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DOCTORAL THESIS

Essays on entry and market profitability in the UK pharmaceuticals

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Declaration of Authorship

I, Weijie YAN, declare that this thesis titled, "Essays on entry and market profitability in the UK pharmaceuticals" and the work presented in it is my own. I confirm that:

- This work was done wholly or mainly while in candidature for a research degree at this University.
- Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated.
- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.
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Abstract

This thesis applies economic methods developed in industrial organization to assess entry barriers and profitability of the pharmaceutical market in the UK. The thesis has two parts. The first part investigates whether incumbent firms strategically proliferate product varieties to delay and deter entry of competitors, and whether such strategy is effective to be a barrier. Three sets of regressions are employed: a non-monotonicity test between number of products and market size, as proposed by Ellison and Ellison (2011); a hazard rate model of entry probability, with focus on whether entry can be influenced by product varieties; and a regression of incumbent's market share post entry to test whether their share is positively correlated with product varieties built prior to entry. The results suggest that product proliferation can be a barrier to entry in the UK, however, evidence on incumbents' strategic incentive is inconclusive.

The second part of the thesis focuses on antibiotic market. With the use of antibiotics, bacteria start to develop resistance, which has became a global crisis in healthcare. Despite the need for new entries because old molecules are losing effectiveness, research firms are leaving this market. We use nested logit and random coefficients logit model to estimate the price elasticity of demand between drugs in order to assess the profitability of the market and to evaluate policy interventions of shifting consumption away from molecules that cause higher resistance. We find that price-cost margin of this market is 35.2% on average but varies by molecules and drug types (branded/generics). We also find that some interventions can be effective to shift demand but with prices to pay.

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List of Abbreviations

ADHD	Attention-Deficit Hyperactivity Disorder
AG	Authorized Generic
AIDS	Almost Ideal Demand System
AMR	Antimicrobial Resistance
ATC	Anatomical Therapeutic Chemical
AZ	AstraZeneca
BLP	Berry, Levinsohn & Pakes
BPI	British Pharmaceutical Index
CCG	Clinical Commissioning Group
CDC	Centers for Disease Control and Prevention
CPI	Consumer Price Index
DDD	Defined Daily Dose
DH	Department of Health
DNA	Deoxyribonucleic Acid
DTP	Direct to Pharmacy
EARS	European Antimicrobial Resistance Surveillance network
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EEC	European Economic Community
EMEA	European Medicines Agency
EU	European Union
FTC	Federal Trade Commission
GDP	Gross Domestic Product
GMM	Generalized Method of Moments
GP	General Practitioner
GSK	GlaxoSmithKline
G7	Group of Seven
HHI	Herfindahl–Hirschman Index
IIA	Independent of Irrelevant Alternatives
IMS	Intercontinental Marketing Services
IO	Industrial Organization
IV	Instrumental Variable
MA	Market Authorization
MHRA	Medicines and Healthcare products Regulatory Agency
MPEC	Mathematical Programming with Equilibrium Constraints

MRSA	Methicillin-Resistant Staphylococcus Aureus
NFP	Nested Fixed Points
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OECD	Organisation for Economic Co-operation and Development
OFT	Office of Fair Trading
OTC	Over-the-Counter
PCT	Primary Care Trust
PHE	Publish Health England
PPRS	Pharmaceutical Price Regulation Scheme
PoM	Prescription only Medicines
P4P	Pay-for-Performance
RCL	Random Coefficients Logit
R&D	Research and Development
SPC	Supplementary Protection Certificate
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

Chapter 1

Introduction

Health care closely relates to the quality of life of human beings. World Health Organization (WHO) estimates that globally on average 6.3% of gross domestic product (GDP) was spent on health services in 2015. As an important input into health production, pharmaceutical market achieved $996 billion sales in 2017, up by 2.9% from the previous year.[1] Apart from its extensive market size, pharmaceuticals attracts attention of economists and policy makers alike because of the need to strike a balance between giving firms incentive to undertake expensive and risky R&D, while at the same time making medicines accessible and affordable for patients. In response to this dual objective, this market is often regulated. An innovator is grated a monopoly via patents or market exclusivity, but when protection period is over rigorous competition is expected to kick in. For a healthy functioning of this mechanism, freedom of entry is a prerequisite. This thesis applies methods from empirical Industrial Organization (IO) to study the issues of entry barriers and market profitability in the pharmaceutical industry in the UK.

Pharmaceutical market heavily relies on R&D activities for drug development. Innovative drugs reduce mortality and increase life expectancy. However, bringing a new drug to the market can be very expensive, therefore, R&D incentives should be properly catered. Often, the reward of launching a novel medicine is granted by regulation, e.g. patent protection, data or market exclusivity, which grants the originator to be a monopoly in the market for a sufficiently long period of time so that profit earned exceeds past R&D expenditure.

On the other hand, high monopoly price abates accessibility and affordability of medicines. Around 70% of health expenditure is reimbursed by government in OECD countries, which is fundamentally financed by taxation. To control for government spending on health care, some countries impose direct price controls on drug prices, which include (but are not limited to) price caps and reference pricing. Other countries, although they do not control price directly, regulate profits that firms can make (Jacobzone, 2000). Besides, price cuts or freeze are also commonly used. As an example, the UK system is an exception from direct price control, but the permitted return on capital is regulated typically at 21% (DH, 2013). However, price regulation may often have adverse effects on innovation. Firms tend to avoid

[1] Astrazeneca annual report 2017 (AstraZeneca, 2017).

launching in countries with tight price controls, and price controls may reduce firms' direct R&D intensity by 23.4-32.7% (Danzon et al., 2005; Kyle, 2007; Vernon, 2005).

Introducing competition into pharmaceutical market is one of the solutions to price regulation. Competition is generally useful to drive market price down and can lead to more innovation (Aghion et al., 2005; Arrow, 1972). In the pharmaceutical market, generic versions are able to enter when the granted monopoly period for the originator expires. Entry cost for generics is much lower, as they are exempt from providing their own pre-clinic experiment data and human clinic data when applying for market authorization. As generics typically focus on efficient production and on high volumes to make profits (Finn, 2016), generic companies are able to offer lower prices than the originator. Intense competition between generic firms and the originator is expected to drive down market prices as they sell bio-equivalent products. On the other hand, competition from generics may also stimulate launch of novel drugs. As drugs that lost exclusivity are (should be) no longer profitable, firms would seek new drugs for profit. Scott Morton and Boller (2017) highlight the importance of competition on drug innovation. They argue that competition insures that high prices of novel drugs only reflect their value to the society, and that profits made by pharmaceutical companies are from innovation other than anti-competitive behaviours.

The first question raised in the thesis is whether there are anti-competitive behaviours against entry in this market. Explicitly, it asks whether originators strategically deter entry. By deterring the entry of generics, originators can keep their monopoly position and maintain high profit. This foreclose of competition could be done in many ways. For instance, they can reformulate the product in a way such that a generic version is unable to substitute, which is known as 'product hopping'.[2] One famous case is AstraZeneca's ulcer drug Losec.[3] The originators may also pay a generic firm not to enter the market: the 'pay-for-delay' settlement.[4] Apart from these emerging anti-competitive strategies, this thesis especially investigates whether product proliferation can deter entry in this market. Product proliferation is not illegal, however, it can be anti-competitive if incumbents proliferate products to deter entry. To form a concrete picture, the first part of this thesis tries to answer these questions: 1) whether entry-deterrence investment is effective in delaying entry and 2) whether incumbents have incentive to deter entry with strategic investments.

As entry depends fundamentally on expected pay-offs after entry, the second

[2] 'Product hopping' may also be known as 'evergreening'. Carrier and Shadowen (2016) provide useful information.

[3] Case COMP/A. 37.507/F3 - AstraZeneca. In June 2005, European Commission fined AstraZeneca (AZ) €60 million for its abuse of dominance to delay the entry of generics. AZ is considered to infringe EC and EEA competition rules from 1993 to 2000 by 1) misusing the Supplementary Protection Certificates (SPC) regulation and 2) selectively deregistering its reference market authorizations for generics with the intention to block entry and parallel import.

[4] Discussions about 'pay-for-delay' could be found in Hemphill (2006) and Kesselheim et al. (2011) and Bokhari et al. (2017).

question addressed in this thesis is whether entries are properly rewarded in pharmaceutical market. Regulations on patent and exclusivity are designed to protect innovation incentive of the originators, however, there is evidence suggesting they may not be well rewarded from their innovation under current system (Kyle, 2018). In fact, the cost of bringing novel drugs to the market keeps climbing and many firms have given up R&D on some therapeutic areas that are not profitable, despite the need for news drugs (DiMasi and Grabowski, 2007; DiMasi et al., 2003; Projan, 2003). Antibiotics market is a leading example. We focus on antibiotics in this section because they remain one of the most important and essential classes of drugs worldwide and improvement of health status in the twentieth century is mainly contributed to them (Cutler et al., 2006; Jayachandran et al., 2010). However, because of antibiotic resistance, old antibiotics are losing effectiveness and novel molecules are in urgent need. What exacerbates the story is that novel molecules are far from profitable (Powers, 2004). As a result, Novartis ceased R&D in antibiotics and antivirals in July 2018. Only Merck, Roche, GlaxoSmithKline and Pfizer have active antibiotic programs now, compared to 18 big research pharmaceutical companies in 1990 (Cooper and Shlaes, 2011; Nature Biotechnology, 2018).

Understanding the market profitability is crucial to answer why entry in antibiotics is scarce. Nevertheless, assessing drug profitability is difficult, as cost information is often veiled to researchers. Fortunately, structural demand models from IO offer a solution. Such models estimate price elasticities of products, which can then be used to calculate marginal costs and profitability. Another advantage of structural demand models is, with estimated parameters, the ease to estimate counterfactual scenarios. Therefore, such models are often used to simulate results from change of market structure or policy interventions, e.g. mergers, import quotas and taxation. Making use of this advantage, this thesis also tries to assess the possibility of interventions, aiming at promoting proper use of antibiotics.

The main dataset used in this thesis is provided by IMS, which covers transactions of pharmaceuticals from wholesalers to retail pharmacies in the UK for 20 years between 1996 and 2016. Because of data limitation, the focus of the thesis is only on the UK market. One feature of the UK health care system is that almost all prescription drugs, such as antibiotics, are reimbursed by the National Health Service (NHS), and patients only pay a flat prescription fee for each prescription. Hence, this system rely on general practitioners (GPs) to control for pharmaceutical expenditure. To encourage GPs' price sensitivity, NHS allocates personal drug budget to each general practitioner (GP) in England since the April of 1999 (Jacobzone, 2000), which turns out to be successful (Carthy et al., 2000; Scoggins et al., 2006).

The thesis is organized as follows. The first and second chapter form the first part of the thesis. In these two chapters, we ask whether incumbents have incentive to deter entry with product proliferation and whether such strategy can effectively deter or delay entry, or at least help incumbent preserve market share if entry takes place. To answer the first question, we follow the identification method proposed

in Ellison and Ellison (2011). Their theory suggests that incumbents are more likely to deter entry when probability of entry is not too small or too large, because entry is unlikely to happen when entry probability is small, while it will happen anyway when entry probability is large. As market size is a good predictor of entry probability, the model predicts that number of products launched by the originator should increase monotonically in market size in the absence of entry deterrence incentive, and it should display a non-monotonic pattern otherwise. We use parametric and semi-parametric methods to test incumbents' incentive. To answer the second question, we use a discrete hazard rate model to study whether it is effective in delaying entry by a competitor with product proliferation pre expiration of exclusivity. We then test whether it is more likely for incumbents to maintain their market share post entry if they had controlled more products prior to entry.

Chapter 2 highlights important literature in IO on strategic entry deterrence, and then presents the model on entry deterrence and the UK data. In Chapter 3, three sets of empirical estimates are discussed. These two chapters contribute to the old but growing literature on entry-deterrence strategies with fresh evidence from the UK pharmaceutical market. Although IO theory predicts that product proliferation could be used as entry-deterrence strategy (Schmalensee, 1978), empirical evidence is not conclusive. Our results suggest that product proliferation can be effective to delay entry if the market size is not too small and it can also help incumbents to preserve market share in large-sized markets post entry. However, evidence on non-monotonicity is insufficient.

In the second part of the thesis, we turn to the antibiotics market in the UK. In Chapter 4 and 5, we study the structure and profitability of the antibiotics market, where we focus on estimating the demand with discrete choice models. Ten years sales data of antibiotics in the UK between 2003 and 2013 is used in this chapter. We start with logit demand model and extend it to nested logit and random coefficients logit models, because latter two can provide richer estimates. We find that molecules launched after 2000 accounts for only 0.01% of market share, which could not be profitable. For commonly used antibiotics, the average price-cost margin is around 35.2%, but the profitability of different molecules can vary a lot. Moreover, research pharmaceutical companies cannot generate much profit from commonly used antibiotics. This result is not coincident with the fact that research companies are leaving.

Since relying on entry of new molecules to tackle antibiotic crisis is unlikely, 'making the most of existing antimicrobials' is the second-best option (Davies, 2013). The fundamental question in antibiotics market is negative externalities that using a molecule is not only affecting the patient in target but will also reduce the future effectiveness of the molecule and the sensitivity of other patients who live around her, because pathogens are gaining resistance. O'Neill (2016) suggests a 'pay-to-play' policy where firms pay an amount of fee to produce antibiotics if they do not invest in antibiotics development. This policy is expected to force companies to internalize

negative externalities. We carry out simulations to alter antibiotic consumption, in parallel to O'Neill's suggestion. We argue that since broader spectrum antibiotics tend to lead larger externalities, the cost of producing those molecules should be higher if externalities are enclosed.[5] To assess how the cost-side intervention work, we simulate counterfactual scenarios where the cost of producing wider spectrum antibiotics were higher and we calculate the change of consumer surplus, producer profit and total surplus.

Chapter 4 focuses on the data and econometric model of demand, and Chapter 5 presents the empirical results. This part of the thesis contributes to the on-going policy discussions on fighting against antibiotics resistance with quantitative empirical evidence from the UK market.

[5]Broad-spectrum antibiotics, that act against a wide range of disease-causing bacteria, are more likely to induce resistance because more families of bacteria are sensitive to one molecule. Therefore, using one molecule is increasing the resistance of more families of bacteria.

Chapter 2

Product proliferation as entry deterrence

2.1 Introduction

Do firms strategically proliferate products when facing threat of entry? This question is studied theoretically in many textbooks of Industrial Organization (thereafter, IO). One of the earliest contributors to this body of research is Schmalensee (1978), who claims that product proliferation prior to entry can lead to entry deterrence, and can shield incumbent's market share if entry were to take place.

Although there is extensive theoretical research on this topic, empirical evidence on strategic product proliferation is thin. The reasons being that too often it is difficult or almost impossible to track the date when a market is open for entry, making challenging the examination of incumbent's actions. In addition, a companion complexity is identification of incumbent's entry deterrence separately from other profit maximizing strategies. The first part of the thesis will study these issues in the pharmaceutical market in the UK.

Investigating entry barriers, as argued by Fisher (1979) and Harbord and Hoehn (1994), is fundamentally an assessment of market power, as incumbents can exercise more market power when entrants are deterred. A pioneer work by Caves et al. (1984) documents that firm's profit is increasing in minimum efficient scale of a market. Entry barriers can protect profit, and preserve market share if entry occurs. In another work, Dixit (1980, 1982) illustrates how incumbents strategically create entry barriers. By investing in sunk cost prior to entry, incumbents can signal a credible commitment for aggressive responses against entry and deter entry. Because of the anti-competitive potentials of such strategies, economists have long been interested in finding empirical evidence on whether firms create entry barriers strategically, which, however, turns out to be difficult.

Some of the existing literature documents that investment, in the form of advertising, R&D and capacity expansion, can help incumbents to maintain leading positions and deter entry (Geroski and Toker, 1996), and have been used strategically (Conlin and Kadiyali, 2006; Paton, 2008; Weiman and Levin, 1994). Whereas, others find no supportive evidence of entry deterrence (Ghemawat and Caves, 1986;

Hall, 1990; Lieberman, 1987). However, little observation of evidence does not mean such strategies are not taking place, as argued in Lynne et al. (2008). If there are many potential entrants, the profitability of the first entrant would be eroded fast, and thus little investment by incumbent would be sufficient to deter entry.

Specific to product proliferation, entry deterrence has been discussed from at least three perspectives. First, it has been highlighted that it reduces size of submarket for each product, and thus, enhances the effect of economies of scale (Church and Ware, 2000). The authors claim that it can either make the submarket insufficient for an entrant, or make potential entrants believe that they will face aggressive competition if they attempt to enter. Second, still relates to economies of scale, it has been shown that product proliferation can help incumbents to generate relative cost advantages over potential entrants, at least in the short term (Gilbert, 1989). Third, incumbents can create reputation and loyalty to consumers via product proliferation and so limit demand for entrants (Demsetz, 1982; Harbord and Hoehn, 1994; Schmalensee, 1982). These effects closely relate to the objects of the first two chapters.

In these two chapters, we investigate whether firms proliferate products strategically to deter entry using 20 years sales data from the UK pharmaceutical market. First, by employing the non-monotonic relation between entry probability and entry-deterrence investment from Ellison and Ellison (2011), we examine the strategic incentive of incumbents to deter entry. Second, we test whether product proliferation is effective to deter entry. Specifically, we test the following two additional hypotheses. One, do more products launched by an originator during its market exclusivity period lower the probability of entry by other firms (generics and other branded drugs). Two, conditional on entry, do more products launched (prior to entry) help incumbents maintain greater market share.[1]

Pharmaceutical market is ideal to examine entry deterrence behaviour because of several market features. First, it can provide many observations within a given period, as each molecule that experiences the expiration of its legal protection can be considered as a distinct case (Reiffen and Ward, 2005). Another advantage of this market is that incumbents, potential entrants and, most importantly, researchers can observe the date when a market is 'open' for entry. In the UK, all pharmaceutical products need market authorization (MA) prior to entry. MA is granted either by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK or by European Medicines Agency (EMEA) in EU. MA aims to ensure safety and effectiveness of drugs and requires data from pre-clinical test and human clinical trials. The UK regulation protects the originator's drug for 10 years to recoup investment cost. This period is either 10 years 'data exclusivity' if MA was granted prior to 2001, or follows the '8+2(+1)' formula if it took place after that date.[2] However, replication

[1] Since by our definition, there will be only incumbent firm in each sub-market, which is the originator. We use originator and incumbent interchangeably throughout the chapters.

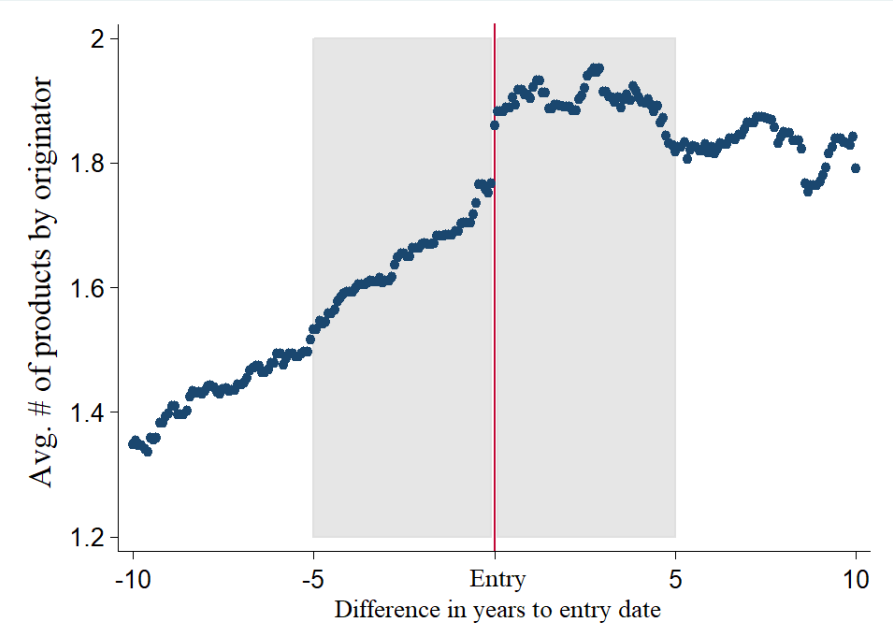
[2] Eight years data exclusivity plus 2 years market exclusivity, with one additional year if there is significant new indication or significant clinical benefit over existing therapies.

of clinical data can generally be expensive so that generics are exempt from such data requirement. When the legal protection of the originator expires, the market is open for generic entry. Generic entrants can refer to the originator's data when applying for market authorization of their generic version, which considerably reduces entry cost and is expected to increase entry probability. The launch of generic versions threatens incumbents, as it can bring intense competition into the market and cut the originator's profit. Therefore, originators should be motivated to react strategically ex ante and plan for post entry competition anticipating the expiration of protection. In addition, it is also possible for another brand drug to enter a market with their own data before expiration of exclusivity. While such entry probability is low, since entry cost is high, incumbent may also act strategically to this challenge. Background on relevant legal protection is provided in Section 3, following the review of literature in Section 2. We outline the theory model built in Ellison and Ellison (2011) in Section 4.

Product proliferation in general can help firm to take higher market share and increase its profitability, and sometimes can even decrease firm's marginal cost (Barroso and Giarratana, 2013; Bayus and Putsis Jr, 1999; Kekre and Srinivasan, 1990; Moreno and Terwiesch, 2016). Therefore, number of products a firm has in the market is considered to be positively and monotonically correlated with its market share if this strategy is not used for other purposes. This monotonicity relationship is therefore useful to identify firm's entry deterrence motive from profit-maximization actions. As argued in Ellison and Ellison (2011) and Dafny (2005), firm's entry deterrence motive will break this monotonicity. The incumbent will launch more products when entry probability is at its median, while they will launch at a lower rate when there is very low or very high probability of entry. The intuition behind it is that incumbent has no incentive to deter entry: 1) when there is low probability of entry as entry would not occur; and 2) when there is very high probability of entry as entry would occur anyway. While when the entry probability is at its median, incumbent would be able to deter entry if it launches more products than necessary for profit-maximizing purposes. This non-monotonicity can help us to identify entry deterrence strategies. Moreover, as market size is a good predictor to the entry probability (Scott Morton, 1999), this non-monotonicity also holds between number of products and the market size.

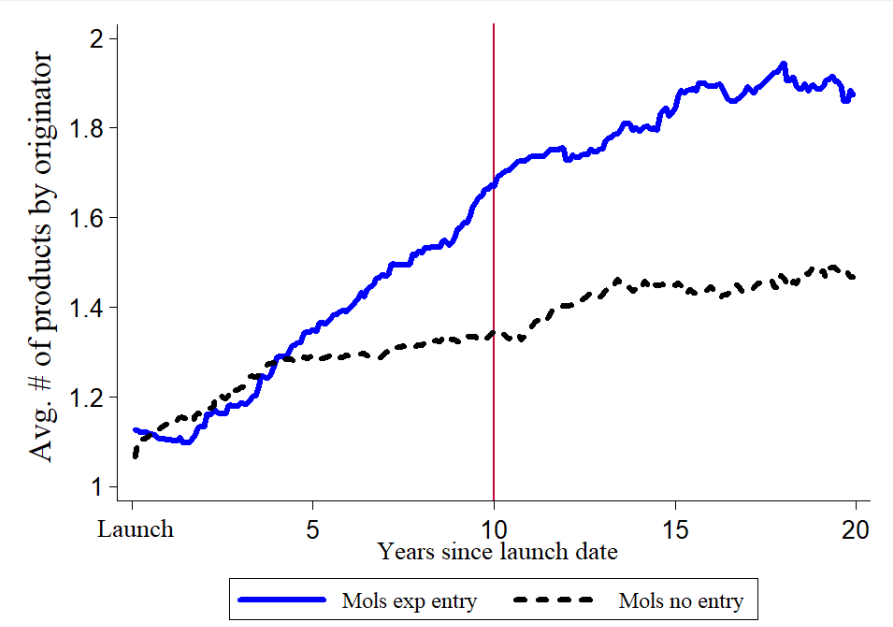
Data details are presented in Section 5. The main dataset we use is provided by IMS, which contains prices, sales, and drug characteristics for each drug sold in the UK between 1996 and 2016. The richness of the dataset allows us to identify incumbents' product portfolios and to determine the market structure before and after the entry of a competitor. The data also provides the launch date for each drug, so that we can identify the originator and entrants. We define a market as a combination of distinct molecule and its therapeutic class (see data section for detail). For our purpose, the originator is defined as the first firm who sells a molecule within an therapeutic class, based on the earliest launching date of that molecule as recorded

FIGURE 2.1: Trend of product proliferation by originators before and after entry by the first competitor.



