	.0001152	15						Low middle
Haiti	23	.0001152	12						Low
Oman	22	.0001101	7	1		1			HighnonOECD
Sudan	22	.0001101	2						Low middle
Montenegro	21	.0001051	8						Upper middle
Iraq	19	.0000951	7						Low middle
Afghanistan	18	.0000901	5						Low
Lao People's Democratic Republic	17	.0000851	1						Low middle
Bahamas	17	.0000851	17						HighnonOECD
Paraguay	17	.0000851	8				64	13.1	Low middle
Bahrain	17	.0000851	11			1			HighnonOECD
Congo, the Democratic Republic of the	16	.0000801	1						Low
Mongolia	16	.0000801	5	1					Low middle
Syrian Arab Republic	15	.0000751	3	1	1	1			Low middle
Monaco	13	.0000651	9						HighnonOECD
Myanmar	11	.0000551	3						Low
Papua New Guinea	11	.0000551	1	1					Low middle
Trinidad and Tobago	10	.0000501	2	1	1		40	18.6	HighnonOECD
Madagascar	10	.0000501	3						Low
Belize	10	.0000501	7	1					Low middle
Guinea	10	.0000501	1						Low
Nicaragua	9	.0000451		1	1		66	12.7	Low middle
Niger	9	.0000451	2						Low
Fiji	7	.000035							Low middle
Martinique	6	.00003							
Burundi	6	.00003	1						Low
Sierra Leone	6	.00003							Low
Libya	6	.00003	9						Upper middle
Yemen	6	.00003	3						Low middle
Mauritius	6	.00003		1			47	17.2	Upper middle
Swaziland	5	.000025							Low middle
Angola	5	.000025							Upper middle
Central African Republic	5	.000025	1						Low
Andorra	5	.000025	4	1	1				Low

Table 17: List of Countries with Characteristics and Trial Distribution (Cont'd)

country name	total trial	share	interven-tional trial	experi-mental	noncom-mercial	bolar	ici rank	ici index	income group
Liberia	5	.000025							Low
Togo	5	.000025							Low
Virgin Islands, U.S.	4	.00002	3						HighnonOECD
Kyrgyzstan	4	.00002	1						Low
American Samoa	4	.00002		1					Upper middle
Runion	4	.00002	1						
Guadeloupe	3	.000015	1						
Sint Maarten (Dutch part)	2	.00001							HighnonOECD
Vanuatu	2	.00001							Low middle
Azerbaijan	2	.00001	3	1	1				Upper middle
Equatorial Guinea	2	.00001							HighnonOECD
Uzbekistan	2	.00001		1					Low middle
Grenada	2	.00001							Upper middle
Bhutan	2	.00001							Low middle
Solomon Islands	2	.00001							Low middle
Timor-Leste	2	.00001							
Chad	2	.00001							Low
Palestine, State of	2	.00001							
Somalia	2	.00001							Low
Barbados	2	.00001	2	1					HighnonOECD
Marshall Islands	2	.00001							Low middle
Mauritania	2	.00001	1						Low
French Polynesia	1	5.01e-06							HighnonOECD
Bermuda	1	5.01e-06	1						HighnonOECD
Guyana	1	5.01e-06							Low middle
New Caledonia	1	5.01e-06							HighnonOECD
Saint Kitts and Nevis	1	5.01e-06							HighnonOECD
Macao	1	5.01e-06							HighnonOECD
United States Minor Outlying Islands	1	5.01e-06							HighnonOECD
Northern Mariana Islands	1	5.01e-06							Upper middle
Saint Lucia	1	5.01e-06		1	1				Upper middle
Djibouti	1	5.01e-06	4						Low middle
Brunei Darussalam	1	5.01e-06	1						HighnonOECD
Lesotho	1	5.01e-06							Low middle
Antigua and Barbuda	1	5.01e-06							Upper middle
Namibia	1	5.01e-06							Upper middle
Eritrea	1	5.01e-06							Low

Table 18: OLS Regression of count of trials, by trial sponsor

	Total b/se	Public b/se	Originators b/se	Non-originato b/se
1.Product Patent	−0.089***	−0.066***	−0.029*	−0.029***
	(0.021)	(0.011)	(0.015)	(0.010)
1.Prior to drug's launch in country	−0.005	−0.005	−0.002	0.003
	(0.008)	(0.003)	(0.005)	(0.005)
1.pp_dcy#1.prelaunch	0.063***	0.056***	0.016	0.021**
	(0.020)	(0.010)	(0.015)	(0.009)
1.pp_dcy#1.research	−0.037	−0.019	−0.023	0.004
	(0.023)	(0.012)	(0.014)	(0.009)
1.prelaunch#1.research	0.007***	0.005***	0.001	0.001
	(0.002)	(0.001)	(0.001)	(0.001)
1.pp_dcy#1.prelaunch#1.research	0.027	0.012	0.016	−0.003
	(0.023)	(0.012)	(0.014)	(0.009)
1.pp_dcy#c.log_ici_index	0.114***	0.074***	0.048***	0.035***
	(0.010)	(0.008)	(0.006)	(0.005)
1.prelaunch#c.log_ici_index	−0.016***	−0.011***	−0.002	−0.007***
	(0.003)	(0.002)	(0.002)	(0.002)
1.pp_dcy#1.prelaunch#c.log_ici_index	−0.095***	−0.073***	−0.032***	−0.032***
	(0.010)	(0.008)	(0.006)	(0.004)
1.pp_dcy#1.research#c.log_ici_index	−0.015*	−0.017**	−0.003	−0.013***
	(0.009)	(0.007)	(0.005)	(0.004)
1.prelaunch#1.research#c.log_ici_index	0.002	0.005***	−0.002**	0.001
	(0.002)	(0.002)	(0.001)	(0.001)
1.pp_dcy#1.prelaunch#1.research#c.log_ici_index	0.018**	0.024***	0.001	0.013***
	(0.009)	(0.007)	(0.005)	(0.004)
Log(# other countries with product patent)	0.009	0.003	0.006	0.001
	(0.008)	(0.004)	(0.005)	(0.003)
No product patent*Log(# other countries with product patent)	0.002	0.001	0.000	0.003
	(0.007)	(0.004)	(0.005)	(0.002)
Drug age	−0.003**	−0.001	−0.003***	0.001
	(0.001)	(0.001)	(0.001)	(0.001)
Drug age^2	0.000	0.000	0.000***	0.000
	(0.000)	(0.000)	(0.000)	(0.000)
Years since first patent application	0.002***	0.001**	0.001***	0.000
	(0.001)	(0.000)	(0.000)	(0.000)
Log(DALYs)	0.018***	0.011***	0.008***	0.004***
	(0.003)	(0.002)	(0.001)	(0.001)
Missing ICI index	0.007	−0.151***	0.064***	0.030**
	(0.027)	(0.016)	(0.016)	(0.014)
Missing DALY	0.025**	0.012*	0.020***	−0.003
	(0.012)	(0.007)	(0.006)	(0.005)
Intercept	−0.076***	0.115***	−0.095***	−0.050***
	(0.027)	(0.014)	(0.017)	(0.015)
N	1539747	1539747	1539747	1539747
Adjusted R^2	.24	.169	.139	.129
Fixed effects		Year Country Drug		

* p<0.10, ** p<0.05, *** p< .01.