Note: We focus on a time window that is not too far away from the entry event (i.e. 5 years of monthly data on the left and 5 on the right $-5 < t < 5$). Product varieties is measured as different formulations. The market is approaching the entry by+ the first competitor if it is to the left and the market is in post-entry stage if it is on the right-hand side.

FIGURE 2.2: Trend of product proliferation by originators since launch.



Note: Product varieties is measured as different formulations. The origin is the launch date of the originator. In the 10th year, exclusivity of the originator is likely to expire. The departure of product varieties between two groups starts roughly 5 years after launch date.

in the IMS data. Entrants are the second or later firms that sell drugs containing the same molecule in the same therapeutic class. Thus, we select 733 originators that are at risk of entry for analysis, where we have clear track on whom and when entered into those markets. In our data, 204 molecules (markets) experience entry by the end of our study period.

We find that incumbents indeed introduce additional product varieties when approaching the entry of the first competitor. We measure drug varieties by formulations, as Huskamp et al. (2008) we find it is common for incumbent to reformulate a drug prior to entry. Figure 2.1 illustrates a clear increasing trend in product numbers by incumbents until entry; a trend that fades away after entry.[3] In Figure 2.2, we also show the trends of product varieties of originators for molecules that experienced entry and molecules that do not experience entry since the launch of the original drug. This figure presents similar increasing trend for the former, whereas the trend for the latter group is much flatter. The departure of product varieties between two groups starts roughly 5 years after launch date, and markets that have no entry persistently have fewer products. Market size expansion is, of course, one factor that induces this pattern. In addition, we interpret this configuration as incumbents' entry-deterrence motive. Incumbents proliferate products on the one hand to meet increasing market demand, and on the other hand to launch excessive varieties in an attempt to deter entry.

With the encouraging pattern presented by the raw data, we turn to formal tests in the next chapter. Before that, in the next section, we discuss related literature on entry deterrence.

2.2 Literature review

In this review, we first outline several studies in general IO literature that relate to entry deterrence, we then move to studies with specific focus on the pharmaceutical markets.

2.2.1 General approaches in IO

Although we only focus on product proliferation, this strategy is well connected to a broader literature on entry deterrence. Khemani and Shapiro (1990) argue that incumbents should expect entry if their short-run profit exceeds long-run profit. However, potential entrants do not always know incumbents' profitability. Thus, whether an entrant will enter or not depends on its belief about the profitability of the incumbent, or more precisely the marginal cost, as the price is observed (Martin, 2010). The author claims this uncertainty gives incumbent the opportunity to deter entry by mimicking the behaviour of a low marginal cost firm, which is often done

[3] The discrete jump at the time of entry by competitor represents the originator launching an additional generic version in the same month as the competitor. We do not observe exact dates only months, so launch maybe in fact a few days before or after entry by competitor.

by a commitment to the output level prior to entry. For instance, incumbent can sign a long-term contract with buyers/wholesalers. If the marginal cost of production is small but the fix cost of building capacity is high, the incumbent can also set up a capacity level and commit to produce at full capacity. Dixit (1980, 1982) shows that the commitment can be created by investing in sunk cost prior to entry. If the cost is not recoverable or at least partially, the incumbent can signal a credible commitment of the output level post entry, and so deter entry. However, such strategy is not costless, as the output level is not the one that maximizes profit, which means the incumbent sacrifices short-run profit in order to gain profit in the long run by deterring entry. Moreover, if the profit earned in post entry game is higher than that in deterrence game, the incumbent will choose to accommodate entry.

Another strategy is to commit to play aggressively if entrants attempt to enter, i.e., predatory behaviour, which limits expected profit for entrant (Demsetz, 1982; Harbord and Hoehn, 1994). However, the success of this strategy is conditional on its credibility, which depends on entrants' information on incumbent's cost. In the famous chain-store paradox model, Selten (1978) shows that if an incumbent operates in several markets and entry can happen in each single market sequentially, and if the entrants have complete information and have full calculating ability to work out the full game, playing aggressively cannot be a credible strategy. Because the entrant knows that the incumbent will be better off if it does not deter entry in the last market, and the second to the last and so on, until in the very first market. He argues that this reasoning is counter-intuitive, as it is very unlikely that entrants have full information. Indeed, Fudenberg and Tirole (1986) and Kreps and Wilson (1982) show that if entrants have imperfect information, predation strategy can be credible. In addition, incumbents can even strategically veil the true information to deter entry. The chain-store model is applicable to pharmaceutical market, as an incumbent is likely to have many original drugs in multiple therapeutic classes that face entry sequentially.

The entry deterrence effects of product proliferation are considered to be powerful from at least three aspects. First, Church and Ware (2000) claim that it reduces size of (sub)market for each product, and thus, enhances the effect of economies of scale. It can either make the submarket insufficient for an entry, or make potential entrants believe that they will face aggressive competition if they dare to enter. Schmalensee (1978) uses a spatial framework (Salop circular model) to model competition between an existing product and a new product. Since the location of the existing product would not change, the new entrant would expect suffering from the initial crowding if it enters, which lowers his willingness to enter. Moreover, he argues that all entry deterrence strategies should be credible otherwise, their deterrent effect would cease. Therefore, incumbents can only deter entry by expanding products before the threat of entry appears, while it is not credible for them to launch new products to surround an entrant after entry takes place, as that would lead to 'mutually damaging warfare'. On the other side, Judd (1985) argues that only when

exit cost is high, can product proliferation deter entry, as incumbents can always choose to withdraw a product ex post entry if the cost of removing that product is low. In fact, exit barriers are common, which exist if an incumbent cannot move its capital into another activity easily, such as specific assets for a production technology (Caves and Porter, 1976, 1977). Therefore, product withdrawal by incumbent is unlikely to be costless and thus, product proliferation may be credible to deter entry.

Second, Gilbert (1989) argues that product proliferation can imply a barrier to entry because it generate cost advantages for incumbents over entrants. Imitating an extra brand can induce higher marginal cost for an entrant, as economies of scale or scope are obscure for a beginner in a market. Some empirical evidence support this argument. Kekre and Srinivasan (1990) jointly examine the effect of product line extension on market share, price, cost, inventory and profit. They find that a broader product line leads to a higher market share, increased profitability as well as reduced marginal cost.

Moreover, Caves and Porter (1977) highlight that proliferation can reduce cross-elasticities of demand between incumbent's products and potential entrants' products, i.e., instead of shifting demand to entrants' products, incumbents can shift demand from one to another product within its product portfolio. As a result, potential entrants have to make extra effort to offset the "goodwill" assets of the incumbents, and thus it either increases entrants' costs or reduces their potential market size. This argument links to the third effect of product proliferation that it can help incumbents create reputation and loyalty to consumers, and so limit demand for entrants (Bain, 1956; Demsetz, 1982; Harbord and Hoehn, 1994; Schmalensee, 1982).

Additionally, Bonanno (1987) suggests that product positioning may also deter entry. He shows that under the threat of entry, incumbent firms may locate their product differently than the case where the monopoly is protected. He also shows that the incumbent may launch 'strictly more' products when facing the threat of entry than the number of products that is actually needed to deter entry. Moreover, competition among incumbents may influence entry. Donnenfeld and Weber (1995) argue that rivalry between incumbents may facilitate entry, as firms may offer limited quality and engage in entry deterrence, while collusion among incumbents may accommodate entry.

However, evidence from empirical studies is mixed. Lieberman (1987) examines capital investment behaviour between incumbents and entrants in 38 chemical industries and find no difference between their strategies. This reads as incumbents do not occupy excessive capacity to deter entry. Ghemawat and Caves (1986) also find that profitability of capital-intensive industries is not higher than others, opposite to the entry deterrence theory. Hall (1990) analyses DuPont's behaviour in the TiO_2 industry. She finds that DuPont's marginal cost were decreasing in its capacity. She concludes that although DuPont's behaviour was indeed a strategy to increase capital pre-emptively, its strategy was consistent with profit maximization in every period and thus should not be discouraged.

On the other hand, some studies have documented incumbents' strategic responses when facing entry threat. For instance, Geroski and Toker (1996) find that firms invest in innovation and advertising to maintain their leadership, which reduces market turnover and deters entry. In the case study of the Southern Bell Telephone Company, Weiman and Levin (1994) document that this company dramatically expanded capacity prior to its patent expiration; it increased geographic reach of its system from 2000 to 8600 pole miles, and toll wire coverage from 5000 to over 55000 miles. Similarly, Conlin and Kadiyali (2006) also find that hotel capacity in Texas, US is positively correlated with market concentration, suggesting they expand capacity to deter entry.

Bergman and Rudholm (2003) observe that limiting-pricing is used to deter entry in the Swedish pharmaceutical market, as incumbents lower their price strategically in response to potential entry when their patent is about to expire. Seamans (2013) studies the price cut of U.S. cable TV when incumbents face both entry and information asymmetry. Incumbents lower price to emit a signal that their production costs are low. However, if entrants have full information on the incumbents' cost, limit price can no longer work. He then distinguishes two kinds of entrants who have/don't have cost information and doesn't find significant difference. Cookson (2017) uses difference in differences model to test whether casinos will invest in physical capacity to deter entry when they face entry threat. He finds that casinos invest more to expand floor space (physical capacity) when they are informed about an entry plan near to them (within 100 miles), which provides evidence to strategic entry deterrence. Goolsbee and Syverson (2008) suggest a way to identify threat of entry from actual entry. They use passenger airline data and define the threat of entry when South-western airline starts to operate in both end points but before it actually flies the route itself. They find that incumbents cut fare significantly even when they only face the threat of entry.

Moreover, empirical support on advertising as entry barrier is also inconclusive. Some works (Gasmi et al., 1992; Thomas, 1999) observe that incumbents respond to entry aggressively with advertising. Bunch and Smiley (1992) find that advertising can be used as a way to build consumer loyalty by incumbents, and therefore may deter entry. Sutton (1991) suggests advertising can raise the fixed cost of entry, lower incumbent' marginal cost, and so deter entry. Paton (2008) surveys 800 advertising managers and he discovers that nearly 25 percent of them state that one aim of their advertising is to deter entry. Geroski (1995) finds similar results. However, other studies, e.g., Kessides (1986), Roberts and Samuelson (1988), and Scott Morton (2000) do not find supportive evidence.

2.2.2 Entry deterrence in pharmaceuticals

In the pharmaceutical market, originators face entry threat from both generics and 'me-too' or follow-on drugs. Like other industries, generics tend to enter markets with higher profitability more and quicker, see for example, Reiffen and Ward (2005)

and Saha et al. (2006). Competition in this industry appears to increase over time. In the case of US, Grabowski and Kyle (2007) observe that the Hatch-Waxman Act significantly reduces effective monopoly years of the originators. The authors find that generic firms challenge originators' patent more often and earlier with paragraph IV filings, even if the probability of winning the lawsuit is low, once successful they can make large profit. They find this phenomenon is stronger when market size is larger, and they call it 'Prospecting'. First mover advantages is significant in this industry. Andrade et al. (2016) find that follow-on drugs face fiercer competition, and market share is negatively correlated with entry order. Yu and Gupta (2014) note that early generic entrants enjoy substantial higher profit and market share than latter entrants. In addition, Gallant et al. (2010) suggests that a generic firm's entry decision is affected by technical spillovers, and whether or not it enters a new market depends on its experience and profits in other markets. They find on average, each former entry reduces cost by 7% at the next entry.

On the other hand, researchers observe that entry of generics mainly affects originators' price strategies and advertising. Caves et al. (1991) note that in the US market, generic entry leads to small fall in branded drug's price, and that entry of other generics depresses the price of former generic drugs, whereas they also find that prices of branded drugs tend to increase during the time between patent expiration and entry events. Market share of branded drugs do shift to entrants, while the magnitude seems small compared to the big price discounts offered by generics. Berndt et al. (2003), Frank and Salkever (1997), and Grabowski and Vernon (1992) also find that instead of competing with generics on price, incumbents tend to increase price to segment the market. By doing so, incumbents can maintain brand-loyal and relatively less price sensitive consumers. Regan (2008) suggests that each generic entrant leads to an average 1% increase of the branded price. Lu and Comanor (1998) claim that launch price is more likely to be challenged by competition from branded drugs but not by generics, which may lead to higher launch price. They also document that branded products employ a skimming strategy where prices decline moderately over time, while by contrast, generics adopt a penetration strategy under which prices increase gradually. DiMasi (2000) finds similar pattern that drugs are priced higher if they have gains over existing therapy, and are priced at discount otherwise. As most drugs are launched with discounts, he argue that entry directly reduces pharmaceutical expenditure.

As for advertising, Caves et al. (1991) find that originator's advertising expenditure starts to decline prior to entry. Nevertheless, Huskamp et al. (2008) observe that although promotions of the original drug decline before entry, that saving is shifted to advertise a reformulated version of the original drug before generic entry. They argue that reformulation appears to be a common strategy of the originator to extend market exclusivity and maintain market share.

Entry of me-too drugs also raises concern. Hollis (2004) claims me-too drugs may reduce the incentive to undertake pioneering innovation, and they may waste

resources if their incremental benefits are small. Moreover, Arcidiacono et al. (2013) show evidence that me-too drugs are likely to increase pharmaceutical spending, partly because they introduce variety to consumers. On the other side, Grabowski and Vernon (1990, 1994) and Grabowski et al. (2002) claim that investment in pharmaceutical is risky. They find the distribution of returns for newly introduced drug between the two periods 1980-1984 and 1990-1994 are both highly skewed. Their sale revenues peak between the 10th and 13th year, and decline gradually thereafter. Moreover, they find that only one third of the new drugs have present values in excess of average R&D costs, and the top products account for more than half of the returns generated by their cohorts. DiMasi and Faden (2011) and DiMasi and Paquette (2004) argue that me-too drugs are not just low-cost imitation of the originator. In many cases (one in five), they even have superior rating (higher therapeutic effectiveness) than the originator. They also find that competition in pharmaceutical industry is increasing as monopoly periods for originators diminish over time.

The welfare effects induced by the entry of me-too and generic drugs have been discussed in empirical works. Bokhari and Fournier (2013) focus on drugs for the treatment of attention deficit hyperactivity disorder (ADHD). They find that entry of me-too and generic drug can induce large welfare gain by introducing varieties and reducing prices. Branstetter et al. (2016) quantify the welfare effects of generic entry via Paragraph IV challenges. Using hypertension drug sales data between 2000 and 2008 in the US, they find that consumers gain $ 42 billion and a producers lose $ 32.5 billion from early entry, accounting for a social welfare gain of $ 9.5 billion.

Importantly, literature has shown that originators delay or deter entry of generic competitors strategically. Pay-for-delay, launching of authorized generics (AG) and evergreening/product hopping are commonly used strategies. Pay-for-delay settlement, refers to the payment that patent holder pays to a generic entrant not to enter the market. This agreement is often between the patentee and the first patent challenger prior to patent expiration, and there are large number of cases in the US under the Hatch-Waxman regime. The reward of successful settlement is obvious. If the patentee can delay the challenger (typically a generic producer) from early entry if the patent were to be declared valid, it can enjoy a longer protection of the patent (Hemphill, 2006). In a relevant paper, Bokhari et al. (2017) show why pay-for-delay can be a equilibrium outcome. In the EU, although the first challenger does not enjoy statutory 180-days exclusivity, pay-for-delay cases are not rare (EC, 2009). In addition, strategy to launch (or the threat to launch) authorized generics by the patentee or another authorized third party, may facilitate pay-for-delay deals.[4]

Entry deterrence strategies that directly link to the object of this research are launching of AG and evergreening, as these strategies increase product varieties.

[4]Estimated by Federal Trade Commission (FTC), authorized generics can reduce first filer's revenue by 40-52% during the exclusivity period, and by 53-62% in the following 30 months (FTC, 2011). Therefore, the first filer may not reject pay-for-delay settlement in order to avoid direct competition with the authorized generics.

Hollis (2003) and Hollis and Liang (2007) argue that authorized generics can diminish incentives generated by Hatch-Waxman act for generic firms to challenge brand drug patents, which may deter entry and lead to higher price. Indeed, they find prices for brand drugs in AG markets increase more than those in no-AG markets do. Reiffen and Ward (2007) find that the equilibrium price for market with AG is higher than that in market without AG, suggesting that AG can increase the brand firm's profits. They find that this effect is stronger in small size markets. By contract, Berndt et al. (2007b) claim that despite increasing rate of authorized generics, the rate of Paragraph IV certifications challenging is higher than before, and thus, there is no evidence on the entry deterrence effect of authorized generics. Berndt et al. (2007a) further show that authorized generics can result in lower generic prices, and benefit consumers, whereas its longer run effects on share and price is at minimum. Similarly, Appelt (2015) give evidence that whether incumbent launch authorized generics depends on market size and substitutions from nearby market, which, however, have no significant impact on entry of independent generic drugs.

Evergreening or product hopping involves the originator reformulating the product in a way such that a generic version is unable to substitute it (Carrier and Shadowen, 2016). At the meantime, the originator may invest heavily to convince doctors to switch to updated versions, and may withdraw older ones from the market. Consequently, the entry (or import of) generic versions may be delayed because the reference drug is no longer available in the market. In addition, even though the generics entered, pharmacists may find it difficult to substitute a generic version to the updated branded one, as they are not substitutable. Carrier (2010) argues that product hopping may jointly work with pay-for-delay settlements. By delaying generic entry, such settlements can give the originator the opportunity to switch the market to the updated versions. However, Hemphill and Sampat (2012) argue that despite of increasing cases of incumbents' evergeening strategies, early challenges through Paragraph IV can maintain competition in the market. The primary patents of a product are unlikely to be challenged, while later expiring and lower quality patents are, limiting the effectiveness of evergreening. They find that effective years of monopoly is stable across therapeutic classes and over time.

In summary, entries in pharmaceutical market are affected by many factors and they, either by me-toos or generics, can steal a substantial amount of market share and profit from the originators. Hence, incumbents are motivated to act against them, but with varies strategies. In the first two chapters, we will focus on product proliferation as the possible strategy to deter entry. Background information of the UK and EU legislation system on pharmaceuticals will be provided in the next section and will be used to construct the variables of interest.

2.3 Legal protection in the EU and UK

Market authorizations and patents provide legal protection for the originator to exempt it from generic competition for a period of time. Since 1965, all pharmaceutical products need market authorization (MA) prior to launch, to ensure safety and effectiveness based on the Council Directive 65/65/EEC (and Medicines Act 1968 in the UK). In order to get MA, all applicants (originators) normally have to provide information from pre-clinical test and human clinical trials. However, given the understanding that replication of such data can be expensive, generic entrants are exempt from such requirement and can refer to the originators' data when applying for market authorization of their generic versions of the same molecule - as long as they can provide that their generic version is bio-equivalent to the originator.

Furthermore, the intellectual property right, based on Article 39.3 of the TRIPS Agreement, protects the data supplied by the originators against 'unfair commercial use'. It implies that in some countries such data should not to be used to authorize generic versions. Test and clinical trial data were protected as trade secret until 1987 in the European community, when the 87/21/EEC Directive (and the 65/65/EEC Directive amendment) was introduced. This amendment protects the originator's data for a pre-determined period, during which generic entrants cannot refer to such data to get market authorization. This data exclusivity period varies from 6 or 10 years across European countries. In the UK, data exclusivity consists of 10 years, referring to the official report of the Parliament in 30th June 1987 (Cook et al., 1991). The period of data exclusivity starts from the date of first market authorisation registered anywhere in the European community. Although this data exclusivity runs in parallel and irrespective of patent production, it often extends the monopoly position of the originator beyond the patent expiration, as ten or more years can elapse between the filling of primary patent and the launch date (Cook et al., 1991; Kyle, 2016). Moreover, data exclusivity only protects novel substance (molecules), while subsequent improvements to a drug, such as new therapeutic indications, dosage strength, or formulations, are not granted for an additional period of protection.[5]

Pharmaceutical companies can get licence either from national authorization in each member states of EU or the centralized agency, European Medicines Agency (EMEA), since 1995 when it was created. The difference between the centralized and decentralized licensing regime is that drugs can be sold in all member states if they are licensed from EMEA, while they can only be sold in a specific country if they get licence from the local agency. In addition, under the mutual recognition process, preceding countries that received MA applications do not have to start their own review but can refer to the decision by the first agency that approves the drug (Kyle, 2016). In the UK, Medicines and Healthcare products Regulatory Agency (MHRA) is currently the agency that is responsible for medicine market authorization. Moreover,

[5]The Queen v The Licensing Authority established by the Medicines Act 1968 (acting by The Medicines Control Agency), ex parte Generics (UK) Ltd, The Wellcome Foundation Ltd and Glaxo Operations UK Ltd and Others. Case C-368/96. European Court Reports 1998 I-07967.

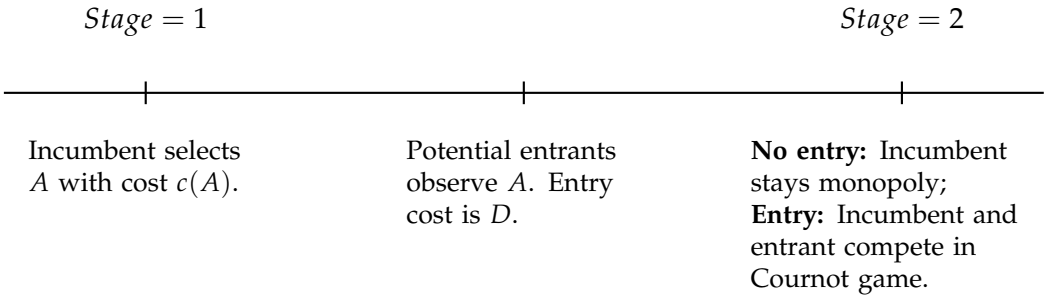
National Institute for Health and Care Excellence (NICE) also assesses drug's cost effectiveness and issues recommendations for the National Health Service (NHS) in England.

One notable change in the EU market authorization system is the harmonization of the '8+2+1' formula introduced in 2001/83/EC Directive and amended by the follow-on Directive 2004/27/EC and Regulation 726/2004/EC. Market authorization applications made from November 2005 and onwards will follow this new rule. Under this new system, all member states of EU will have harmonised 8 years of data exclusivity from the first authorisation date in the EU, followed by 2 years of 'market exclusivity'. This 10-year protection can be extended by one additional year if a 'significant new indication' or 'significant clinical benefit over existing therapies' is granted for this relevant medical product. Although generic entrants cannot market their versions during data exclusivity and market exclusivity period (and possibly the additional year), they can make use of originator's pre-clinical and human clinical trial data after the first 8 years of data exclusivity. Comparing the old and new systems in the UK, the overall protection period for the originator remains 10 years. However, generics may apply for MA two years in advance under the new system. Although MA cannot be issued before the expiration of market exclusivity, the new system may reduce the gap between the expiration of market exclusivity and the launch of generic products, as they can start preparations for launch two years earlier (Kyle, 2016). Moreover, as the old system, the new system does not consider additional strengths, formulations, administration routes, presentations, and variations and extensions as new sources for another market authorization other than the initial one.

Running in parallel with the market authorization system is patent protection. In the EU, patent life lasts normally for 20 years since filing during which the originator has an exclusive right to prevent generics from marketing their products. However, the effective patent protection period for drugs marketed after MA is generally short, as it may take a long time for firms to get enough data for MA. In order to compensate for the loss of patent protection and to protect innovation in the pharmaceutical market, Supplementary Protection Certificate (SPC) was introduced in 1992 in the EU.[6] SPC offers same protection as the basic patent (*sui generis*) and it extends patent life of medicines up to 5 years since patent expiration or 15 years since market authorization, whichever is less. Moreover, as noted in Kyle (2016), the EU regulators tend to prevent the linkage between patent and exclusivity. It means that regulators may review generics even if the originator may still have some valid patents. Since investing around a secondary patent is easier than a primary product patent, generics may enter earlier.

[6]Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products entered into force in 1993. It has been replaced by Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products.

FIGURE 2.3: Strategic investment and entry model



One side effect of this de-linkage is that patent information is difficult to link to drugs in the UK/EU other than in the US. Although both regulatory data protection and patent aim at protecting the innovation of the originator, the interaction between MA and patent (and SPC) is complex, as distinct laws govern them. One medical product can have several patents, while only one MA will be granted. Therefore, how to implement patent production to the entire product depends on specific conditions, which vary across different cases. Since we do not obtain patent information for our products, we rely on MA information and firms' launch date as recorded in IMS to determine when a molecule (or market) is open for generics to entry.

2.4 Model of entry and strategic entry-deterrence

In this section, we follow Ellison and Ellison (2011) to use a simple and highly stylized theory model to illustrate the entry game. We use this model to motivate our empirical estimation and identification of potential entry deterrence strategies, which will be presented in the next chapter. This game has two stages. In the first stage, the incumbent (firm 1) decides whether to invest A with cost $c(A)$. Potential entrant can obverse incumbent's investment at some time point between stage 1 and stage 2 and decides whether to enter the market with entry cost D in the second stage. The incumbent and the entrant have to share the market if entry takes place and are assumed to play Cournot game and each earn π_1^d and π_2^d accordingly. If entry does not take place, the incumbent will remain as the monopoly and earn π^m. Figure. 2.3 summarizes the timing of the game.

In the standard entry literature, a firm will enter the market as long as its expected payoff earned at stage 2 ($E(\pi_2^d)$) is larger than its entry cost,

$$E(\pi_2^d) - D \geqslant 0 \tag{2.1}$$

Although this condition is simple and intuitive, it fails to consider the question that why entry sometimes happens tomorrow but not today. Delayed entry is common in pharmaceutical markets, as generics do not always enter immediately when legal protection expires. A simple answer is uncertainty about future profit. Entrant will

be more likely to wait when uncertainty is large. The logic is put forward by Titman (1985), who illustrates why a firm decides to delay the development of a vacant land. He shows that when uncertainty of the optimal building type in the future is high, the firm is more likely to delay a decision to develop, as the option to make decision in the future is more valuable. The question of the option to wait is a more frequent subject of interest in finance and management, where various authors argue that in presence of uncertainty of future cash flows, it is valuable for firms to delay irreversible (at least partially) investment decisions, with the hope of gaining higher payoffs in the future. The options of investing and not investing can be seen as two assets. If the market were to be complete, one could hedge two assets at an optimal time (Dixit, 1989; McDonald and Siegel, 1986; Weeds, 2002). To derive a closed form solution, most models require expected future cash flows to be stochastic and to follow a geometric Brownian motion. Moreover, one should also notice that entry cost D might include costs that go beyond the fixed cost incurred at entry, e.g., opportunity cost of not entering (Folta and O'Brien, 2004). Therefore, D does potentially vary overtime prior to entry and may induce delay of entry. Reasons discussed above justify why we use hazard rate models to estimate entry in the next chapter.

Having considered the entrant's decision, we turn to incumbent's reaction. One essential assumption to generate a testable hypothesis for empirical work is that entry is not deterministic, and the incumbent does not know the entry cost D with certainty; otherwise the incumbent can always deter entry by lowering entrant's expected payoff (Ellison and Ellison, 2011). Therefore, incumbent's belief about entry cost of a first entrant is stochastic with cumulative probability $F(D)$.

In stage 2, firms set quantity to maximize profits. The incumbent either takes monopoly profit if no entry, or shares the market with the entrant as duopolist if entry takes place. The idea of this model is that incumbent's investment A can have potentially two effects: it can help incumbent to maximize profit as well as influence rival's entry probability F by reducing rival's expected profit during post-entry competition. It may also induce uncertainty and delay entry as explained previously.

Suppose the incumbent earns monopoly profit $\pi^m(A) \equiv \pi^m(x_1^m(A), A)$ if it remains as monopoly, and it earns duopoly profit $\pi_1^d(A) \equiv \pi_1^d(x_1^d(A), x_2^d(A), A)$ if enter occurs. The rival can earn $\pi_2^d(A) \equiv \pi_2^d(x_1^d(A), x_2^d(A), A)$ if it enters. To maximize the expected profit, the incumbent has to choose the optimal investment (A) and output levels in each situation ($x_1^m(A)$ and $x_1^d(A)$):

$$\max_{A, x_1^m, x_1^d} E(\pi_1) = F\left(\pi_2^d(A), D\right)\pi_1^d(A) + \left[1 - F\left(\pi_2^d(A), D\right)\right]\pi^m(A) - c(A). \quad (2.2)$$

In order to have a unique equilibrium solution, we assume that $\pi^m(A)$ and $\pi_i^d(A)$ are differentiable and concave, and $c(A)$ is increasing in A at an increasing rate (i.e. $c'(A) > 0, c''(A) > 0$). By solving the first order conditions and subsequent best response functions, it is simple to find the optimal level of x_1^m, x_1^d and x_2^d. Suppose

their optimal levels are x_1^{m*}, x_1^{d*} and x_2^{d*}, then the optimal investment level A^* is the solution, satisfying the following first order conditions:

$$0 = \left\{ F\left(\pi_2^{d*}(A^*)\right) \frac{\partial \pi_1^{d*}(A^*)}{\partial A} + \left(1 - F\left(\pi_2^{d*}(A^*)\right)\right) \frac{\partial \pi^{m*}(A^*)}{\partial A} - \frac{\partial c(A^*)}{\partial A} \right\} + \left[\pi_1^{d*}(A^*) - \pi^{m*}(A^*)\right] f\left(\pi_2^{d*}(A^*)\right) \frac{\partial \pi_2^{d*}(A^*)}{\partial A}. \tag{2.3}$$

To simplify the notation, we suppress D in the analyses that follow. Let denote the first term in brackets by $g(A^*)$, which can be considered as the investment without strategic entry-deterrence incentive. This means that the incumbent sets $A = A^*$ to maximize profit in stage 3, taking the entry probability $F\left(\pi_2^{d*}(A^*)\right)$ as given. Then let $h(A^*)$ denote the second term, which represents the motive for strategical investment to fight entry. Such incentive increases when the difference between the monopoly and duopoly profit gets larger, and when the entry probability mass is higher. Incumbent turns to over-invest if investment lowers the rivals expected payoff ($\partial \pi_2^{d*}(A^*)/\partial A < 0$) and under-invest in the opposite case.

A straightforward way is to test whether the optimal levels of investment A^* differ under different incentives. This is not easy in practice. Ellison and Ellison (2011) suggest an indirect way to test the existence of the entry-deterrence term $h(A^*)$, whose logic is the following. Suppose there is a market characteristic z (e.g. market size) that is a common factor between investment $A(z)$, investment cost $c(A(z), z)$ and profits $\pi(A(z), z), \pi \in \{\pi^m, \pi_1^d, \pi_2^d\}$. Then assume that under certain conditions, A^* is monotonically increasing (or decreasing) in z if the incumbents has no entry-deterrence incentive. If the data reveal a non-monotonic relation between A^* and z, then this non-monotonicity has to be introduced by the incentive term, $h(A^*)$.

On the other hand, suppose the incumbent has no entry-deterrence incentive, then the optimal level of investment A^* should satisfy $g(A^*) = 0$. Differentiating $g(A^*)$ with respect to z, it can be shown that the sign of dA^*/dz is determined by two terms:

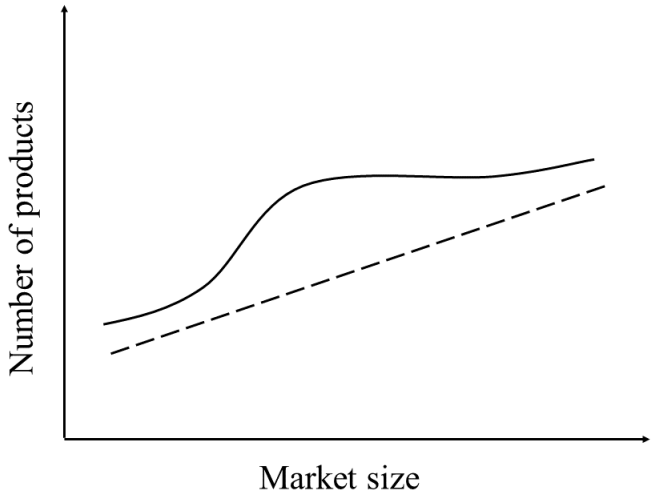
$$F(\pi_2^{d*}) \cdot \frac{\partial^2 \pi_1^{d*}}{\partial z \partial A} + \left(1 - F\left(\pi_2^{d*}\right)\right) \cdot \frac{\partial^2 \pi^{m*}}{\partial z \partial A} - \frac{\partial^2 c(A^*)}{\partial z \partial A} \tag{2.4}$$

and

$$\partial \pi_1^{d*}/\partial A - \partial \pi^{m*}/\partial A. \tag{2.5}$$

Further, suppose the rival's expected profit π_2^{d*} is increasing in z (i.e. $\partial \pi_2^{d*}/\partial z > 0$), dA^*/dz is monotonically increasing (decreasing) if both terms are positive (negative). The first term (Eq. 2.4) is positive when z is increasing, in which case the marginal benefit from investment is raising more than the increase of marginal cost

FIGURE 2.4: An illustration of non-monotonicity between number of products by incumbent and market size



of investment.[7] The second term (Eq. 2.5) is positive if z is increasing, and therefore the marginal benefit from increased investment is higher in duopoly than monopoly. Ellison and Ellison (2011) provide a detailed discussion about such conditions.

We take product proliferation as a specific example of investment. Intuitively, conditions for monotonicity normally hold in the pharmaceutical industry. When market size (z) increases, entrants are likely to expect higher profits from the market. Suppose one more product variety (say, a new presentation, and strength or pack size) can benefit a certain proportion of patients. Benefit from product proliferation is then proportional to market size, while the marginal cost of developing such new product variety is not (first term > 0). Moreover, suppose the incumbent can have certain product varieties that entrants cannot easily copy, such 'unique' set of varieties can benefit the incumbent more when it competes with entrants, than if the incumbent is in a monopoly situation (second term > 0). Therefore, if the incumbent has no entry-deterrence incentive, we would expect to find a monotonic increasing relation between numbers of products before entry with the market size. Figure 2.4 illustrate the non-monotonic relation between number of products by incumbents and the market size if entry deterrence motive presents, suggested by the theory model.

2.5 Data

The main dataset we use is the 1996-2016 British Pharmaceutical Index (BPI) series provided by Intercontinental Marketing Services (IMS), which covers transactions of

[7] In fact, first term (Eq. 2.4) can be zero when investment cost is proportional to z and profit is proportional to z as discussed in corollary 1 in Ellison and Ellison (2011). Under this condition, the sign of dA^*/dz is solely determined by second term (Eq. 2.5).

pharmaceutical products from wholesalers to pharmacies in the UK between June 1996 and May 2016. The data set includes product characteristics such as manufacturer name (unless it is a generic), generic or branded specification, molecule, formulation, strength, and product and pack launch date in the UK. In addition, we obtained secondary data on authorization dates from EMEA and MHRA to validate the product launch dates as recorded in the IMA dataset. In this section, we describe key features of originators and entrants.

2.5.1 Market, originator and entrant

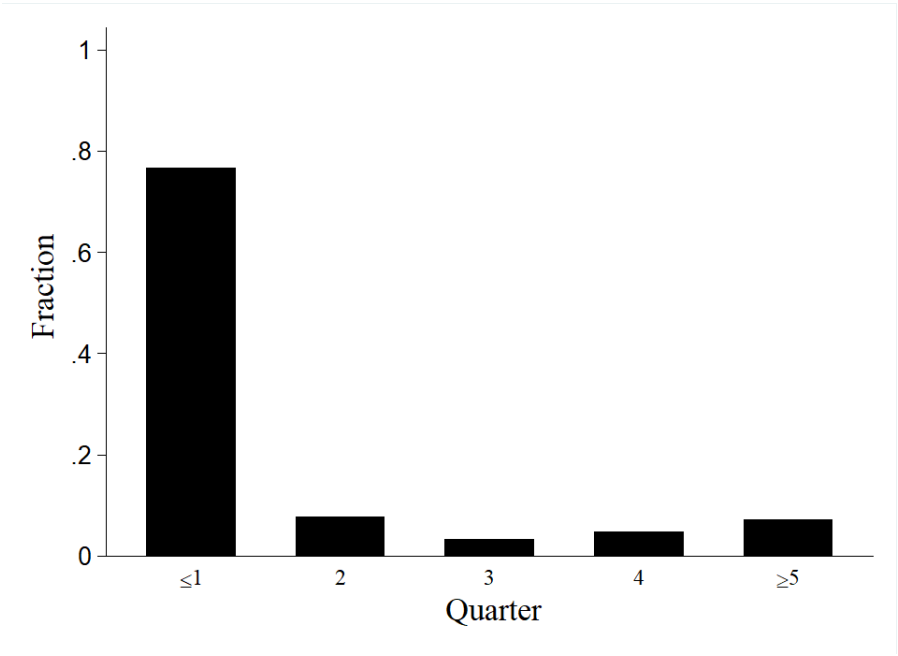
We define a market by drug's main active molecule(s) and its associated three-digit anatomical therapeutic chemical code (ATC3).[8] Drugs are in the same market if their molecules and ATC3 code are the same. As discussed in the last section, the grant of market authorization and the substantial protection of a drug are generally based on its molecule, but not on new updates, i.e. new formulations, route of administration, dosage strength and extensions. Including ATC code in market definition is important, as one molecule may have multiple ATC codes if it is available in drugs with clearly different therapeutic uses. For example, chloramphenicol (an antibiotic) has more than one ATC3 codes. The therapeutic use of its eye drop is clearly different from that of its tablet that is for systemic use. Therefore, it would be more appropriate to consider them as different markets.

The originator is the first firm to obtain market authorization of a molecule within an ATC3 class. All later firms are considered as competitors, as they in fact have to decide whether to enter and compete with the first firm. However, identifying the originator is difficult. EMEA and MHRA do not have clear indication for originators in their data and in addition, some historical data is missing. EMEA only accepts applications since 1995 and not all drugs apply MA through EMEA. MHRA data only contains drugs that are still in the market by the time the data is extracted from their system (June 2017), so that we do not have information on drugs that were withdrawn from the market before that date. On the other hand, IMS data records product launch date for each drug in the UK, which could be a proxy for the MA granted date. Product launch date is the first month that IMS records sales of a product, which should always be later than MA grant date but with limited delay. Launch date for drugs with identical molecule by one firm may vary, as one formulation might be released earlier than others. We assign the earliest launch date, among all drugs by one firm with same molecule, to the MA date of that firm in that market. The originator of a market, therefore, is the firm with oldest MA date.[9]

[8] ATC code is assigned to active substances contained in a drug based on their therapeutic indication by the WHO. It has 7 elements and is classed at 5 levels: the main group (first letter), therapeutic group (two digits), pharmacological subgroup (second letter), chemical subgroup (third letter) and the finest subgroup of active substance (another two digits). ATC3 is at pharmacological subgroup level.

[9] In rare cases, more than one firm has the same original market authorization date for the same molecule because of mergers and acquisitions between firms, joint adventures or transfer of product lines between firms. In either case, the product launch date might be listed under both firms' names. We check each case manually and merge sales of both firms.

FIGURE 2.5: Difference in quarters between real product launch date in IMS and MA date in EMEA for matched originators.



To check the reliability of IMS's launch date as an indicator of market entry, we compare the launch date for originators in IMS data with their real MA records in EMEA data if they applied MA through EMEA. In Figure 2.5, we plot the time difference in quarters between the two dates. For 205 molecules whose MA were granted by EMEA, we find that dates are matched ($\leq$ one year difference or 4 quarters) for over 90% cases (190/205), and 157 molecules of them are launched in the UK within the first quarter. Therefore, we are confident that product launch date in IMS data is a reasonable proxy for real MA date and we rely on it in our analysis.

After identifying the MA date for each firm and market, it is possible to identify the entrant, who is the first competing firm that enters the market after the originator. Those competitors could be either generic firms, or the manufacturers of follow-on patented drug of the same molecule, as both types of entrants can significantly reduce the profit of the originator. Furthermore, we only consider entry probability for a market but not for each individual entrant, because one new firm is sufficient to end originators' monopoly position and induces a structural change of the market. In the entry probability section, we explain how to integrate hazard rate from individual to market level.

2.5.2 Market at risk and entry events

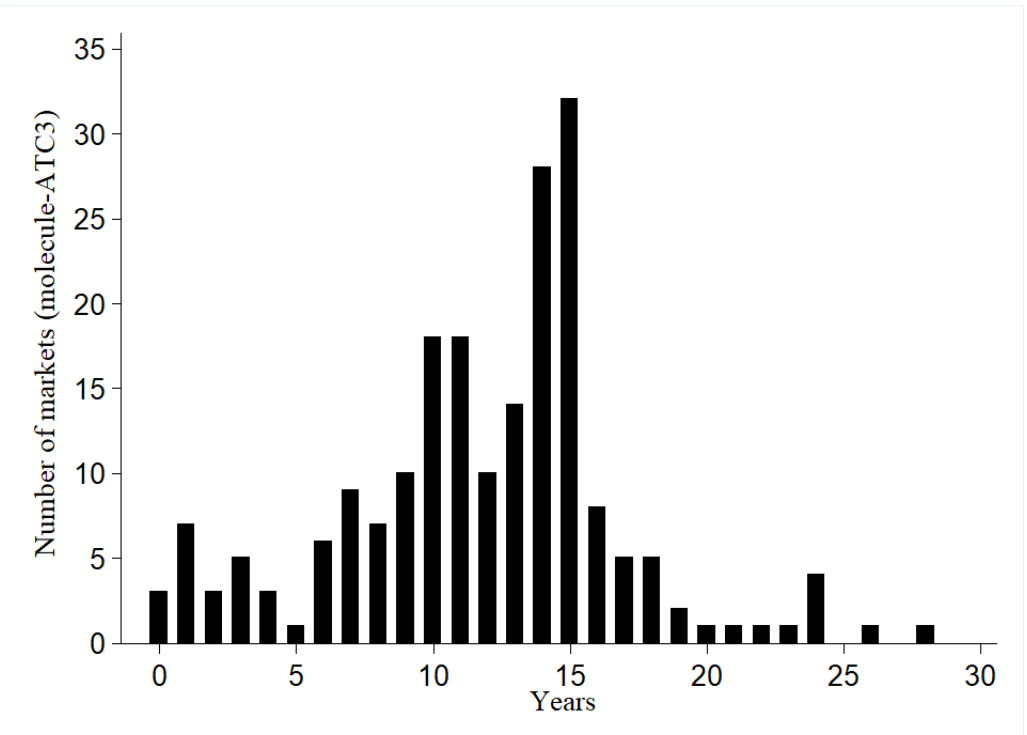
As mentioned before, entry of a competitor in this market can either by other branded firms who launch a product in the same molecule-ATC3 class or by generic variants of the same drugs. We consider either to be an entry event.

TABLE 2.1: Molecules at risk and entry events by ATC classes

ATC Code and Description		MA of the originated molecule			
		1986 - 2006		Since 1986	
		At risk	Entry	At risk	Entry
A	Alimentary t.& metabolism	45	18	73	19
B	Blood + b.forming organs	27	3	43	3
C	Cardiovascular system	61	33	72	34
D	Dermatologicals	25	6	34	6
G	G.u.system & sex hormones	33	16	41	16
H	Systemic hormones	12	2	17	2
J	Systemic anti-infectives	65	17	81	17
K	Hospital solutions	9	1	9	1
L	Antineoplast+immunomodul	54	21	101	21
M	Musculo-skeletal system	35	16	42	18
N	Nervous system	81	50	111	51
P	Parasitology	4	0	4	0
R	Respiratory system	30	7	44	7
S	Sensory organs	30	4	41	5
T	Diagnostic agents	4	1	5	1
V	Various	7	3	15	3
Total		522	198	733	204

Note. J07 Vaccines are excluded. Among all entry cases, there are 11 entries before the start of our study period (June 1996).

FIGURE 2.6: Difference in entry years between the originator and the first competitor.



Since our study period is between 1996 and 2016, not all molecules can be included in the risk set. We exclude original molecules that were launched before 1986, as their data protection could have already expired before the study period begins, but also because it is difficult to construct originator's strategic variables and market structure prior to entry threat. Similarly, molecules that got MA after 2006 may also be potentially problematic, as they are still under legal protection by the end of our study period. If protection for the originator was so strong that no competitors could enter prior to market exclusivity, then those molecules are technically not at risk, and hence we should exclude them from analysis. However, as we will see shortly in the chapter, competitors can enter even before 10 years age up (Figure 2.6). Thus, to account for this, we estimate our entry model with and without molecules that were under exclusivity by the end of 2016. Furthermore, in a stricter scenario, we could even exclude all early entries if we believe regulation is strong enough. Results from these three types of data will be compared in the hazard rate model for entry probability.

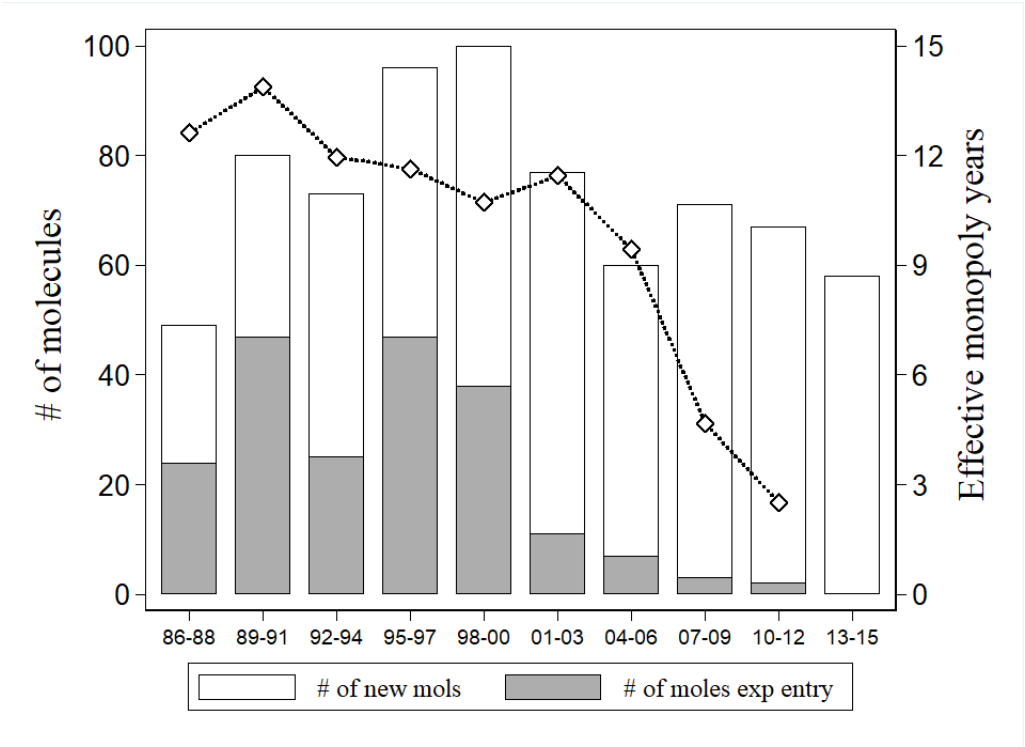
We exclude multi-molecule drugs. In those cases, we cannot identify which molecule is the main active substance and thus, we cannot tell whether a drug has a competing version or not if its molecule combination is not exactly the same as that of the originator.[10] We also exclude vaccines (2-digit ATC code J07) from our data for related reasons. Moreover, we only focus our attention on Prescription only Medicines (PoM), which counts around 75% of single molecule medicines. Over-the-Counter (OTC) drugs are excluded as they could also be sold in supermarkets, whose sales information is not included in IMS data.

We identify 733 molecules that were granted first MA since 1986 as they are at risk, 204 of which (27.8%) actually experienced entry. Table 2.1 summarizes number of molecules at risk and numbers of those that got entries within each 1-digit ATC category. Number of entry cases is diversified across different therapeutic classes. The nervous system class has the highest number of entries (51), followed by molecules treating cardiovascular system diseases (34). In some categories, there are few entry cases, e.g. parasitology and systemic hormones. Table 2.1 also presents molecules at risk for the narrower selection, where originators got MA between 1986 and 2006. Comparing the two selections, 211 molecules are still under legal protection by 2016, and 6 of them experienced entry. Furthermore, we match our data with WHO's indication on whether an ATC3 level is used to treat chronic diseases or not. We note that in the UK entries are concentrated in chronic diseases, which is also a feature observed by Scott Morton (2000) for the US market.

For molecules that experienced entry, we plot a histogram of the difference in years between the launch of the originator and entry of first competitor (Figure 2.6).

[10] For example, based on the coding of the IMS data, we sometimes observe 'water' as one of the 'active' molecules in some combinations. It is not easy to tell if two combinations differ or not only because one contains 'water' and the other does not. There are still other molecule and combinations where we cannot tell whether they are the same, e.g. chlorothiazide v.s. hydro-chlorothiazide. We assume molecules are distinct if their names are different.

FIGURE 2.7: Number of molecules launched, number of molecules experienced entry and the average effective monopoly years over time between 1986 and 2015.



In many markets, entry takes place after the 10th year, i.e. after the legal protection expiration. There is a peak in the 15th year, which might relate to the joint effect of patent and SPC. Furthermore, one peculiarity worth noting is that for 55 cases entry took place before the 10th year. As discussed before, it could be for a number of reasons. First, our IMS data only records drug launch date in the UK, however, exclusivity clock starts ticking from the time when the drug gets MA from any EU countries. If a drug got MA in Germany first and only enters UK six years later, it may look like that competitor entered 6 years before exclusivity finishes. Second, as discussed before, it may be because of me-too and follow-on drugs, who applied MA for the same molecule with their own data individually. Last, launching of an authorized generic by a generic manufacturer with the agreement by the originator may cause early entry. In all cases of early entry, the effective monopoly year of the originator will be sacrificed. As mentioned earlier, as a robustness check of our main results, we repeat our analysis by omitting these cases.

It is also important to know the change of effective monopoly year over time. In Figure 2.7, we plot the average effective monopoly year of the originator that experienced entry, number of newly launched molecules and number of new molecules that experience entry between 1986 and 2015. Competition in the UK pharmaceutical market seems to increase over time. The average effective monopoly year for a molecule launched in 1986-1988 is slightly longer than 12 years, while that of molecules launched later in 2004-2006 seems three years shorter (around 9 years).

Although there is selection bias in recent year (i.e. after 2006) because only molecules that experience entry are used to compute the monopoly years, its decline trend is obvious. The shrink of monopoly year may perhaps be correlated to the implementation of the '8+2(+1)' formula in 2005, as discussed earlier. The new regime allows entrant to access to the originator's data and submit MA application 2 years in advance than the old regulation when data was protected for 10 years; this can speed up the launch of generics. Similar trend has been observed in the US market by previous studies as well, but for other reasons, see for example DiMasi and Paquette (2004), Grabowski and Kyle (2007), and Hemphill and Sampat (2012). On the other hand, firms tend to launch less new molecules since 2000. Over 190 new molecules were launched between 1995 and 2000, roughly 32 molecules per year, whereas the number decreases to 20 in 2013-2015. Molecules launched before 2000 tend to experience higher entry rate. Declining new drug introduction might be a common issue globally. Cases are the same in the US as documented in Higgins and Graham (2009). The authors worry that the decline in drug approvals since 1996 may be the result of Paragraph IV patent challenge, which disincentivises R&D.

2.6 Conclusions

Whether incumbent firms invest strategically and create barriers to entry remain a question in the pharmaceutical industry, as entry by competitors can cut down market prices, and therefore benefit patients and taxpayers.

In this chapter, we first briefly surveyed literature on entry and entry deterrence from both general view in industrial organization and from pharmaceutical market. Second, we illustrated the entry deterrence model from Ellison and Ellison (2011), where they suggest using the non-monotonicity relation between market size and investment vis-a-vis product proliferation to test incumbents' strategic incentive, which is used to motivate our empirical testing in the next chapter. We then presented entry and competition pattern in the UK pharmaceutical market using 20 years sales data.

The data suggests that originators do have more product varieties (more formulations), approaching entry and approaching expiration of exclusivity (Figure 2.1 and 2.2), compared with markets that did not experience entry in our study period. It gives preliminary evidence of incumbents' entry deterrence behaviour. Moreover, although originated drugs enjoy 10 years exclusivity, early entry, prior to expiration, is not uncommon. Furthermore, competition in this industry is increasing. The effective year of monopoly for incumbent shrinks over time, especially after 2005, which may be a result of the implementation of the new '8+2(+1)' rule. However, increasing competition may disincentivise investment as less molecules were launched in recent years, which may raise concern.

In the next chapter, we will present and discuss three empirical models and their results. They are employed to test incumbents' entry deterrence incentive, the effectiveness of product proliferation on entry probability, as well as the effect of such strategy on preserving market shares post entry.

Chapter 3

Empirical tests on entry deterrence

3.1 Introduction

In the previous chapter, we outlined IO theory on using product proliferation strategy to deter entry, and came across some preliminary evidence from 20 years of UK data in pharmaceutical industry. In this chapter, we turn to empirical models to test such effects. We first test whether incumbents launch additional products to deter entry. We then test the effect of product proliferation on entry probability. Last, we test if more product varieties held by incumbent pre entry can help preserve market share post entry.

Summary statistics are presented in Section 2. Following that, in Section 3, we empirically identify incumbents' entry deterrence incentives. Specifically, we test whether number of products by incumbents increases non-monotonically in entry probability. As shown previously by the theory model in Chapter 2, their relation should be non-monotonic with the presence of entry deterrence motive. Ellison and Ellison (2011) use market size as a proxy for entry probability, as rivals are more likely to enter if a market is large, while they do not find pronounced evidence that supports strategic product proliferation in the US pharmaceutical market. We follow their methodology. We start with modelling the global non-monotonic pattern with parametric models. Since having more than one product is a necessary condition for product proliferation, we use a two-part model to estimate the effect of pre-entry market size on the number of products by incumbents. We first model the correlation between market size and the probability that an incumbent launches more than one product, and we model the effect of market size on number of product conditional on the positive outcome of the first step. In addition, as non-monotonicity may occur locally, we use semi-parametric test on monotonicity following Hall and Heckman (2000) and Ellison and Ellison (2000). We find some weak support for this non-monotonicity.

In Section 4, a hazard rate model with complementary log-log link is applied to examine entry deterrence effect of product proliferation on the first entrant. Results from our model reveal that more product varieties controlled by incumbent can lower rival's entry probability after controlling for other factors. This effect is significant overall, which is most compelling in middle-sized markets and mildly

significant in large-sized markets, whereas the effect is not present in small-sized markets. The intuition is that product proliferation is more likely to reduce entrants' expected payoff below entry cost when market size is larger. However, this effect is not obvious in small-sized markets, as the profitability of these markets is already low. The result is consistent with the entry deterrence model shown in the previous chapter in the sense that incumbents in the middle-sized market may be more likely to respond as entry deterrence strategies can be more successful. This exercise relates to Scott Morton (2000) and Kyle (2006). Scott Morton (2000) uses a Poisson model to study whether incumbents invest in advertisement expenditure pre-patent expiration to lower the number of entries in the US market, and she concludes advertising is not a barrier to entry. Kyle (2006) finds that number of existing products in a market can lower probability of launching new drugs with data from G7 countries. This result is interpreted by the author as a competition issue induced by market structure and is not linked to incumbents' entry-deterrence strategy.

In Section 5, we test whether product proliferation pre entry can help incumbent preserve market share post entry. Literature suggests that incumbents that compete with entrants in quantities tend to over-invest to deter entry. This suggests a positive correlation between investment and profit. Using a reduced form regression, we focus on the effect of ex-ante product varieties on originators' market share within three years post entry. Proliferation is a helpful strategy to shield demand. We discover that adding one additional formulation helps the incumbent to preserve around 9% of its market share. We then separate markets into 3 groups by pre-entry market size and determine that this effect is strongest in large-sized markets. This empirical work relates to the literature on persistence of fist-mover advantages, which has been studied in Bronnenberg et al. (2009). They find that early entrants persistently have higher market shares. Sutton (2007) also finds that a dominant position by a manufacturer tends to persevere. However, due to the coverage of their data, they do not provide information on the mechanism that causes persistence. Our result sheds some light on this topic, by suggesting that entry product proliferation might be one possible factor.

Combining results from these three sets of regressions, the picture of entry and strategic entry deterrence is clearer. Product proliferation can help incumbents delay or deter entry in middle and large markets, and it can shield incumbents' share in large-sized markets. However, tests only reveal weak evidence of non-monotonicity between number of products and market size. Robustness check is in Section 6. We conclude the first two chapters of the thesis in Section 7.

3.2 Summary statistics

In Table 3.1, we present summary statistics of incumbents' characteristics and market structure. Markets that experienced entry prior to the start of our study period

TABLE 3.1: Summary statistics

Variable	Description	Obs	Mean	Std. Dev.	Min	Max
	Pre entry					
Drugs_{t-1}	# of products by an incumbent each year (1 year lag)	6613	1.12	0.29	1	3.62
Sales_{t-1}	log of market revenue each year (1 year lag)	6613	13.11	3.04	0	20.12
MolFirm_{t-1}	# of other mols operated by an incumbent as a monopoly (1 year lag)	6613	17.08	13.42	0	45
Nearby_{t-1}	# of other mols in the same ATC3 class (1 year lag)	6613	4.79	4.56	0	23
SPC_{t-1}	= 1 if the market is covered by SPC (1 year lag)	6613	0.12	0.33	0	1
Drugs_f	# of products held by incumbent prior to MA expiration (2 years average)	645	1.10	0.23	1	2.58
Sales_f	log of market revenue prior to MA expiration (2 years average)	645	12.92	3.35	1.53	20.12
	After entry					
MonoYear	# of years as monopoly in a market	184	12.80	4.35	1	28
s_t	market share of the originator ex-post entry	522	0.72	0.28	0	1
	Fixed market features					
Chronic	= 1 if treating chronic diseases	716	0.66	0.48	0	1
EMEA	= 1 if originator applied for MA through EMEA	716	0.33	0.47	0	1
8+2(+1)	= 1 if the market is covered by '8+2(+1)' rule	716	0.16	0.32	0	1

Note. Markets that experience entry on or before May 1996 are excluded, as we cannot construct their characteristics pre entry. There are cases incumbents' sales information are missing before expiration of MA protection, and we exclude these cases. MonoYear is missing if no entry takes place. £1 is added to all sales value for taking logarithm.

(May 1996) are excluded from the analysis. The main variable is the number of products incumbents sell before entry. We construct this variable in two ways. First, we calculate the time-varying contemporaneous product numbers (Drugs_{t-1}), which is the number of products sold by incumbents in the previous year in the market. This is because entry probability may change with variations in product proliferation is the last time period. Second, we generate a time-invariant version (Drugs_f) by computing the average number of products incumbents have during the 2 years that precede the expiration of market exclusivity, as one may believe incumbents are more likely to react strategically just before expiration date. It is averaged over 2 years to eliminate outliers and unnecessary fluctuations. If entry by competitor occurred before expiration date, we replace the time interval with 2 years prior to the entry date observed in the data. Furthermore, instead of using the actual number of products, we believe that the inverse of a Herfindahl-Hirschman Index is more appropriate, as not only it accounts for the number of products, but also for the heterogeneity in the size of each product. Thus, we use the inverse of the sum of squares of the market share of each product by an incumbent as a proxy for product proliferation. The formula is $Drugs = 1/\sum(s_j^2)$ where s_j $(j = 1, 2, ...J)$ is the market share in value of the total J drugs sold by the incumbent. Indirectly we emphasize that only products that are 'important' and have sizeable market shares are feared as strategic tool to deter entry. On average, incumbents only maintain 1.12 important products (calculated for Drugs_{t-1}), while they can have up to 3.6 (for Drugs_{t-1} and 2.58 for Drugs_f) important ones in the market (see Table 3.1).

Market size is a key variable as it directly affects firms' profitability and hence entry probability by a competitor. Sales revenue pre-entry has often been considered as a good proxy for profitability post entry (Appelt, 2015; Caves et al., 1991; Reiffen and Ward, 2005; Saha et al., 2006; Scott Morton, 1999). The ex-ante market size (Sales_f) is measured by the log of market revenue and is constructed over the same time interval used to calculate Drugs_f. It has mean value of 12.92 ranging between 1.53 and 20.12. This market specific variable will be used as control for the incentive models developed in the next chapter, as well as in the post entry share model. We also categorize that variable in small, middle and large, based on 33 and 66 percentiles of the distribution of that variable. We also generate contemporaneous moving market size (Sales_{t-1}) as entry probability can potentially change when market size dose change. The log of yearly total sales approximates contemporaneous market size for previous 12 months.[1] We have chosen to use yearly data to avoid strong seasonality within one year. Sales_{t-1} ranges from 0 to 20.12 with mean at 13.11. All sales values are adjusted by UK CPI to account for inflation. As discussed earlier, markets that are still under protection by 2016 may cause concern, as it is not possible to generate pre-entry product number and market size. We replace them by their values in the last two years (2015-2016) of our data.[2]

Firm-specific characteristics of incumbents and competition from nearby markets are as important when modelling entry as market structures. In fact, as firms can have different business strategies, firm characteristics may affect entry probability of competitors. Also, discussions of the 'chain-store paradox' model infer that number of remaining monopolistic markets operated by incumbents may influence their strategy against entry, and hence influence entry probability. As illustrated in the theory, incumbents are more likely to act aggressively to the entrant in the current market if they operate in other stores that have not experienced entry so to prevent sequential entries (Fudenberg and Tirole, 1986; Kreps and Wilson, 1982; Selten, 1978). Inspired by this, we use variable (MolFirm_{t-1}) to capture how many other molecules the incumbent still operates in as a monopoly in the previous year. This variable is firm specific and time-varying. It ranges between 0 and 45, with mean 17.08. MolFirm_{t-1} may additionally help to control for some unobservables at firm level systematically. In regressions, instead of using its value, we categorize it into 4 groups: No other molecules the incumbent operates in as monopoly (0, base), moderate amount (1-15), medium amount (16-30) and large amount (30+). Moreover, competition from nearby markets can affect entry decisions, as the entrant does only compete with the incumbent in the market it plans to enter, but also with products from nearby markets (Appelt, 2015; Regan, 2008). To capture this, we compute number of other molecules within each ATC3 class (Nearby_{t-1}). This variable is ATC3 specific and varies over time. On average, each class has 4.79 more molecules,

[1] In some cases, sales value of a drug can be zero. To deal with the problem of taking log of zero sales value, we add £1 to all sales revenues.

[2] Another concern is that newer markets tend to have smaller size in very early years, not because their potential market size is small, but rather because they are new to patients.

with max at 23. We also categorize this variable in two groups in regressions: small amount (< 10) and large ($>= 10$).

In addition, we calculate number of years of being monopoly (MonoYear) for incumbents that experienced entry. Being monopoly longer may help incumbent to generate higher brand loyalty and 'goodwill' as discussed in previous studies and thus, may help maintaining market share post entry (Appelt, 2015; Caves and Porter, 1977; Hudson, 2000; Hurwitz and Caves, 1988). Incumbents have 12.8 years monopoly length on average, with range 1 to 28 in our data.

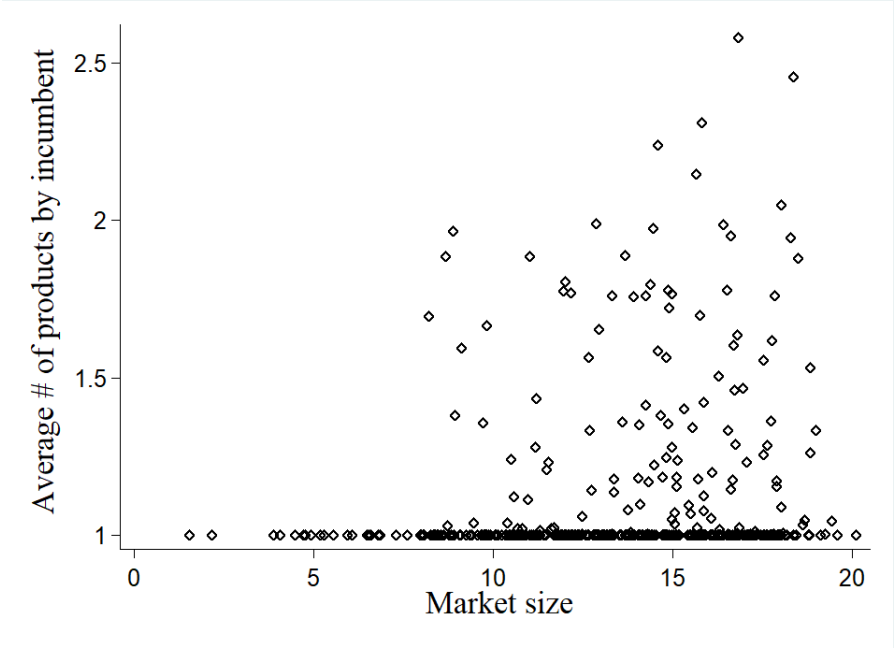
Some other variables are also controlled in the analysis. Chronic index is a variable that indicates if a molecule treats chronic diseases. EMEA index labels markets of which the originator applied for MA through EMEA. The originator can sell the drug in all European countries with MA from EMEA, while it can only sell a drug in a specific country with its local MA. Thus, application channels might affect firms' strategic behaviour and therefore needs to be controlled. We also control for if the MA falls in the 8+2(+1) rule or not. Whether an originator is protected by SPC may also affect entry probability and we should control for it. However, one difficulty in the SPC index is that real SPC information of a drug is not observable; we can only label a drug as covered by SPC if it is launched after January of 1993 and if it is within the first 5 years after market protection. Finally, another characteristics is whether a molecule is under legal protection (within 10 years since originated MA). Since this variable is perfectly collinear with duration dummies in hazard rate model, it cannot be identified.

3.3 Empirical testing on entry-deterrence incentive

Having discussed the theory model in Chapter 2, we do empirical test in this section, using the data discussed previously. Since incumbents are more likely to react strategically if they are no longer under legal protection, in this section, we focus on markets that have lost exclusivity or have experienced entry of competitors. In Figure 3.1, we plot number of products maintained by incumbents two years prior to expiration of protection, against with (log) market size. This figure shows that the distribution of product numbers is correlated with market size. Incumbents are less likely to have many products in small-sized market, and they tend to have more products when markets get bigger. Variance increases as well as does the average. Furthermore, we find that in 62% markets incumbents have only one product, irrespectively of market size.

To test the monotonicity relation between number of products by incumbents and market size prior to expiration of exclusivity (or entry), we conduct a cross-sectional regression. We begin with a parametric approach to test global relation and then move to semi-parametric tests for local non-monotonicity.

FIGURE 3.1: Number of products by incumbent along market size.



3.3.1 Parametric approach

With the first parametric model, we estimate the econometric equation:

$$Drugs_{fk} = \beta_0 + \beta_1 Sales_{fk} + \beta_2 Dev_k + M_k\gamma + \epsilon_k, \tag{3.1}$$

where the dependent variable $Drugs_{fk}$ is number of products in market k fixed prior to expiration. The variable of interest is the log of sales revenue pre protection expiration $Sales_{fk}$ and the deviation term Dev_k. The later term is used to capture non-linearity and it has the form: $(Sales_{fk} - \overline{Sales_f})^2$, where $\overline{Sales_f}$ is the mean market size across all markets. Non-monotonicity occurs if the linear term and the deviation term are of different sign. Variables (M_k) in the equation are controls of market features: 8+2(+1), EMEA, Chronic, ATC3 class dummies.

Endogeneity of market size is not a serious issue here, as discussed in Ellison and Ellison (2011), because we only model their correlation but not causality. Second, if there is an omitted variable, it affects both $Sales_{fk}$ and deviation Dev_k in the same direction, hence will not bias the conclusion. However, it may influence standard errors and reduce the power of the monotonicity test.

Since most markets have only one type of formulation, regardless of market size, it suggests that the focus of the model is on markets that have shown some evidence of product proliferation, i.e. markets with more than 1 product. We use two models to address this issue. In the second model, we only consider markets with more than one product. We conclude that there is non-monotonicity in size if the model reveals that number of products is negatively correlated with market size, conditioning on having more than one product. In addition, inspired by the literature on

zero-inflated data, a two-part model is more appropriate. It allows censoring mechanism (many zeros) of data. In this model, we first use a probit model to estimate the probability of having more than one product, and then estimate a linear regression model conditional on positive outcomes (more than one product). To fit into the model, we subtract 1 from the dependent variable, and compute the 'extra' number of products as $Extra$ which is equivalent to $Drugs_f - 1$. The equations are as follows:

$$\Pr(Extra_k > 0 \mid Sales_{fk}, Z) = \Phi(\beta Sales_{fk} + Z_k\gamma) \tag{3.2}$$

$$E(Extra_k \mid Extra_k > 0, Sales_{fk}, H) = g(\alpha Sales_{fk} + H_k\theta) \tag{3.3}$$

$\Phi(\cdot)$ is the cumulative distribution function of a standard normal density and $g(\cdot)$ is an appropriate density function for $Extra_k \mid Extra_k > 0$. Controls (Z_k, H_k) are used in each part but could be different. If non-monotonicity in size holds, we would expect the coefficient of market size in the probit part β be positive, while that in the conditional regression part α should be negative.

Last, since we want to separate out incumbents' entry deterrence incentive from other profit maximizing incentives, we might consider using a 'difference' approach. The process is as follows. We find two time points for a market. At one time point, the incumbent has weak entry deterrence incentive and at the other time point, it has strong entry deterrence incentive. If incumbent's unilateral incentives do not change much between these two time points, then we can detect pure entry deterrence incentive by taking the difference between the two time points. Since incumbents might gain entry deterrence incentive significantly while their unilateral incentives do not change much when the expiration of data protection is approaching, we take three years before expiration of protection and one year before as the 2 time points. In this model, we regress market size on the difference of product numbers between these two time points.

Regression results are shown in Table 3.2. The first two columns uses the first specification. They are different in the control variables. In the first column, only Chronic and EMEA index are used. To better control for specific characteristics of different therapeutic classes, we impose ATC3 class dummies in column (2). Year dummies are also included to capture unobserved macro-economic shock. We use ATC3 and year dummies in the rest of regressions as well except for column (5), where the original Chronic and EMEA index dummies are used. In column (3), we only use markets that have more than one product. Results from the two-part model are displayed in column (4). Results from the 'Diff' models are reported in the last two columns.

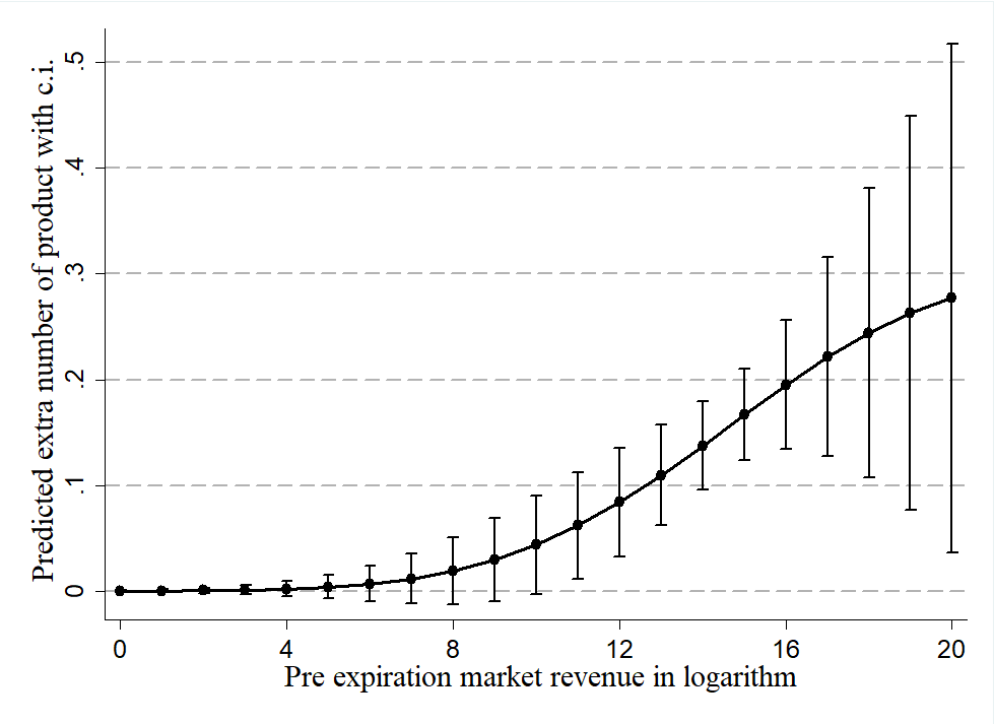
As expected, it is difficult to have a non-monotonic pattern globally. As revealed by column (1) and (2), number of products is significantly increasing with market size. By controlling therapeutic classes and years, the coefficient of market size increases slightly from 0.015 to 0.018. However, the effect of the deviation term is not

TABLE 3.2: Regression results of entry-deterrence incentive.
Dependent variable: $Drugs_f$

	(1)	(2)	(3)	(4)		(5)	(6)
Variables				probit	regress	Diff	
$Sales_f$	0.015***	0.018***	-0.005	0.228***	-0.005	-0.003	-0.009
	(0.005)	(0.006)	(0.027)	(0.049)	(0.027)	(0.004)	(0.006)
Dev	0.001	0.001		-0.010		-0.000	-0.001
	(0.001)	(0.001)		(0.011)		(0.001)	(0.001)
Chronic	-0.001					-0.020	
	(0.028)					(0.024)	
EMEA	-0.048					0.009	
	(0.035)					(0.030)	
Constant	1.161***	0.480*	1.087*	-4.457***	0.087	0.059	0.035
	(0.189)	(0.253)	(0.633)	(1.100)	(0.633)	(0.057)	(0.316)
Observations	454	454	132	260	260	387	387
R^2	0.073	0.469	0.720			0.005	0.368
ATC3		x	x	x			x
Year		x	x	x			x

Note. Standard errors are in parentheses. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$.

FIGURE 3.2: Predicted extra number of products against market size.



significant in both models. If only markets that have more than one product are considered, column (3) suggests that number of product is negatively correlated with market size (-0.005), while the coefficient is not significant. The two-part model suggests similar results. Column (4) suggests that the probability that incumbent has more than one product is increasing strongly with market size (0.228), while market size turns out to have negative effects on product varieties conditional on having more than one products. However, the coefficient of market size for the linear part is also not statistically different from zero. When taking the difference of product numbers at two time points in column (5) and (6), we do not find any significant non-monotonicity globally as well. These two column suggest that whether incumbent expand product variety or not between three and one year prior to expiration is not affected by market size nor the deviation of market size. To visualize the result, we plot the estimated extra number of products v.s. market size in Figure 3.2 based on results from the two-part model. It shows that product varieties seem to be monotonically increasing in market size, while it only shows a decreasing trend at the very right end.

3.3.2 Non-parametric approach

Non-monotonicity may not be global, as the non-strategic profit maximizing incentive may be so strong that entry deterrence incentive can only be revealed by data locally. A local regression might be the solution. Several papers have proposed different ways to test monotonicity non-parametrically. In this study, we mainly follow the work by Hall and Heckman (2000) as it has better detecting power when the data is flat. We fist calculate the test statistics from the data, and compare that to the critical value (at 95 confidence level) generated from a normal distribution. If the test statistics is larger than the critical value, we can conclude that the data is highly likely to present non-monotonicity.

The basic idea of the test is that although the data is increasing globally, it is not likely to increase monotonically if there are enough local downwards in the data. Suppose we have n observations. Suppose number of product A_i is generated by a function of the market size r_i: $A_i = g(r_i) + \varepsilon_i$ where $1 \leq i \leq n$ and ε_i is independently and identically distributed with zero mean and variance σ^2, $\sigma > 0$. For any triplet (k, s, m) where k, s, m are integers and $0 \leq k \leq s - m \leq n - m$, we carry out local regression $A_i = a + br_i$ on the interval $i \in \{k+1, s\}$ based on local least squares. Therefore, we can find $\hat{a}(k, s), \hat{b}(k, s)$ that minimize sum of squared residuals S, where

$$S(a, b \mid k, s) = \sum_{i=k+1}^{s} (A_i - a - br_i)^2.$$

We let

$$Q(k, s) = \sqrt{\sum_{i=k+1}^{s} (r_i - \frac{\sum_{j=k+1}^{s} r_j}{s-k})^2}.$$

The test statistic is then

$$T_m = \max\left\{-\hat{b}(k,s)Q(k,s) : 0 \leq k \leq s-m \leq n-m\right\}$$

and T_m has variance σ^2 for each pair.

Hall and Heckman (2000) argue that the most difficult case is when $g(r_i)$ is a constant function and A_i follows normal distribution. Therefore, it is possible to conclude that the data is not monotonic if we can reject the null hypothesis. We apply a monotone regression to the data and obtain the estimated $\hat{\sigma}^2$ from residuals to calibrate for the distribution of the test statistics, since A_i is monotonically increasing in r_i under the null hypothesis. We then use Monte Carlo simulations to simulate the distribution of t_m when it follows normal distribution with variance $\hat{\sigma}^2$. Probability value is calculated by comparing the proportion of cases $T_m > \hat{t}_m$.

As the test may be generalized over different dimensions, most control variables in our data do not support local regression as it only uses a small number of observations each time. To partial out the effect of such control, we apply Robinson's transformation (Robinson, 1988) for partial linear regression. The process works as follows. Suppose, $y_i = X_i\beta + g(Z_i) + \varepsilon_i$, then the conditional expectation of y_i given Z_i is, $E(y_i \mid Z_i) = E(X_i \mid Z_i)\beta + g(Z_i)$. Let $g_y(Z_i) = E(y_i \mid Z_i)$ and $g_x(Z_i) = E(X_i \mid Z_i)$, therefore, $g_y(Z_i) = g_X(Z_i)\beta + g(Z_i)$. Subtracting it from the original equation, we have:

$$y_i - g_y(Z_i) = (X_i - g_X(Z_i))\beta + \varepsilon_i$$

It suggests that we can estimate the partial linear regression in two steps. First, we regress Z_i non-parametrically on y_i and x_i separately to obtain $\varepsilon_{yi} = y_i - g_y(Z_i)$ and $\varepsilon_{Xi} = X_i - g_X(X_i)$. We then obtain parameters for the parametric part through $\varepsilon_{yi} = \varepsilon'_{Xi}\beta + \varepsilon_i$ by simple least squares.

Results are shown in table 3.3. The first test, labelled as HH, uses the approach proposed by Hall and Heckman (2000) and the second one (EE) uses the one in Ellison and Ellison (2000) where they test whether a model is misspecified if we assume a monotonic relation. We run each test for 4 times with different specifications. First, we use market size and number of products averaged 2 years prior to expiration (Level) and then move to the model where we consider the difference of product numbers between 1 and 3 years before to expiration, as considered in the parametric regressions. Under each selection of samples, we also do test with and without partial effects of control variables. By using the 2-year average, both tests do not show non-monotonicity between number of products and market size. For example, in HH test without partial out effects of other controls, the test statistics (0.781) is smaller than the critical value (1.024), indicating that we cannot reject the null hypothesis at 95% confidence level that the data is monotonically increasing. However, HH test detects non-monotonicity when we use the 'difference' approach (with and without partial out effects of control variables). In summary, results from non-parametric tests give some but weak evidence that incumbents may have entry

deterrence incentive and launch more products to deter entry prior to expiration of legal protection of their drugs.

TABLE 3.3: Non-parametric testing of monotonicity

		Level		Difference	
		No partial	With partial	No partial	With partial
HH	Test statistics	0.781	0.788	0.949	0.948
	Critical value	1.024	1.012	0.849	0.849
	P-value	0.645	0.583	0.005	0.008
EE	Test statistics	-0.537	-0.569	0.524	0.381
	Critical value	0.282	0.164	0.945	0.791
	P-value	0.233	0.250	0.110	0.123
Obs.		454	454	387	387

3.4 Entry probability

In this section, we use a discrete-time hazard model to test whether product proliferation can delay entry. Entry occurs when the expected profit of a potential entrant is higher than its entry cost. Our model assumes that entry only depends on contemporaneous market structure. It implicitly implies that contemporaneous market structure and entry events are not affected by future entries or changes in market structure. The ideal model is to estimate the entry probability for each potential entrant. However, there are two difficulties. First, it is difficult to decide which are potential entrants. Although some firms are more likely to enter if they have already obtained similar technology (King and Tucci, 2002), many firms are 'brand new' to the pharmaceutical market and it is impossible to know their characteristics prior to their entry. Second, the data do not provide full information for unbranded generic manufacturers so we cannot identify them separately. Therefore, we only model the entry probability as market opportunity and we model the probability of having a first entrant, no matter who that is. Under this setting, only current and past market structure and incumbents' characteristics can affect entry; not the characteristics of the entrants.

The link between individual and market entry probability is as follows. Suppose there are J potential entrants and K markets. Each potential entrant j can choose whether or not to enter market k. The survival function for j to stay away from market k until time t is $S_{jk}(t) = Pr\{T > t\}$. Therefore, the survival function of market k, i.e. the period the originator remains as monopoly, is the intersection of all J entrants that stay out from that market, $S_k(t) = \bigcap_{\forall j} S_{jk}(t)$. By definition, the hazard function for entrant j into market k at time t is $\lambda_{jk}(t)$, which equals to $-\frac{d}{dt} log S_{jk}(t)$. We assume it has a continuous proportional form so that $\lambda_{jk}(t) = \lambda_0(t) exp(\mathbf{x}_k(t)\beta + \mathbf{x}_j(t)\gamma)$, where $\lambda_0(t)$ is the baseline hazard at time t and $\mathbf{x}_k$ are co-variates that are market

specific but are common for all potential entrants in that market. Characteristics of entrant $\mathbf{x}_j$ are also important factors to predict entry probability. However, they are unobservable to us. Thus, we use ϵ_j to capture the unobservable.

To integrate from individual hazard to market level, we assume that entry decisions by entrants are independent from entering different markets and from other entrants, so that we have $S_k(t) = \Pi_{\forall j} S_{jk}(t)$ and

$$\begin{aligned}\lambda_k(t) &= -\frac{d}{dt} log S_k(t) = -\frac{d}{dt}\sum_{\forall j} log S_{jk}(t) = \sum_{\forall j}\lambda_{jk}(t) \\ &= \sum_{\forall j}\lambda_0(t) exp(\mathbf{x}_k(t)\beta + \epsilon_j) \\ &= \lambda_0(t) exp(\mathbf{x}_k(t)\beta)\sum_{\forall j}\epsilon_j \\ &= \widetilde{\lambda_0(t)} exp(\mathbf{x}_k(t)\beta) \end{aligned} \tag{3.4}$$

with $\widetilde{\lambda_0(t)} = \lambda_0(t)\sum_{\forall j}\epsilon_j$. Since unobserved characteristics ϵ_j of the potential entrant j is common to all markets, the summation over all potential entrants is a constant and is absorbed by the new baseline hazard $\widetilde{\lambda_0(t)}$. Therefore, the hazard at market level (Eq. 3.4) has the normal form, which depends only on the baseline hazard and market characteristics. In the following equations we suppress the tilde above $\widetilde{\lambda_0(t)}$.

Entry can actually take place at any point in time during a year, but we only observe them at discrete points in time (yearly). Thus, we assume the underline hazard be continuous and generate discrete hazards at each time interval. Let time be grouped into intervals with boundaries $0 = t_0 < t_1 < ... < t_G = \infty$, so what we observe is whether entry occurs or not within an interval. The discrete hazard that market k will experience entry in the interval g, conditional on not having entered before, is given by:

$$\begin{aligned}\lambda_{kg} &= 1 - Pr\{T_k > t_g \mid T_k > t_{g-1}\} \\ &= 1 - exp\{-\int_{t_{g-1}}^{t_g} \lambda_k(t|\mathbf{x}_k(t))dt\} \\ &= 1 - (1 - \lambda_0(g))^{exp(\mathbf{x}_k(t)\beta)}. \end{aligned} \tag{3.5}$$

It follows directly a complementary log-log form for the hazard. The advantage of the complementary log-log function is that the variance-covariance is identical to that in the underlying continuous proportional hazard model. Therefore, the selection of time interval length is irrelevant to the estimates and thus we can easily change time intervals.

We estimate the model in the following econometric form, which estimates the probability of first entry by a competitor in market k at year t conditional on no entry

happened before in that market:

$$\log\left(-\log(1-\lambda_{kt})\right) = \alpha(t) + \beta Drugs_{k(t-1)} + M_{k(t-1)}\gamma + F_{k(t-1)}\theta, \tag{3.6}$$

where $Drugs_{k(t-1)}$ measures incumbent's product proliferation. It is lagged one year to control for potential endogeneity. Its coefficient should be negative if it deters or delays entry. We use market structure variables $M_{k(t-1)}$ and incumbent characteristics $F_{k(t-1)}$, as controls and they are lagged in the same way the product proliferation variable. Duration dummies of being monopoly $\alpha(t)$ capture the baseline hazard ($\log\left(-\log(1-\lambda_0(t))\right)$), which measures the average (across markets) entry probability as time passes. Calendar years are also included in all regressions to capture the change of other macro-economic variables that may affect entry probability.

One potential caveat of this approach is omitted variable. For instance, if it omits variables that affect hazard, then the hazard model is misspecified, which can lead to biased estimates. One example maybe if the incumbent also undertakes advertising which changes the hazard of entry. In such cases, it would enter the model with an additional error term, which would lead to unobserved heterogeneity in the model.

FIGURE 3.3: Survival distribution of being monopoly by market size.

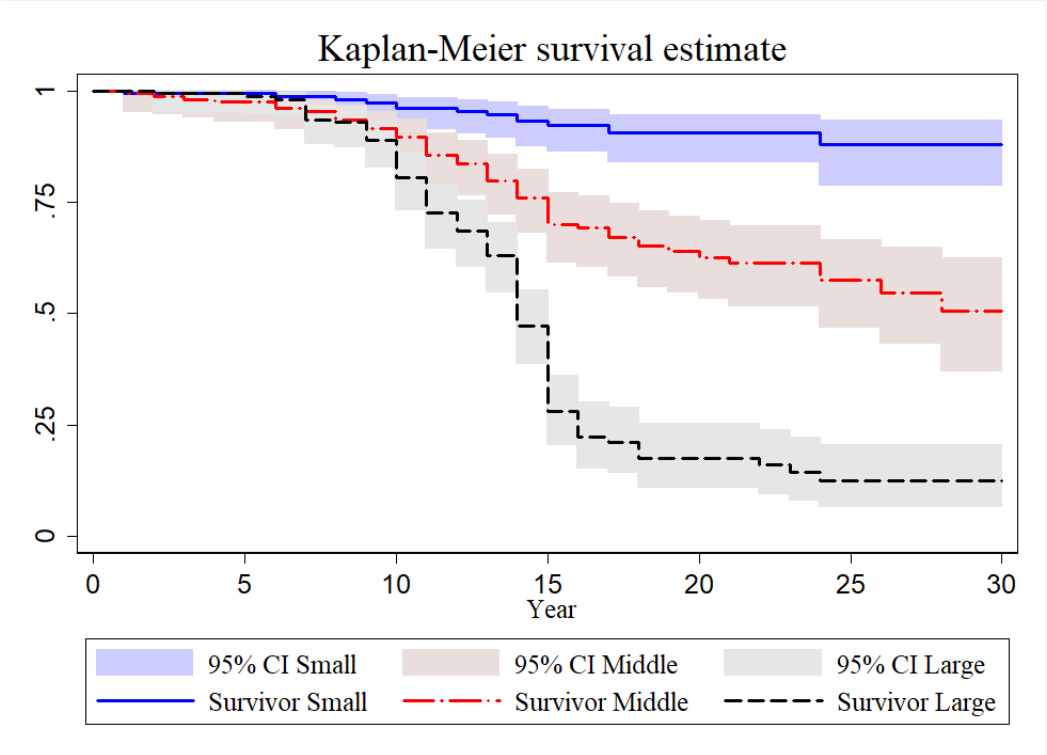


Figure 3.3 illustrates the survival probability of being a monopoly in a market grouped by size as time passes. We have 508 markets that are at risk at the beginning, and 184 of those experienced entry events. Markets are separated into small, middle and large groups by their sizes as described previously. Each group contains 33% of total markets. Kaplan-Meier curve (with 95% confidence interval) shows that entry

probability is diverse by market size. Unsurprisingly, entry probability is lowest when market size is small, as entrant can expect lower profits post entry in these markets. Entry probability is higher when market size is large, and entries are more concentrated between the 10th and 15th year since the launch of the original drug. Entry probability for middle-sized market is located between the other two market sizes. This finding is consistent with Grabowski and Kyle (2007) and Hemphill and Sampat (2012), who find that generics are more aggressive for higher sales drugs, where they have higher probability to enter and tend to enter earlier in the US.

The parameters estimated for entry probability are listed in Table 3.4. We use three sets of data. We use the most strict definition in the first three columns that we only consider markets where entry takes place after exclusivity expiration and we exclude all early entries. This is under the assumption that protection is strong and incumbents only start to react when their protection ends. In the middle three columns, we relax this assumption. We allow early entry to take place, but exclude markets that are still under protection by the end of 2016. The last 3 columns are the most realistic ones, where incumbents react to all entries, as protection is not strong enough to block them. In each group, the first column indicates the overall effect of product proliferation. In the subsequent column, we add market size groups. In the last column in each group, we further add the interaction between product numbers and market size group to test whether effects of product varieties on entry probability defer by market size. Variables are all lagged one year if contemporaneous values are used. Duration dummies and calendar year dummies are included. We cluster observations of a market over time as observations are repeated for an incumbent over time until entry or censoring takes place.

To explain the table, we take the last group as an example, as it is the preferred one. Most coefficients have the expected signs. In models without interaction terms, coefficients for product proliferation are negative and significant. When interacted with market size, the coefficient of the main variable (Drugs_f) is no longer negative and it is not significantly different from zero. However, coefficients of the interaction term with middle and large market sizes are negative, which are also statistically significant in column (9). It suggests that entry deterrence effect presents in middle and large sized markets and is stronger in the former, but is not effective in small markets.

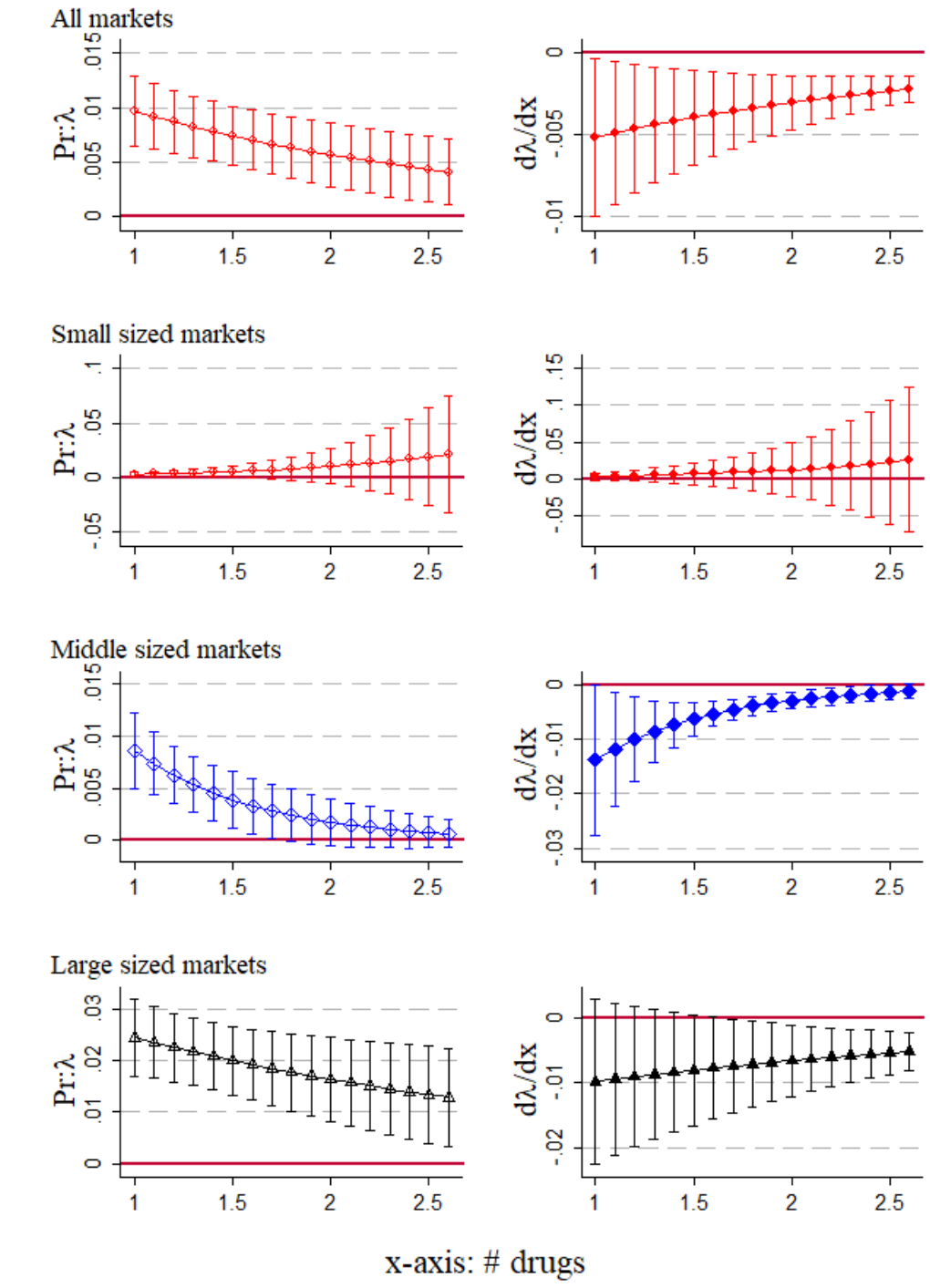
Coefficient of market size is significantly positive in all models, indicating that entry pressure increases with market profitability. Comparing to small sized ones, middle and large sized markets tend to have higher entry probability as coefficients associated with middle and large sized markets are positive when interaction terms are included (in column (9)). In addition, in the preferred data set (last one), entry might be less likely to occur if the incumbent has more molecules where he stays as monopoly, while the coefficient is not statistically significant. Furthermore, substitution from other molecules in the same therapeutic class has no significant impact on entry probability. Change of regulations and MA application channel do not have

TABLE 3.4: Effect of product proliferation on entry probability.
C-loglog regressions. Dependent variable: $\log(-\log(1-\lambda_{kt}))$

	No early entry			1986-2006			Since 1986		
Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Drugs_{t-1}	-0.572**	-0.494**	-0.003	-0.594***	-0.543**	0.418	-0.533**	-0.496**	1.217
	(0.238)	(0.233)	(1.078)	(0.224)	(0.221)	(0.866)	(0.224)	(0.221)	(0.861)
Middle		0.364	1.138		0.448	1.831		-0.281	2.748**
		(0.460)	(1.398)		(0.349)	(1.182)		(0.354)	(1.273)
Large		0.449	0.947		0.454	1.503		-0.006	1.724
		(0.578)	(1.406)		(0.466)	(1.182)		(0.445)	(1.138)
Middle $\times$ Drugs_{t-1}			-0.696			-1.248			-2.808***
			(1.184)			(0.987)			(1.080)
Large $\times$ Drugs_{t-1}			-0.454			-0.938			-1.623*
			(1.116)			(0.902)			(0.890)
Sales_{t-1}	0.423***	0.403***	0.403***	0.346***	0.319***	0.316***	0.331***	0.312***	0.315***
	(0.042)	(0.068)	(0.069)	(0.034)	(0.063)	(0.064)	(0.032)	(0.051)	(0.052)
Chronic	0.260	0.283	0.281	0.214	0.248	0.240	0.253	0.304	0.280
	(0.232)	(0.234)	(0.235)	(0.199)	(0.202)	(0.203)	(0.198)	(0.203)	(0.204)
SPC_{t-1}	-0.292	-0.283	-0.282	0.136	0.161	0.163	0.147	0.128	0.148
	(0.377)	(0.390)	(0.390)	(0.308)	(0.318)	(0.317)	(0.308)	(0.318)	(0.319)
8+2(+1)	2.101***	2.171***	2.170***	0.011	0.053	0.050	0.217	0.300	0.279
	(0.771)	(0.779)	(0.778)	(0.561)	(0.567)	(0.569)	(0.443)	(0.449)	(0.451)
MolFirm_{t-1} (1-15)	1.576	1.462	1.466	0.330	0.224	0.220	-0.506	-0.583	-0.586
	(1.069)	(1.085)	(1.085)	(0.580)	(0.588)	(0.593)	(0.478)	(0.490)	(0.489)
MolFirm_{t-1} (16-30)	1.274	1.232	1.226	0.238	0.195	0.174	-0.572	-0.604	-0.629
	(1.071)	(1.089)	(1.089)	(0.584)	(0.593)	(0.600)	(0.487)	(0.499)	(0.498)
MolFirm_{t-1} (30+)	1.546	1.471	1.472	0.038	-0.035	-0.047	-0.803	-0.798	-0.810
	(1.094)	(1.111)	(1.111)	(0.613)	(0.623)	(0.629)	(0.497)	(0.510)	(0.509)
Nearby_{t-1} (10+)	0.484	0.542	0.523	0.362	0.390	0.375	0.323	0.321	0.308
	(0.421)	(0.456)	(0.463)	(0.263)	(0.272)	(0.273)	(0.232)	(0.241)	(0.242)
EMEA	0.060	0.193	0.190	-0.430	-0.316	-0.317	-0.519	-0.461	-0.462
	(0.360)	(0.366)	(0.368)	(0.304)	(0.305)	(0.306)	(0.316)	(0.318)	(0.320)
Constant	-10.522***	-10.020***	-10.554***	-9.001***	-8.964***	-9.978***	-8.447***	-8.016***	-9.861***
	(2.249)	(2.343)	(2.562)	(1.255)	(1.358)	(1.386)	(1.161)	(1.160)	(1.280)
Observations	2,670	2,523	2,523	5,460	5,199	5,199	6,345	6,071	6,071
Log Likelihood	-424.4	-405.9	-405.8	-602.2	-583.2	-582.6	-632.9	-613.6	-611.6
Entry events	138	135	135	171	168	168	176	173	173
Markets	460	402	402	498	440	440	691	632	632

Note. Robust standard errors are in parentheses. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$. Errors are clustered at market level. Variables are lagged one year if contemporaneous values are used. Duration dummies and calendar year dummies are included in all regressions. Observations and markets at risk have slightly smaller sample size because of missing observations when constructing market size group.

FIGURE 3.4: Predicted entry probability (left) and marginal effects (right) against number of products by market size group.



significant effect on entry probability.

Since the model is highly non-linear, we plot the marginal effect of number of products and predicted entry probability in Figure 3.4 based on the specification of the last dataset. Change of entry hazard is on the left and change of marginal effect ($\partial\lambda_{kt}/\partial Drugs_{k(t-1)}$) is displayed on the right. The first two plots consider the effect of product numbers for overall market based on results in column (7). The latter six plots are computed separately for each market size group based on column (9), where other variables are set at sample mean within each group. Standard errors are constructed by delta-method and the error-bars present them at 95% confidence level. Entry probability is decreasing in number of drugs in middle and large sized markets, while there no significant trend when market size is small. Marginal effect of product proliferation gives an explicit illustration. The marginal effect is not significant when market size is small. In large-sized markets, it is not significantly different from zero at the beginning, while it becomes negatively significant for larger number of products (> 1.5). In middle-sized market, product numbers tend to consistently have negative effects on entry probability. Our estimates suggest that product proliferation by the incumbents pre entry has deterrence power, which tends to be stronger when market size is larger.

3.5 Share of incumbent

Pre entry product proliferation may benefit incumbent also if entry were to take place. In fact, a reason why incumbents may invest prior to entry is to protect profit after entry taking place. Given that profit is hard to measure in absence of cost information, we consider market shares of incumbents as measure of profitability, as done in many other studies.

Market shares are determined by many factors, such as prices, product breadth, marketing forces by firms, i.e. factors considered in market attraction models (Nakanishi and Cooper, 1974). However, many contemporaneous determinants of profitability are endogenous and are typically not easy to instrument. To get around the endogeneity problem, our reduced form regression only includes variables that are time invariant. We test whether product proliferation prior to entry can slow down the reduction of incumbents' market shares post entry. As this variable is fixed in advance, it is unlikely to be endogenous in post-entry games. Similar reduced form regressions are used by others to study the persistence of leadership, see for example, Bronnenberg et al. (2009).

We aggregate our data to yearly observations and use panel regression to estimate the effect of product proliferation on incumbents' market share:

$$s_{kt} = \beta_0 + \beta_1 Drugs_{fk} + \sum_{j=1}^{3} \alpha_j t_k + M_k\gamma + F_k\theta + \epsilon_{kt} \tag{3.7}$$

The dependent variable is market share of the incumbent in market k and within year t. The number of products pre-expiration (or pre-entry if entry happens prior to the expiration of protection) in each market is $Drugs_{fk}$, which is a Herfindahl-Hirschman style measure and is not changing by time. Since the main variable of interest is fixed for each market, we cluster our data at market level, so to deal with potential correlation of errors. The log of market revenue pre-entry is used to proxy the market size, which is included in market feature variables M_k. Since product number may have different effects by market size, it is interacted with market size group dummies. It is also interacted with time to investigate the change of its effects by time. We additionally include monopoly length of the incumbent as the incumbent might find it easier to maintain market shares if there are advantages associated with the length of incumbency, as patients or prescribers may get used the original drug with time.[3] Since by definition, we should only have one incumbent in each market k, we ignore the notation for firms.

TABLE 3.5: Change of incumbent market share post-entry

Year after entry	Mean	Std. Dev.	Change of mean from previous year
0	1.00	-	-
1	0.79	0.22	-0.21
2	0.71	0.27	-0.08
3	0.65	0.31	-0.06
4	0.64	0.31	-0.01
5	0.63	0.32	-0.01

Table 3.5 lists the average change of incumbents' market share after entry. Originators' shares drop dramatically in the first year (21%), while they get stable after two years. To estimate the effect of ex-ante product proliferation on the post entry share, we focus on the first three years after entry.

Regression results for the effect on originator's post-entry share are shown in Table 3.6. We use s_t as dependent variable for the first 5 regressions. In column (2), we add market size group to the regression. In column (3), we interact product varieties with market size group. From column (4) to (6), we regress market share on product numbers separately for small, middle and large sized markets. To be consistent with the hazard rate model, we use the same group method to separate market size. Since there are more entries taking place in middle and large sized market, we would expect more observations in these two groups.

The coefficient of interest is the number of products, which is positive and mildly significantly, see in column (1) and (2). It suggests that one additional product can protect around 9% more market share for incumbent. When number of products is interacted with market size group, the significance goes away. Results in separate

[3]Clinical inertia has been documented in literature. See for example, Khunti et al. (2013), Phillips et al. (2001), and Suri et al. (2013).

TABLE 3.6: Effect of product proliferation prior to entry on originators' market share post entry

Variables	(1)	(2)	(3)	(4) S	(5) M	(6) L
$Drugs_f$	0.090*	0.094*	-0.048	-0.258	0.069	0.142**
	(0.051)	(0.051)	(0.305)	(0.335)	(0.086)	(0.059)
Middle		0.081	-0.043			
		(0.118)	(0.390)			
Large		0.101	-0.093			
		(0.149)	(0.398)			
Middle $\times$ $Drugs_f$			0.107			
			(0.316)			
Large $\times$ $Drugs_f$			0.170			
			(0.310)			
$Sales_f$	-0.011	-0.020	-0.020	-0.069	-0.019	-0.010
	(0.009)	(0.017)	(0.017)	(0.043)	(0.044)	(0.020)
Year=2	-0.089***	-0.089***	-0.089***	-0.053	-0.131***	-0.079***
	(0.011)	(0.011)	(0.011)	(0.040)	(0.026)	(0.012)
Year=3	-0.138***	-0.138***	-0.138***	-0.142	-0.207***	-0.117***
	(0.018)	(0.018)	(0.018)	(0.107)	(0.041)	(0.019)
MonoYear	0.010**	0.009**	0.010**	0.028	0.013**	0.004
	(0.004)	(0.004)	(0.004)	(0.023)	(0.005)	(0.007)
Chronic	0.017	0.022	0.023	0.329	0.099	-0.068
	(0.054)	(0.055)	(0.056)	(0.224)	(0.081)	(0.071)
EMEA	0.038	0.035	0.038	0.000	-0.142	0.089
	(0.090)	(0.092)	(0.093)	(0.000)	(0.273)	(0.086)
Constant	0.705***	0.752***	0.910**	1.211***	0.799	0.779**
	(0.161)	(0.201)	(0.388)	(0.466)	(0.600)	(0.353)
Observations	515	515	515	37	112	366
# markets	182	182	182	14	40	128
R^2 within	0.253	0.253	0.253	0.136	0.424	0.229
R^2 between	0.0381	0.0417	0.0442	0.198	0.130	0.0509
R^2 overall	0.0687	0.0703	0.0734	0.0852	0.203	0.0665

Note. Robust standard errors are in parentheses. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$. Since the main variable is market specific, we cluster our errors at market level. 8+2(+1) is dropped because markets that experienced entry are all older than the implementation of the new rule. Bayer stopped marketing its antineoplastics drug fludarabine when generics versions entered the market. Some markets are missing due to missing co-variates.

regressions by market size group suggest that product proliferation has significant effect only in large sized markets, as is shown in column (6). The coefficient indicates that an additional product by the incumbent pre entry can shield market share by 14.2%.

Year dummies persistently show similar effects in all regressions. Relatively to the first year, the reduction of market share is larger in later years, which is consistent with Table 3.5. Furthermore, more years as monopoly help the incumbent to maintain market share post entry. One additional year leads to 1% more share on average. In separate regressions by market size, this effect is only significant in middle sized market.

3.6 Robustness check

In Section 3.4 we used the HHI as measure of effective number of drugs. In this section as robustness check, we use the actual number of formulation varieties as measure of product proliferation. Results are reported in the appendix Table A.2 for the hazard rate model. In all regressions, entry probability increases in market size as expected. However, number of products are no longer significant. Comparing two regression results, one may conclude that only important products are effective to deter entry.

Furthermore, product numbers prior to entry may affect the change of market share post entry differently as time goes by, as discussed in Section 3.5 . Therefore, in supplementary regressions, we include the interaction of product numbers and time by each market group. Results are shown in the appendix Table A.1. However, coefficients associated with interactions terms are not significant.

Moreover, in a few markets, the originator maintains the whole market share post entry, even though there are other drugs available. To ensure that results from post entry share model are not driven by these markets, we repeat the same analysis only with markets where the entrants have positive shares. Results are shown in appendix Table A.3. New results twist numbers slightly, but do not change the conclusions that product proliferation prior to entry can help shield incumbents' market share post entry and such effect is strongest in large-sized market.

3.7 Conclusions

In the first part of the thesis, we systematically studied whether incumbents invest in product varieties to deter entry prior to expiration of their exclusivities with 20 years pharmaceutical sales data in the UK. Based on the monotonicity theory between number of products and market size (Ellison and Ellison, 2011), we tested if incumbent firms have incentive to strategically deter entry through product proliferation with parametric and non-parametric regressions. Then, we used hazard rate

model to test entry deterrence effect of product proliferation, and used simple share regressions to test whether proliferation can shield market share for incumbents.

The UK data reveals some evidence that incumbents proliferate products to deter entry. First, more products maintained by incumbents prior to entry can reduce entry probability and delay entry. Second, more products marketed can help incumbents to preserve market shares after entry take place. Both effects are stronger when market size is larger. We find weak evidence of non-monotonicity between product numbers and market sizes; only two non-parametric tests give supportive results.

One caveat about this study is that, it only considered product numbers as measure of product proliferation, while it does not consider product updates. For instance, in the case of evergreening/product hopping, instead of keeping both the old and updated versions of a drug in the market, incumbents can keep only the updated one, withdraw the old, and invest to convince doctors to switch to the new drugs (Carrier and Shadowen, 2016). Although the total number of products does not change, this strategy is well-known to have entry deterrence power. However, such cases are not captured in this study.

Nevertheless, our results provide important empirical evidence on impact of product proliferation on entry and post entry shares. We conclude from this exercise that product proliferation can be a barrier to entry in the UK pharmaceutical market.

Chapter 4

Demand of antibiotics in the UK

4.1 Introduction

One of the main contributors to the improvement of overall health status in the 20th century is the development of pharmaceuticals for infectious and communicable diseases. With the discovery of sulfa drugs and penicillin in the 1930s and 1940s, the mortality rate from infectious diseases has largely declined (Cutler et al., 2006; Jayachandran et al., 2010). Since then, antibiotic drugs remain one of the most important and essential class of drugs worldwide. However, the use and overuse of an antibiotic drug can reduce not only its own future effectiveness (own-resistance) but also the effectiveness of other molecules (cross-resistance), as bacteria develop resistance to it. As reported by the European Antimicrobial Resistance Surveillance Network (EARS), several resistances are at worrying levels, because of both human and agricultural use (EARS, 2015).[1] Antimicrobial resistance (AMR) can trigger substantial economic loss to the society. For instance, for the 150 million annual prescriptions written in early 1980s in the US, one estimates places the unaccounted costs due to resistance to be between $0.1 and $35 billion (Phelps, 1989). Similar costs are estimated to be £5-21 billion in the UK (Smith et al., 2005). In addition, resistance may result in 23-25K more deaths annually in the EU and the US each (CDC, 2013; ECDC/EMEA, 2009). If the devastating drug-resistance problem remains unsolved, estimates suggest that about 10 million lives a year, and 100 trillion dollar output globally would be at risk by 2050 (O'Neill, 2016).

Despite the rising concern of resistance, many research-led pharmaceutical companies have abandoned investment in antibiotic research (Spellberg et al., 2004).

Material presented in this and next chapter is based on collaborative work with Farasat Bokhari and Franco Mariuzzo.

[1] The positive correlation between antibiotic resistance and their consumption is revealed by Goossens et al. (2005, 2007) and Malhotra-Kumar et al. (2007) and Tacconelli et al. (2008). EARS (2015) reports that *Meticillin-resistant Staphylococcus aureus* (MRSA) confers resistance to the most commonly prescribed β-lactam antibiotics, including penicillins and cephalosporins (Grundmann et al., 2006), causing over 18,000 deaths each year in the United States (Klevens et al., 2007). Some more examples are *Carbapenem-resistant Enterobacteriaceae*, *Escherichia coli* and *Streptococcus pneumoniae* (Boucher and Corey, 2008; EARS, 2015; Gupta et al., 2011; Klevens et al., 2006).

Most classes of antibiotics were discovered between 1930 and 1970, and the innovative pipeline has dried up since then (Cooper and Shlaes, 2011; Mossialos et al., 2010; Power, 2006). Recently, in July 2018, Novartis has joined the list of defector companies. Currently, only Merck, Roche, GlaxoSmithKline and Pfizer have active antibiotic programs, this is compared to 18 big research pharmaceutical companies in 1990 (Cooper and Shlaes, 2011; Nature Biotechnology, 2018). Lack of profitability, compared to drugs in other therapeutic classes, is likely to be the main reason for lack of investment (Projan, 2003). Thus, to better understand why top pharmaceutical companies have lost interest in investing in antibiotic research, it is crucial to understand the profitability that antibiotics have in the pharmaceutical market.

Medical studies estimate 30% to 60% of antibiotics prescribed for human use are either unnecessary or inappropriate (Luyt et al., 2014). Misuse and abuse of antibiotics remains an irrefutable contributor to antibiotic resistance, especially the excessive prescription of broad-spectrum antibiotics in primary care (Steinman et al., 2003a,b). Antibiotics can be classified as narrow- or broad-spectrum. Narrow-spectrum drugs work against a select group of bacteria and will not kill other microorganisms in the body, thus helping slow down AMR. However, they can only be prescribed when causative pathogen is known. The cause of infectious has oftn to be discovered via lab tests and this process can be costly and time consuming. The alternative, broad-spectrum antibiotics, are prescribed more generally, when the causative pathogen is unknown, and thus tend to contribute more to AMR (Davies and Gibbens, 2013; Kaier and Moog, 2012; Wood et al., 2007). The implication is that since there is a cost to finding which narrow-spectrum antibiotic is appropriate, broad-spectrum antibiotics are prone to be over prescribed relative to the narrow-spectrum antibiotics.

Economists argue that the undesirable consumption pattern in the antibiotic market is coupled with negative externalities of consuming antibiotics (i.e. drug resistance), which fail to be internalized (Brown and Layton, 1996; Laxminarayan and Brown, 2001). Patenting is normally considered as one tool. The basic idea is that appropriate patent length and breadth will encourage firms to incorporate negative externalities (Eswaran and Gallini, 2016; Herrmann, 2010; Horowitz and Moehring, 2004; Laxminarayan, 2002). Pigouvian tax is another instrument. For both of them, the simple logic behind is that people will use less antibiotics if the price is higher (Coast et al., 1996; Rudholm, 2002).[2] Similarly, Hollis and Ahmed (2013) suggest using taxation to reduce the agricultural use of antibiotics. However, regulators still worry that if the demand of antibiotics were inelastic, such interventions would have little or no effect (O'Neill, 2016).

In the next two chapters, we will use 10 years of UK antibiotics data and answer the following questions. How do companies in the antibiotic market perform? Whch companies benefit most in this market? In particular, we are interested in the

[2]One can also subsidize wanted ones (narrow-spectrum agents). While, subsidizing some antibiotics may potentially induce a higher consumption on overall antibiotics.

distribution of profitability across different molecule groups, age of molecules, and of course firms. Second, we want to know whether policy interventions could alter antibiotics consumption, especially, encouraging people to use more narrow- and less broad-spectrum molecules to help slow down resistance increment. The success of this intervention depends on the substitution pattern among these drugs. Thus, we need to understand the price elasticities of demand and market power companies have. Furthermore, because intervention often comes with market distortion, we are also interested in quantifying the implication for social welfare.

In order to answer these questions, we use structural models to estimate the demand of antibiotics, which helps to check the profitability of the market and price elasticities among drugs. Based on the parameters estimated, we can simulate counter-factual scenarios for several interventions. First, we investigate whether the sales of broad-spectrum drugs would fall if their marginal cost were higher. One may think of it as cost-side interventions that require firms to internalize larger negative externalities of broad-spectrum antibiotics consumption. Second, we impose tax at multiple levels on broad-spectrum antibiotics to calculate detailed market change. Aforementioned scenarios closely relate to the potential of implementing Pigouvian tax on antibiotic market. This exercise contributes to the on-going policy discussions on fighting antibiotics resistance with quantitative empirical evidence.

Our main data is provided by IMS. An inspection of the dataset shows that the total volume of antibiotics has increased in the UK between 2003 and 2013, but sales value has decreased, because of drop in prices. As many as 44 million packs of antibiotics were sold in 2004 with a value of £208 million in real terms after UK CPI adjustment, whereas in 2012, while total sales volume reached around 60 million packs, its value was only £126.7 million. Novel molecules are far from being profitable. Nine new molecules entered the market since 2000, but their total sales volume reached less than 0.01% of the total market level. Commonly used molecules contribute to more than 80% of the market shares in volume. We focus on those to estimate the profitability of antibiotics in the UK market. We find that markets for commonly used molecules are highly concentrated. Only limited number of firms are competing under the same molecule, suggesting that profit margins may still be large. Upon backing out marginal costs from the structural econometric model we infer the price-cost margins which are key for understanding market profitability.

Discrete choice models (logit, nested logit and random coefficients logit) are used in demand estimation, as they can deal with large number of differentiated products and limit the number of parameters to be estimated. In such models, we derive demand for a hypothetical decision maker, who in reality represents the joint decision by a physician and a patient, and we assume away issues related to the principle-agent problem. While the principle-agent problem is important, its modelling is beyond the scope of this thesis.

We jointly estimate demands and supplies under Nash-Bertrand equilibrium,

where multi-products firms choose prices to maximize their profits in an oligopolistic setting. We start from a logit model and then turn to nested logit and random coefficients logit models because the latter two can over-come the Independence of Irrelevant Alternatives (IIA) problem and provide richer estimates. In nested logit models, drugs are grouped according to their molecules, consistent with prescribing procedure. This structure allows us to have a closer substitution pattern within each molecule rather than across molecules. However, we recognize that such grouping may sometimes act as restrictive (Berry et al., 1995; Nevo, 2000, 2001), and we therefore extend our estimations to random coefficients logit model, where we allow for individual tastes (e.g. price, molecule spectrum and pack varieties of products) and for a free substitution pattern between products. Some methodological details suggested in recent works have also been carefully considered, e.g., the starting point of search algorithm (Knittel and Metaxoglou, 2014), tight inner loop (Reynaert and Verboven, 2014) and optimal instruments (Berry et al., 1999; Reynaert and Verboven, 2014).

The chapter is organized as follows. We review related literature on antibiotic crisis in Section 2. Background information of the antibiotics market in the UK is presented in Section 3. The econometric modelling of demand estimation is in Section 4. We conclude this chapter in Section 5. Results are presented and discussed in the next chapter.

4.2 Literature review

4.2.1 Optimal use of drugs with externalities

The discrepancy between optimal solutions for individuals and social planners originates from externalities of treatment (Francis, 1997). Although controlling the prevalence of a communicable disease is not impossible, in general, eradicating the disease is challenging. Gersovitz and Hammer (2004) argue that any optimal solution should consider the trade-off between prevention and treatment, which are drivers of two externalities: (i) infection externality -where one infected person can infect others-, and (ii) prevention externality -where the prevention by one individual can reduce others' infection probability-. The authors suggest that tax/subsidy policies are available to be used to mitigate the issue (Gersovitz and Hammer, 2005). In the case of vaccines, Geoffard and Philipson (1997) argue that the fundamental issue in preventing diseases from happening is that the extinction of disease leads to lower/no demand for vaccines, and thus, it is not possible to rely on individual pharmaceutical firms to achieve eradication of diseases. Kremer and Snyder (2015) find that manufacturers of vaccines may exploit the advantage of income inequality where poor people are not or less vaccinated in order to charge high prices to the rich. Brito et al. (1991) show that compulsory vaccination for all individuals is strictly dominated by the choice of not to vaccinate because of free rider problem.

They suggest using government interventions, such as tax and subsidies to achieve the optimal solution. Mechoulan (2007) argues that a social planner would typically choose to eradicate the disease, if possible. However, negative externalities yielded by drug resistance complicate the solution and thus, a mixed regime of monopoly and competition can perform better. Moreover, infectious diseases can only be eradicated if they are eliminated globally, but this requires strong international cooperation, which not always is there (Barrett, 2003).

Drug resistance, leading to further considerations for optimal use, exacerbate the balance between the prevalence and treatment of antimicrobial drugs. Borrowing the idea from natural resource economics, Tisdell (1982) and then Brown and Layton (1996) model an antibiotic as a non-renewable resource whose susceptibility decreases with use. Furthermore, Herrmann and Gaudet (2009) model the dynamics of antibiotic efficiency as a common pool renewable resource. They find that, because antibiotic producers care about the prevalence of diseases (market size) and the effectiveness of antibiotics, the steady state of efficacy of open-access equilibrium can be lower or higher than the social optimal one, depending on the parameter sets. A seminal paper by Laxminarayan and Brown (2001) adopts susceptible-infected-susceptible (SIS) epidemiological models. They consider two separate molecules as two non-renewable resources which develop resistance with their own past consumption. Because different molecules lose susceptibility at different rates, their model predicts that molecules that are more effective should be used first, instead of being used simultaneously. They also suggest that optimal tax should be considered to address externalities. In a more recent paper, Herrmann and Nkuiya (2017) model two molecules, one of high quality and one of low quality, having a common susceptibility pool. They find that if susceptibility is non-renewable, the high quality drug will be used up before the low quality one. If susceptibility is renewable, both quality drugs or the low quality one will be remain in the market in a steady state.

4.2.2 Policy interventions to promote proper use of antibiotics

Based on aforementioned concerns, there is ongoing discussion of policy interventions aimed at directing the optimal use of antibiotics. Coast et al. (1996) suggest reasons for why the externalities of using antibiotics are typically ignored. First, because the absolute cost of externalities for an individual is small. Second, because the implicit discounted cost of time preference or uncertainty is small. Finally, because costs are difficult to measure. They argue that government interventions, such as transferable permits, charges, and regulations, should be implemented (Coast et al., 1998; Smith and Coast, 1998; Smith et al., 2006). Rudholm (2002) proposes using Pigouvian tax to eliminate the departures of market equilibrium from the global optimal resource allocation. Moreover, Laxminarayan and Weitzman (2002) suggest that albeit government recommendations of antibiotic use is necessary, a decentralized advisory system is preferable to uniform drug treatment as the latter is more

likely to place high selection pressure on bacterial pathogens. In addition to considering proper use, Herrmann et al. (2013) address the optimal innovation of a new antibiotic molecule. They show that, a company innovates far away from generics existing in the market, as susceptibility of similar antibiotics is earlier to lose exerted by existing drugs. They argue that the market incentive of innovation differs from the social optimal level, and as a result, firms do not innovate at the appropriate distance (in product space) from existing molecules. It follows that optimal patent breadth designs or additional R&D subsidies are needed to incentivise firms to innovate at the right point. They further argue that only if this condition is satisfied can tax/subsidy interventions work as corrective mechanism to drive antibiotic consumption to the social optimal level. In a study about malaria, Laxminarayan et al. (2006) suggest that even a partial subsidy can delay the cumulation of resistance of artemisinin-based combination treatments (ACTs).[3]

In order to force producers to internalize externalities of antibiotic consumption, another approach is the optimal design of patents. Antibiotics have a long history with the development of the patent system. The aggressive marking of penicillins in the 1950s led to the growth of drug regulations in the U.S. (Sampat, 2015). At that time, regulators mainly concerned about patent monopolies in antibiotics, because of high price and excessive prescribing of combinations of existing molecules, which had little effectiveness (Sampat, 2015). Safety and efficacy concerns about new drugs also helped to create the modern regulatory institutions (Sampat, 2015). Recently, optimal patent breadth and length for antibiotics have received considerable attention, as a result of drug resistance. Horowitz and Moehring (2004) and Towse and Kettler (2005) suggest using longer patent to reward antibiotic investment. Mechoulan (2007) proposes to re-activate patent after a certain period of competition. These works argue that extended patent life can encourage monopoly producers to internalize the externality. Higher prices may also be useful for taking control of excessive use. Similarly, the 'wildcard' is proposed to give R&D incentives. Wildcard is designed to give a company the right to extend the patent of its best-selling drugs up to 2 years in the U.S or 5 years in the EU if the company successfully brings a novel antibiotic into the market (Outterson et al., 2007). However, Outterson et al. (2007) argue that neither the extension of patent life nor wildcard can be the solution, as the reward from the former is too little and the cost (to society) of the latter is too large.

Not only the length of patents but also the breadth of patents should be used as instruments. Laxminarayan (2002) argues that (similar) antibiotics contribute to a common pool of resistance. The entry of a new molecule that is close to the original one will deplete the effectiveness of the originator rapidly. He suggests extending the breadth of patent instead of their length. Gallini (1992) agrees with this view and argues that rivals are likely to invest around the patented product and enter the

[3] Artemisinin-based combination treatments (ACTs) are widely used as cheap treatment for malaria, while it rapidly cumulate resistance and thus, should not be used as monotherapy.

market. She suggests giving broad patent breadth to reduce imitation instead of extending patent length. However, Eswaran and Gallini (2016) claim that competition can, under some circumstances, limit the development of resistance. The idea is that entry of a new molecule can have two offsetting effects on resistance. It may contribute to the resistance of the originator by transferring cross-resistance (the main focus in previous literature), and it can also reduce resistance by stealing the market share of the originator. Therefore, competition from the new entrant may help to prolong the life of the originator if resistance reduction by market stealing is larger. They recommend having relatively narrow patent breadth (based on the spectrum of antibiotics) and to adjust the length to the optimal level accordingly, so that competition of drug varieties can preserve the susceptibility of the originator. When innovation is cumulative, Gallini (2017) argues that patents can facilitate innovation if protection of follow-on research and technology transfer is guaranteed.

4.2.3 Empirical studies on antibiotic use and GP's incentives

In addition to theoretical discussions, empirical studies confirm that antibiotic consumption may be sensitive to policy interventions. Currie et al. (2011) study antibiotic prescribing in China. Using a field experiment, they find that, by giving a clear signal to physicians that the patient had knowledge of inappropriate use of antibiotics, antibiotic prescription dropped by 25%, so did drug expenditure (from $21.32 to $15.48). They conclude that over-prescribing of antibiotics in China is not led by demand of patients, but rather, by incentives of physicians, who may have limited knowledge of proper antibiotic use, want to prevent potential infections or are driven by monetary rewards. Two experimental interventions conducted in China find that 'pay-for-performance' (P4P) intervention with financial incentives and explicit tight requirement on antibiotic prescription (lower prescribing rate leads to higher performance score) can have positive effects (Gong et al., 2016; Yip et al., 2014).

Another example is the P4P reform in Sweden, which requires physicians to select narrow-spectrum antibiotics more often. Ellegård et al. (2018) find significant switches in antibiotic consumption from broad- to narrow-spectrum antibiotics in treating respiratory tract infections in children because of the reform. However, one criticism on P4P is that the programme may not necessarily improve the overall quality of health services but rather, shift resources towards measured quality at the expense of an unmeasured dimension (Mullen et al., 2010). Therefore, it is unlikely to improve antibiotic prescribing, unless appropriate antibiotic prescribing is included in the measurement of performance (Mullen et al., 2010).

Apart from direct quantity regulation on antibiotic prescribing, increased costs of prescribing antibiotics may also reduce consumption. By taking advantage of a reform in Taiwan in February 2001 which increased the cost for physicians to prescribe antibiotics to cure respiratory infections, Bennett et al. (2015) find that antibiotic consumption reduced significantly after the reform. They also find that concentration

of health services is negatively associated with antibiotic consumption. They argue that antibiotic prescribing is used for patient retention under intense competition. Their results indicate that antibiotics are likely to be over prescribed in practice and their consumption is sensitive to price, which leads to the question of how elastic the consumption is.

4.2.4 Over- and mis-use of antibiotics

Finally yet importantly, not only externalities knock antibiotics consumption from the optimal level, but also the fact that a considerable proportion of antibiotic prescribing is either unnecessary or inappropriate. Medical studies have examined antibiotics prescribed for hospital inpatients. They monitor patients' treatments through their hospitalization period and compare the appropriate treatment that ought to be conducted with the real practices that are carried out by doctors. Hecker et al. (2003) find that 30% of antibiotic therapy is unnecessary, e.g., misuse of antibiotics when there are no syndromes of bacterial infections or the actual treatment duration is longer than the recommended one. In other studies, inappropriate use of antibiotics in hospitals reaches 50% or 60% of overall prescription (Dellit et al., 2007; Luyt et al., 2014).

Antibiotic abuse in community and primary care is also worrying. Fleming-Dutra et al. (2016) document that one in three antibiotics prescribed in the US for outpatients are unnecessary. Recent studies on English primary care show substantial (23%) over-prescribing of antibiotics, especially in respiratory tract conditions (Pouwels et al., 2018; Smieszek et al., 2018). Similarly, Hawker et al. (2014) find that more than half of patients with non-bacterial infectious diseases, including coughs, colds and viral sore throats, are prescribed an antibiotic. Bartlett et al. (2013) claim that 40% to 75% patients are mistakenly treated with antibiotics when they seek treatment for viral respiratory tract infections. In particular, broad-spectrum antibiotics are prescribed excessively in primary care, although commentators discourage their use. Steinman et al. (2003a) report that broad-spectrum antibiotics prescription has doubled between 1991 and 1999, while they are mis-prescribed for 22% of adults and 14% of children who have conditions that are primarily viral. In another study, Steinman et al. (2003b) find that more than half of broad-spectrum antibiotics are mis-prescribed to patients with the common cold and non-specific upper respiratory tract infections.

4.3 Antibiotic market and data

As reported by Public Health England (PHE), the majority of antibiotic consumption (74%) in the UK is for general practice, followed by 18% for hospital use (PHE, 2015a). Our database is provided by IMS, which contains monthly drug sales information for pharmacies in the UK between April 2003 and March 2013. It covers most

antibiotic use (general practice and hospital outpatient) in the UK. The residual consumption in hospital inpatient use, dental practice and other community settings, is not included in the data. Each observation in this data contains the description of the drug package, together with its sales quantity and revenue. Prices are given for a whole pack, as listed on the Drug Tariff. The sales quantity is initially measured in packs, but we are able to construct 'unit' sales with the information about the strength of main ingredient in the package. For instance, we can convert the pack of drug into grams of the main ingredient, or to the number of defined daily dose (DDD) contained by the pack.[4]

Antibacterials for systemic use are categorized under Anatomical Therapeutic Chemical (ATC) classification level J01.[5] Based on our data, the total market for antibiotics is around £160 million per year. Total revenues in real terms after UK CPI adjustment have been decreasing from £208.6 million in 2004 to £126.7 million in 2012. This drop is driven primarily by a decrease in average real prices, which dropped from £0.65 per gram in 2004 to £0.31 per gram in 2012. By contrast, sales in volume have been increasing over the past decade. For instance, in 2012, around 60 million packs of antibiotics were consumed, containing 0.4 billion grams of active ingredients or 0.44 billion DDD adjusted units, up from 44.5 million packs in 2004. This is only partially explained by the rise in UK population, which increased from 60 million to 64 million. The average DDD unit of antibiotic consumption per resident per year also increased from 5.36 to 6.93 between 2004 and 2012.

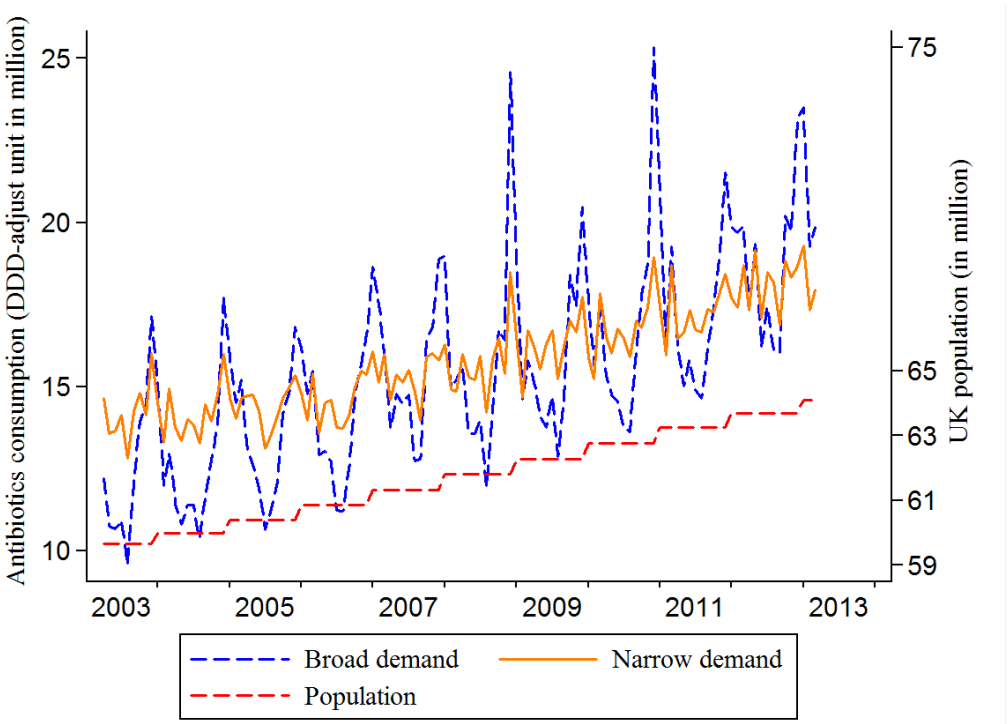
Figure 4.1 plots DDD-adjusted quantity of monthly antibiotics consumption by molecule group, and the UK mid-year resident population against time. Drugs are separated into broad- and narrow-spectrum groups. We follow the categorization used in EARS and PHE. For molecules that are not categorized in their works, we refer to molecule spectrum estimated in Madaras-Kelly et al. (2014, 2015). The figure shows that consumptions for both narrow- and broad-spectrum antibiotics have upward trends despite the increasing concern for the overuse of broad-spectrum antibiotics and frequent interventions aimed at using less of them (PHE, 2015b). The demand trend for broad-spectrum antibiotics seems to be supporting of the argument that current educational interventions have limited effects on switching consumption from broad- to narrow-spectrum agents.[6] In fact, Wood et al. (2007) suggest that broad-spectrum antibiotics are widely used as first-line treatment in primary care in the UK, as they are cheaper since they avoid incurring the cost of testing for the

[4]Defined daily doses (DDD) adjustment is a widely used standardized measurement of quantity, which is the assumed maintenance dose per day for a molecule-route combination used for its main indication adults. DDD is one kind of measurements that allows for compatibility of cross-drug comparison, and does not necessarily reflect the suggested daily use. It is maintained by WHO for all drugs that have an Anatomical Therapeutic Chemical (ATC) code (WTO, 2011).

[5]J01 refers to WHO ATC-DDD system class for systemic antibiotics. Drugs for treatment of tuberculosis are not included, although they are also antibiotics.

[6]Educational interventions mainly aim at leading proper use of existing antibiotics, especially to reduce the use of broad-spectrum agents (Davies and Gibbens, 2013; Scoggins et al., 2006).

FIGURE 4.1: Antibiotic consumption by molecule group and UK population



Note: Antibiotics consumption in DDD-adjusted unit in million (Source: IMS data). UK population in million (Source: Office for National Statistics). It shows constant seasonal fluctuation over time.

TABLE 4.1: Market information by molecule group

		2004			2008			2012		
	Spectrum	Share	Price	HHI	Share	Price	HHI	Share	Price	HHI
Broad-spectrum										
Amoxicillin	13.5	28.39	0.26	0.73	29.80	0.15	0.90	29.76	0.10	0.97
Co-Amoxiclav	29.5	4.46	1.66	0.53	5.13	0.69	0.46	5.37	0.38	0.53
Ciprofloxacin	39.75	2.56	2.39	0.67	2.74	0.31	0.49	1.98	0.24	0.56
Cefalexin	19.25	3.22	0.69	0.72	3.06	0.46	0.53	1.50	0.29	0.52
Levofloxacin	39.75	0.16	2.78	1.00	0.13	2.12	1.00	0.06	1.46	0.51
Ofloxacin	39.75	0.30	1.98	0.48	0.21	0.90	0.45	0.19	1.20	0.47
Narrow-spectrum										
Clarithromycin	12.25	3.37	1.61	0.92	4.64	0.63	0.55	7.96	0.34	0.41
Erythromycin	12.25	11.86	0.58	0.52	10.15	0.42	0.49	7.23	0.27	0.56
Flucloxacillin	4.25	5.95	0.97	0.59	6.18	0.72	0.78	7.02	0.63	1.00
Trimethoprim	4.25	7.01	0.12	0.88	6.63	0.08	0.89	6.29	0.10	0.99

Note: As broad-/narrow- spectrum is a loose concept, this table only shows one possible classification, following EARS and PHE. Amoxicillin has moderate spectrum, which is wider than most narrow-spectrum molecules. The spectrum of trimethoprim is not measured in Madaras-Kelly et al. (2014), but PHE (2015b) categorize it in narrow-spectrum group. Market share for each molecule group is the percentage share of the total market, which is measured by DDD-adjusted quantity. Price is the average pound for a DDD unit. HHI is calculated over different firm based on their quantity shares within each molecule.

causal pathogen and can reduce the risk of treatment failure.[7] Davies (2013) and Peterson (2005) argue that although the consumption of some broad-spectrum antibiotics (e.g., quinolones) decreased in recent years, they are substituted by other broad-spectrum agents rather than by narrow-spectrum drugs. In addition, antibiotic consumption fluctuates seasonally, with peaks in winter and dips in summer. The seasonality is mainly driven by the consumption of broad-spectrum antibiotics (penicillins and macrolides), and is likely to be caused by the surge of respiratory tract infections and virus-induced secondary bacterial infections in cold seasons (Hendaus et al., 2015; Suda et al., 2014).

The detailed market structure of selected antibiotic molecules is presented in Table 4.1. The share listed in this table is the quantity share of the total market with DDD-adjustment. The price is the average British pound for a DDD unit. The top selling broad-spectrum antibiotic is amoxicillin, whose shares are stable (around 29%) over the years. Other broad-spectrum molecules that raise serious concerns in the UK are co-amoxiclav, quinolones (ciprofloxacin, levofloxacin and ofloxacin) and cephalosporins (cefalexin). The share of co-amoxiclav has increased from 4.46% to 5.37%. Notice that the total market demand in DDD has risen by 37% from 321.62m to 441.78m, the absolute surge of the demand for co-amoxiclav is much larger. Although the share of ciprofloxacin decreases from 2.56% to 1.98%, the absolute change of the demand for ciprofloxacin remains positive. The rest of commonly used broad-spectrum agents (levofloxacin, ofloxacin and cefalexin) shows a decreasing trend in demand.[8] Under narrow-spectrum molecules, the share of clarithromycin doubles from 3.37% in 2004 to 7.96% in 2012, while the share of erythromycin drops from 11.86% to 7.23%. The share of flucloxacillin, a narrow-spectrum penicillin, increases from 5.95% to 7.02%. In addition, average price per DDD for each molecule has dropped. For instance, price of amoxicillin has dropped from £0.26 per DDD to £0.1 between 2004 and 2012.

Spectrum of activity for each molecule is listed in the second column in Table 4.1. Although antibiotics are classified as broad- and narrow-spectrum, there was no clear measurement of spectrum until recently. Madaras-Kelly et al. (2014, 2015) calculated the spectrum score for each antibiotic molecule in the following way. For each organism-antibiotic domain pair, an ordinal scale, between 0 (susceptibility $<$ 20%) and 4 (susceptibility $>$ 80%), was given to score the antibiotic susceptibility. The spectrum score associated with an antibiotic is the sum of scores of all organism-antibiotic domain pairs of that antibiotic. In their metric, 60 is the theoretical maximum score and the larger the score the wider the spectrum. In our data, narrow-spectrum penicillin has the smallest score, 4.25, while fluoroquinolones have the highest 39.75. In our estimations, we use spectrum score as drug attribute, which varies by molecules. This will help us to estimate the preference over spectrum

[7] First-line treatment is the treatment that are generally adopted as initial treatment of a given type of disease.

[8] Quinolone antibiotics can also cause serious side effects especially on children (BNF, 2015).

more precisely than a simple, broad-narrow binary grouping. Furthermore, even for a given molecule, its spectrum score is potentially varying across different areas and over time. Importantly, it is decreasing with antibiotic resistance, and thus can be thought of as a potential indicator of antibiotic resistance levels. Due to limited availability of the scores, in this thesis, we only use the static value provided in Madaras-Kelly et al. (2014).

Herfindahl–Hirschman Index (HHI) are calculated over different firms within each molecule. They tend to be rather large in most groups. This may be seen as an indicator of high profit margins in this market. Even though there are 57 different manufacturers involved in antibiotic production, only a limited number of firms are producing the same molecule, making sub-markets (by molecule) highly concentrated. The HHI index for number of molecules has increased over time. HHIs of amoxicillin and flucloxacillin have increased from 0.73 to 0.97 and from 0.59 to one, respectively. Due to the way the dataset has been constructed, some generic manufactures are not separately identified and are lumped together within the molecule, form and ATC4 class as a single generic firm. This aggregation may bias the HHI index upward. Finally, the number of drugs in each molecule group varies a lot. There are more products in molecule groups with high sales, while there are fewer products in finer groups. In general, the message is that the number of products reduced slightly over the years, making the market more concentrated.

GP's role and pricing in the UK system. In the demand system, which will be introduced in the next section, we need to construct a hypothetical decision maker who makes purchasing decisions for a product. Although the decision maker is normally a natural person or a household, as seen in other studies, e.g., Berry et al. (1995) and Nevo (2001), it is less clear who makes decisions in antibiotics markets. As all antibiotics are prescription only medicines (PoM) in the UK, patients need to get prescriptions from general practitioners (GPs) before purchasing any antibiotics.[9] GP's decisions are influenced by many factors. Examples are the NICE (National Institute for Health and Care Excellence) guidelines, the financial incentives from local Primary Care Trusts (PCTs)[10] and education and trainings they receive (Ashworth et al., 2004; NAO, 2007; Scoggins et al., 2006). However, most importantly, those studies show that GP's decisions are based on the physical conditions of patients. Although some possible conflicts between GPs and patients have been documented (Emanuel and Emanuel, 1992), lack of individual level data, makes it difficult to address this potential principle-agent issue in this thesis. Therefore, it is natural to believe GPs are the 'gate keepers' in antibiotic consumption, and they make choices jointly with patients. Indeed, this is a standard assumption as demonstrated by the studies that

[9] Apart from general practitioner, appropriate practitioners also include independent prescribers and supplementary prescribers. We use GP in a holistic way to represent all of them.

[10] In April 2013, Clinical Commissioning Groups (CCG) replaced Primary Care Trusts (PCTs), they are clinically-led statutory NHS bodies and are responsible for the planning and commissioning of health care services for their local area in the UK.

use structural models to estimate demand of pharmaceuticals, e.g., Chaudhuri et al. (2006), Duso et al. (2014), and Ellison et al. (1997). Moreover, pharmacists play little role here, as they only dispense the drug as prescribed by the prescribers.[11]

Bearing in mind that antibiotics are subject to full reimbursement in the UK, it is important to verify if decision makers are sensitive to drug prices. Patients are unlikely to be price sensitive, as they only have to pay a flat fee for each prescription, whereas GPs are price sensitive. Studies find that GPs are in principle aware and sensitive to the cost of prescribing drugs (Carthy et al., 2000; NAO, 2007; Scoggins et al., 2006). This is enforced by NHS's budgeting strategy since the April of 1999 to achieve *cost saving* and *efficiency* (Jacobzone, 2000).[12] To ensure efficiency of prescribing and control for pharmaceutical expenditure, the NHS sets an annual prescribing budget for each PCT at the beginning of each financial year. Meanwhile, PCTs will set individual prescribing budgets for each contracted GP in their group. GPs are responsible for keeping their prescription payment within the budget. Following GP's practice in the year, PCTs continuously track GPs' spending and report it to the NHS Prescription Services. Some PCTs also reward GPs who underspend their budget to achieve cost saving goals (Ashworth et al., 2004). Therefore, we believe that drug price affects GP's decision.

On the other side, the pricing system in the UK may affect firm strategies. Under the UK healthcare system, firms are generally free to set any price for their products, where the NHS will reimburse the pharmacy the NHS price if the drug is subject to reimbursement. The NHS prices of unbranded drugs are weighted market prices based on the information supplied by main generic manufacturers (under scheme M) or wholesalers (under scheme W) under the framework of the Pharmaceutical Price Regulation Scheme (PPRS).[13] Prices for branded drugs are also unrestricted, while the profit for each manufacturer is controlled. Manufactures set their own target profit level annually, which is normally 21% (DH, 2013). They have to return the excess profit back to the NHS, which is known as the 'claw back system'. Although, theoretically this process does not affect the price setting, it may potentially create different price-cost margins between branded and unbranded drugs. Generally, while price cuts and freezes can be applied, there is no price cap or reference strategy imposed in the UK. All pricing pressure in the market comes from competition, leading to a free market equilibrium (ÖBIG, 2006). Such free pricing system facilitates the estimation of price elasticity.

Data preparation. Herein, we explain how we construct the data that we will use in the demand estimation discussed in the next chapter. In our data, most antibiotic drugs contain only one molecule, while there are a few having two or three

[11] Pharmacists reserve the right to choose which generic version to dispense if there are more than one versions available. They also can substitute a generic prescription with a branded version. We do not model these cases.

[12] Government policies could be found on 'NHS efficiency' page.

[13] The websites of Pharmaceutical Services Negotiating Committee (PSNC) and NHS Drug Tariff provide more details on the calculation of drug tariff price.

combined active ingredients, which are treated as different molecules. For example, amoxicillin and clavulanic acid are considered as different molecule combinations to amoxicillin itself, since their indications are different. Enteral (or oral) drugs cover over 90% of the market in value, consisting of 44 molecules with 18 different forms. Parenteral or inhaling antibiotics are used in more limited and serious situations. Under the category of enteral drugs, 18 molecules are recommended by Public Health England to treat common primary community-acquired diseases. We selectively model demand of drugs containing those 18 recommended molecules with an oral routine of administration. We aggregate drugs with tiny shares and construct a representative product based on the formula used in constructing that of the outside option. Details of this method is shown in the next section. By doing this, we shrink our 18 molecules to 16 distinct molecules.

A product is defined as a unique combination of manufacturer, molecule, product-name and form. Different pack sizes and ingredient strengths are aggregated, so as to avoid too many products in the market. We also standardize quantity with daily defined dosage (DDD), which is unique for each molecule-route-of-administration combination.[14] In our system, the market is observed monthly, and a patient chooses one unit of drug (or the outside option) once a month. The total number of consumers available each month is denoted by M_t. Consumers are not the total population but rather, the subset of the population that came across a bacterial infection in the period. Prices are adjusted accordingly. They are calculated from a hypothetical daily spending on antibiotics. With this adjustment, we make the unit sales and prices to be compatible across different molecules and formulations.

The dataset we used in our demand estimation contains 11417 observations with 131 distinct products in 16 distinct molecules (from the original 18) over 120 months (see Table 4.2). We also group the original 18 formulations into four types: tablet, capsule, extended release tablet or capsule, and oral liquid. The share of a product j (s_j) in volume has mean 0.9% with significant variation. Its average price is £1.16 per DDD. All other molecules that are not selected in this modelling are left in the outside option. It means that if the decision maker does not choose any drug from the selected molecules (inside market), she will choose to purchase one product from the outside option. We will discuss the definition of outside option in the estimation and identification section in the next chapter. Based on our definition, the outside market share (s_0) is around 18.2%. The average of the dependent variable ($\ln(s_j/s_0)$) in demand estimation is -5.55. The average spectrum score is 18.3, ranging between 4.25 and 39.75 as mentioned earlier. Most spectrum scores can be found in Madaras-Kelly et al. (2014, 2015), while the scores of some molecules are not included in their

[14] A well-known problem with unstandardised pack size is that a transaction with two packs of 12 pills is not considered as equal to buying one pack of 24 pills, which is not true in many cases. Moreover, as the required dosage is different for different molecules and different route of administrations, using grams (unadjusted by DDD) is also inappropriate. For example, the DDD for oral amoxicillin is 1 gram while for parenteral daptomycin is 0.28 gram.

study. We match such molecules in our data to similar ones in their data according to molecules' families, spectrum and indications.

Moreover, each product has on average two to three different pack types. There are 27 firms in the market whose identity could be identified. For unidentified generic firms, we assume that one typical firm produces only one molecule; different generic firms produce different molecules. With this assumption, a typical (unidentified) generic firm takes around 5% market share, while one identified firm takes around 1.5%. We use dummy ('*Generics*') to control for potential higher market share for the groups of unidentified generic firms.

TABLE 4.2: Summary statistics

Variable	Description	Mean	Std. Dev.	Min	Max
s_{jt}	DDD-adjust share of a drug	0.009	0.029	0	0.331
s_{0t}	Share of the outside option	0.182	0.019	0.13	0.224
$ln(s_{jt}/s_{0t})$	Dependent variable	-5.459	2.465	-15.627	0.929
$ln(s_{j\|g,t})$	Within molecule nest market share	-3.842	2.677	-15.963	0
Price	DDD-adjust unit price in pounds	1.162	1.232	0.038	11.459
Spectrum	Spectrum score of main active molecule	18.30	10.662	4.25	39.75
Packs	Pack varieties	2.684	1.721	1	10
Generics	Dummy: Unidentified generics	0.337	0.473	0	1
Number of observations		11417			

Wholesale price of generics. We obtained the additional dataset 'wholesale price of generics' from Dispex.net.[15] This data set is collected by surveying wholesalers' willingness to sell for unbranded generic medicines. The data reveals that the average percentage price difference between the NHS reimbursement price and the market price is about 44%, with a mode of 53%. Similar discount rates are also found in Kanavos (2007). Unfortunately, due to rebates and unobserved discounts along the supply chain, this data does not record prices with 100% precision. Moreover, as this data set is collected only in quarterly January, April, July and October, we have to expand this data to make it compatible with our monthly data. We do that by filling out missing observations with the nearest available data points. We also match unbranded drugs to be comparable to branded ones (by molecule and form) and assume that the wholesale prices in this dataset are correlated with the prices of branded drugs.[16] We use this data as part of instruments to correct for the price endogeneity in the demand-side regression, as we believe that this additional dataset captures correlations with prices, across molecule and forms

4.4 Structural modelling of demand

Discrete choice models project the impact of price and product characteristics onto people's utility and assume that individuals are rational and choose the unit of a

[15] http://www.dispex.net/

[16] Since we only deal with commonly prescribed antibiotics of which patents have expired long before our study period, we do not have patent or market exclusivity issue in this data.

product that gives them the highest utility. We follow this body of literature and model utility and consumer's choice according to the frameworks proposed by Berry et al. (1995), Berry (1994), Björnerstedt and Verboven (2016), Cardell (1997), and Nevo (2000, 2001), to cite few. We differ from these authors on the way we frame the utility of the outside option. In traditional modelling, the utility of the outside option is normalised to be zero, as it captures a residual unobserved category. This method is very broad and often includes a multitude of products whose product characteristics, among which the price, are not observed by the researcher. As the product that we study in this article is antibiotics, it is hard to believe that the outside option is something other than antibiotic, particularly when the population is defined as consumers that have contracted a bacterial infectious disease in the period. Thus, we define our outside option as the residual category sold in the market, and derive the utility of the outside option from their observable product characteristics, among which prices.[17] This adjustment slightly changes the functional form of the 'traditional' economic model that is employed in the estimation, while it maintains the convenient feature of invertibility of the market share (demand) equation, which is one of the main contributions of Berry (1994) to the literature.

Utility. We consider T markets, each having a mass M_t of consumers. Each decision maker i has contracted a bacterial infection and faces a choice set of J_t antibiotic drugs in period t, where $j = 0, 1, 2, ..., J_t$ and $j = 0$ captures the outside option. As each consumer buys one and only one product in discrete choice models, M_t is also the total market size. However, if more than one drug can be consumed at one time, this discrete choice models may not be appropriate, and one may consider using other demand model. See the discussion in Bokhari and Mariuzzo (2018).

An individual i in market t gets utility U_{ijt} for buying product j, which can be decomposed into a predetermined component V_{ijt} and a residual random variable ε_{ijt}. The predetermined V_{ijt} includes the price p_{jt} of drug j in that market and its observed x_{jt} and unobserved ξ_{jt} drug attributes. It also includes the individual income y_{it} and consumer market-invariant characteristics v_i. Thus, we have:

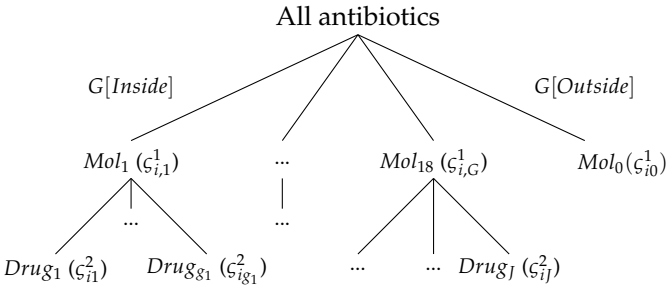
$$U_{ijt} = V(x_{jt}, \xi_{jt}, y_{it} - p_{jt}, v_i; \theta) + \varepsilon_{ijt}, \tag{4.1}$$

with θ denoting the set of parameters.

We start with the random coefficients logit model, because of the richness of its specification. Then, we assume that the individual utility V_{ijt} contains two parts. The first term is the mean utility δ_{jt}, which measures the average utility of consuming drug j across all consumers in that market. This term can be expressed as $\delta_{jt} \equiv x_{jt}\beta + \alpha p_{jt} + \xi_{jt}$. The second term captures individual deviations from the mean, and is denoted μ_{ijt}. If, further, we are willing to assume that the income effect is

[17] See estimation and identification section for further discussion of the market definition.

FIGURE 4.2: Tree structure for nested logit model



linearly separable, then the utility function can be written in full as:

$$U_{ijt} = \delta_{jt} + \alpha y_{it} + \underbrace{[p_{jt}, x_{jt}]Hv_i}_{\mu_{ijt}} + \varepsilon_{ijt}, \tag{4.2}$$

where $H = diag[\sigma_p; \sigma_x]$ is a diagonal matrix that measures the standard deviations of the random coefficients of price (σ_p) and drug characteristics (σ_x) from their mean values α_p and β_x in the mean utility δ_{jt}. Often is the case that we do not observe v_i, therefore, we assume that this component follows a standard multivariate normal distribution $F_v(v)$ (as in Berry et al. (1995) and Nevo (2000, 2001)). If income is not interacted with product attributes, it cancels out when comparing two choices.

Logit and nested logit models can be considered as restrictions of the random coefficients logit model. If we only observe mean utilities but not individual deviations, then equation (4.2) reduces to a pure logit model. Instead, if we believe that drugs with identical main active molecules are more similar than drugs with different molecules, then they can be categorized into groups. Following Cardell (1997), we can construct a nested logit model by decomposing the residual random term ξ_{jt} into $\varsigma^1_{igt} + (1-\sigma)(\varsigma^2_{ijt})$ and the utility function for nested logit model is therefore:

$$U_{ijt} = \delta_{jt} + \alpha y_{it} + \underbrace{\varsigma^1_{igt} + (1-\sigma)(\varsigma^2_{ijt})}_{\xi_{jt}}, \tag{4.3}$$

where ς^1_{igt} are the specific individual tastes for group g and ς^2_{ijt} are individual product tastes. The parameter σ measures the intensity of within group correlations, which is assumed for simplicity to be the same across all segments. As illustrated in the tree structure represented in Figure 4.2, the upper level contains the set of branches: inside groups $G[Inside]$ and the outside group $G[Outside]$. Each of the inside good branches refers to one of the targeting molecules $Mol_1, Mol_2, ...Mol_G$, and the outside good absorbs the remaining antibiotic medicines. The beauty of the nested logit model is that it can mimic the natural process of prescribing drugs, as molecules are often the main consideration in drug prescriptions.

In discrete choice models, a consumer selects the drug j that maximizes his utility. We then have the total decision of consuming product j falls into the region A_{jt}, such

that:

$$A_{jt}(\delta, v, \varepsilon; \theta) = \left\{(\delta, v, \varepsilon) : U_{jt} \geq U_{kt},\ \forall j \neq k\right\}. \tag{4.4}$$

If the distribution of ξ_{ijt} and v_i are independent, then the market share for product j should equal $s_{jt}(\delta, \mu, v, \varepsilon; \theta) = \int_{A_{jt}} dF_\varepsilon(\varepsilon)\, dF_v(v)$, which means to integrate the multivariate probabilities over the mass of consumers in the region A_{jt}. If ε_{ijt} follows i.i.d. Extreme Value distribution, then the market share equation has logit and nested logit closed form solutions, while it needs to be computed numerically for the random coefficients logit model. Berry (1994) has proven that the invertibility of market shares with respect to the mean utility, which means that there is unique δ_{jt} and distribution of μ_{ijt} that makes the market share equal to s_{jt}. With non-zero utility outside option, the above mean utility expressions need be slightly modified, as we will show below.

Demand. Below we present the market share equations (demands) for the logit, the nested logit, and the random coefficients logit model in presence of non-zero outside good utility. We begin with the logit model.

Logit. The logit formula gives:

$$s_{jt} = \frac{\exp(\delta_{jt})}{\sum_{l=0}^{J_t} \exp(\delta_{lt})}. \tag{4.5}$$

As the mean utility of the outside option δ_{0t} can no longer be normalized to zero, because of variation across markets, we adjust the derived demand equations in the following way:

$$\ln\left(s_{jt}\right) - \ln\left(s_{0t}\right) = (x_{jt} - x_{0t})\beta + \alpha(p_{jt} - p_{0t}) + (\xi_{jt} - \xi_{0t}). \tag{4.6}$$

If we let $\hat{x}_{jt} \equiv x_{jt} - x_{0t}$, $\hat{p}_{jt} \equiv p_{jt} - p_{0t}$ and $\hat{\xi}_{jt} \equiv \xi_{jt} - \xi_{0t}$, then the equation is reduced to the standard one. We use $\hat{x}_{jt}$, $\hat{p}_{jt}$ and $\hat{\xi}_{jt}$ in the following equations.

Note that the above equations require the outside good price and the product characteristics (p_{0t}, x_{0t}) to be the result of aggregation over a set of many products belonging to the outside option, as we have to construct one representative product for all drugs in the outside option set. One may assign the mean value of characteristics over all outside drugs to the representative ones. Instead, we make use of the feature of logit family models to determine the characteristics of the outside option. Suppose that the set of the outside option has K drugs, each providing mean utility δ_k. Suppose then, that there exist a representative drug with utility δ_0 associated with the total outside share s_0. Since s_0 is the sum of market shares of all products in the outside market, then δ_0 should equal to $ln(\sum^K exp(\delta_l)$ following the simple logit form. Therefore, δ_0 should lie in the interval between $[\max(\delta_k), \max(\delta_k) + ln(K)]$ for each k. This implies that, we can select the product with highest mean utility

within the set of outside goods as representative. Although we do not observe utilities directly, the average utility does match the market share because of invertibility (Berry, 1994), in which case, the drug with highest utility is the drug with largest market share. We select the drug with highest market share within the outside option group as outside good, and assign to it its price and characteristics, and label those as p_{0t} and x_{0t}. This method is also used to construct the representative for molecules with tiny market shares as mentioned in the previous section.

Nested logit. The within group g share $s_{j|g,t}$ and the group g's share s_{gt} are essential in the construction of demand equations under the nested logit modelling, as the product j share is given by their interaction, $s_{jt} = s_{j|g,t} \cdot s_{gt}$. The nested logit formula yields:

$$s_{j|g,t} = \frac{\exp(\delta_{jt}/(1-\sigma))}{D_{gt}}, \quad s_{gt} = \frac{D_{gt}^{(1-\sigma)}}{\exp(\delta_{0t}) + \sum_{k=1}^{G} D_{kt}^{(1-\sigma)}}, \tag{4.7}$$

where $D_{gt} \equiv \sum_{l \in J_{gt}} \exp(\delta_{lt}/(1-\sigma))$, which captures all products in group g. As in the logit, the utility of the outside option also enters into the derived demand equations as difference between product characteristics:

$$\ln\left(s_{jt}\right) - \ln\left(s_{0t}\right) = \hat{x}_{jt}\beta + \alpha\hat{p}_{jt} + \sigma \ln\left(s_{j|g,t}\right) + \hat{\xi}_{jt}. \tag{4.8}$$

Random coefficients logit. The most convenient way to calculate the share equations for random coefficients logit model is Monte Carlo simulations, where we randomly pick ns draws from the individual distribution $P_v(v)$ to first calculate the probability an individual i chooses the drug j in that market s_{ijt} and then form the average over individuals to get the drug market share s_{jt}:

$$s_{jt} = \frac{1}{ns}\sum_{i=1}^{ns} s_{ijt} = \frac{1}{ns}\sum_{i=1}^{ns} \frac{\exp(\delta_{jt} + [p_{jt}, x_{jt}]Hv_i)}{\exp(\delta_{0t}) + \sum_{l=1}^{J_t}\exp(\delta_{lt} + [p_{jt}, x_{jt}]Hv_i)}. \tag{4.9}$$

Then, it is possible to obtain the demand equations:

$$\ln\left(s_{jt}\right) - \ln\left(s_{0t}\right) = \hat{x}_{jt}\beta + \alpha\hat{p}_{jt} + (\hat{p}_{jt}, \hat{x}_{jt})Hv_i + \hat{\xi}_{jt} \tag{4.10}$$

Oligopoly supply. The supply side is the result of multi-product profit maximizing firms with prices as strategic variables. The resulting equilibrium in the market is Nash in prices. The pricing equations are used for two purposes. Firstly, they are used to back out the marginal costs. Secondly, with the estimated parameters and backed out marginal costs, they can be utilized to solve for new market equilibria in counterfactual scenarios.

In this model, firms are assumed to have constant marginal cost c_{jt}. Each firm $f = 1, \cdots, F_t$ controls the set of prices (p_{ft}) that maximizes its profit, given the prices

of all drugs produced by other firms p_{-ft}:

$$\max_{p_{ft}} \Pi_{ft}\left(p_{ft}, p_{-ft}\right) = \max_{p_{ft}} \sum_{l \in \mathcal{F}_{ft}} \left(p_{lt} - c_{lt}\right) q_{lt}\left(p_t\right) \tag{4.11}$$

where $\mathcal{F}_{ft}$ is the set of products produced by firm f in market t. Since the total unit sales can be expressed as $q_{jt} = s_{jt} \cdot M_t$, we can derive the first order conditions with respect to the set of prices p_t in each market t, leading to a system of J_t first order conditions, which can be expressed as:

$$s_{jt}\left(p\right) + \sum_{l \in \mathcal{F}_{ft}} \left(p_{lt} - c_{lt}\right) \frac{\partial s_{lt}\left(p\right)}{\partial p_{jt}} = 0 \quad \forall j \in \mathcal{F}_{ft} \tag{4.12}$$

The expressions above simply mean that prices equal to marginal cost plus markup. It can be rewritten in matrix form:

$$p_t = c_t + \underbrace{\Delta_t^{-1} s_t}_{m_t} \tag{4.13}$$

where m_t is the vector of mark-ups and Δ_t is essentially the Jacobian matrix, whose element j, k equals to $-\partial s_{kt}/\partial p_{jt}$ if j and k belong to the same firm and zero if j and k belong to different firms. Furthermore, we introduce firms' ownership matrix O_t for each period, which is a $J_t \times J_t$ matrix of ones and zeros. An element is one if two products are produced by the same firm and zero if they are not. Therefore, the matrix of interest Δ_t is defined in compact form as the element-by-element product (denoted with $\circ$) between the matrices:

$$\Delta_t \equiv -\left[\frac{\partial}{\partial p_t} s_t^{'}\right] \circ O_t. \tag{4.14}$$

We rewrite the pricing equation Eq. (4.13) in econometrics form and it is estimated jointly with the demand function:

$$\ln(p_{jt} - \underbrace{\Delta_{jt}^{-1} s_{jt}}_{m_{jt}}) \equiv \ln(c_{jt}) = w_{jt}\gamma + \omega_{jt}, \tag{4.15}$$

where γ are coefficients and w_{jt} represents a vector of observable product characteristics, which includes firm, molecule and form dummies, along with pack size, since we believe that the marginal cost is determined by these factors. The inclusion of pack size as control gives the idea that if products have different pack sizes, their unit marketing cost might be different.

If we assume that marginal costs are unchanged under different counterfactuals, Eq. (4.13) can be though to be a function of a price vector that varies by market. It is possible to solve the system of simultaneous equations w.r.t the price vectors to study new counterfactual scenarios.

4.5 Conclusions

In this chapter, we outlined important features of the antibiotics market and its crisis. We presented the literature on antibiotics an related health issues, along with a description of the data and econometric models for demand estimation. One of the main message is that consuming an antibiotic increases resistance of pathogens, which reduces the effectiveness of future the same drug and of other antibiotic agents. Failure to internalize such negative externalities shifts the consumption away from the optimal level. Theoretical literature models antibiotics as either renewable or non-renewable natural resources with the attempt to find out the optimal solution as a social planner. Among several policy interventions, we saw cost-side interventions, such as taxation. However, whether such interventions can work or not depends on substitutability among drugs, which is not yet clear.

With the UK data, we found that the consumption of broad-spectrum antibiotics is still increasing, despite current educational efforts made to control their use. As the broad-spectrum antibiotics are more likely to exacerbate resistance, we considered whether it is possible to switch consumption from broad- to narrow-spectrum drugs with interventions. We then moved to the econometric model for demand estimation, where we presented the specifications for logit, nested logit and random coefficients logit models. Such models allow us to estimate price elasticities of demands and substitutability between different drugs. Moreover, they also allow us to estimate the profitability of the market, which determines firm's investment incentive for antibiotics R&D.

With these preparations in hand, in the next chapter, we will show our empirical results based on the empirical models that we described. We will first focus on the profitability of the market by molecules groups and by firms. We then present own- and cross-price elasticities of demand within and across groups of spectrum ranges. We will move to several conterfactual scenarios to assess the successfulness of cost-side policy interventions at the end.

Chapter 5

Demand of antibiotics: empirical results

5.1 Introduction

In the previous chapter, we highlighted the importance of assessing the profitability of the antibiotics market due to AMR crisis, and discussed possible policy interventions directed switching consumption from broad- to narrow-spectrum drugs. Using the econometric models introduced in the last chapter, in this chapter we concentrate on the results and discussion that follow.

Our estimates indicate significant heterogeneity of individual taste over the spectrum of activity. The results reveal that even though sales in revenues have decreased over time, as has the average price, profitability has increased due to a more extensive decline in marginal costs. The average price-cost margin for the market is 35.2%, up from 26.3% in 2004 to 46.2% in 2012.[1] Although price-cost margins for the antibiotic market in the UK are high overall, there are noticeable variations across different molecule groups and firms.[2] Broad-spectrum antibiotics tend to have higher margins than narrow-spectrum agents, although the gap shrinks in later years. In addition, innovative big pharmaceutical companies may not necessarily benefit from the market. Molecules from innovators have covered less than 10% of market profit in recent years. This low percentage may be seen as a disincentive for further investment in antibiotic R&D.

In addition, whether cost-side policy interventions can work or not depends on the price elasticity of demand. We find that, share-weighted own-price elasticity is -3.310 on average at product level, with standard deviation of 4.835. The mean cross-elasticity of drugs is 0.172 and the standard deviation is 0.308. More importantly, we find that cross-price elasticities are different by spectrum group of drugs. If the price of a broad-spectrum antibiotic increases by 1%, the share of another broad-spectrum drug will increase, on average, by 0.288%, whereas the share of a narrow-spectrum drug will only increase by 0.148%. Such elasticities confirm that two broad-spectrum

[1] Results reported here are from random coefficients logit model.

[2] To be precise, the price-cost margin includes the profitability of manufacturers, wholesalers and pharmacies, but for the sake of simplicity in this chapter we will abuse the term and call these three agents firm or manufacturer.

drugs are closer substitutes than drugs belonging to different groups. In contrast, drugs with narrow-spectrum molecules have smaller cross-price elasticities, and the share of broad-spectrum drugs is less affected by the price change of narrow-spectrum ones. In addition, newer molecules tend be more elastic to their own price changes than older ones, hinting that the formers are less profitable.

To compute counterfactual market structure, we insert hypothetical marginal cost into the pricing equation and re-compute market equilibrium for each period. Simulated results suggest that cost-side intervention can have compelling effects. The demand for broad-spectrum antibiotics will fall by 27% if their marginal cost were as high as that of narrow-spectrum ones. The share of narrow-spectrum agents will increase by 42%. The loss of social welfare, that actually serves as the social cost of such intervention is £565 per 1000 capita each year (10 years average) or $46 million in total in 2012, of which around 70% is contributed by the loss of consumer welfare. Compared to the £5-21 billion societal cost of AMR in terms of death and direct costs estimated in Smith et al. (2005), this may not be a large cost to bear.

Moreover, a low tax rate may be sufficient to control the consumption of some molecules if tax is selectively implemented on them. In particular, if the tax rate is 5% on the most worrying sub-group of broad-spectrum molecules (i.e. co-amoxiclav, quinolones and cephalosporins), the demand for that group would reduce by 9.83%, and when the tax rate reaches 20%, demand would drop by one third (33.34%). The loss of social welfare would be £10 and £44.8 per 1000 residents per year, accordingly. However, a 20% tax intervention imposed on all broad-spectrum antibiotics may not be sufficient to restrict their overall consumption, as the demand would only decline by 4.86% in total. In all cases, the level of demand reduction is positively correlated with the additional cost imposed to the society. The cost is largely passed (and in some instance over passed, i.e. passed more than the tax increase) on to consumers and social welfare loss can increase more than proportionately with the level of the demand switching, which may raise further concerns.

The rest of the chapter is organized as the following. Some issues related to estimation and identification of demand models are discussed in Section 2. In Section 3, we present our main results of demand estimation. In Section 4, we show profitability of antibiotics by molecule group and manufacturers. Results of price elasticity of demand is shown in Section 5. Section 6 simulates the first counterfactual where marginal cost of producing broad-spectrum antibiotics were as high that of narrow-spectrum agents. Tax simulations are in Section 7 and Section 8 concludes.

5.2 Estimation and identification

Outside market. The first issue to address is the definition of outside market, as there is no unambiguous measurement of it. In most works, the potential market size is defined to be twice or three-times the inside market, which is reasonable for some industries, where the outside option is not observed, for instance, in Berry et al.

(1995), Nevo (2000), and Petrin (2002). However, this assumption is counter intuitive in the antibiotics market, since when patients need an antibiotic they will likely get one. Therefore, we define the market as the number of total antibiotics unites sold in market t and label it M_t. The inside market covers all drugs containing one of the 18 commonly used molecules. The outside market is formed by other antibiotic drugs. This definition assumes that antibiotics are not generally substitutable with other non-antibiotic medicines. However, it comes at the cost of assuming the population of interest as being patients that have contracted a bacterial infection.

Product dummies and additional controls. Recall that a product is a combination of molecule, manufacturer and form. We use product dummies as control in demand side regression. Our data does not have cross sectional variation, because it only reports consumption for the entire UK but not by regions, and thus price variation is the result of heterogeneity over time. Product dummies capture time-invariant unobserved product characteristics that are associated with each product (Nevo, 2001). Because of product dummies, some characteristics that do not vary over time cannot be identified in the linear part because of perfect multicollinearity, e.g. the spectrum of molecule, but these characteristics can still be included in the random part of the random coefficients logit model. To retrieve their coefficients in the linear part, we follow Chamberlain (1982) and Nevo (2000), and use the minimum distance method to back out those estimates from a regression of estimated product dummy coefficients. The procedure are as follows. Let $d = (d_1, d_2, ..., d_J)'$ denote the $J \times 1$ vector of product dummies coefficients, X be the $J \times K$ $(K < J)$ matrix of K product characteristics that we want to recover, and ξ be the $J \times 1$ vector of unobserved product attributes. Minimum distance method simply projects the value of product dummies onto X. Formally, $d = X\beta + \xi$. If we assume $E[\xi|X] = 0$, the estimate of coefficients β associated with K characteristics X is $\hat{\beta} = \left(X'\hat{V_d}^{-1}X\right)^{-1} X'\hat{V_d}^{-1}\hat{d}$ where $\hat{d}$ is the vector of estimated coefficients of product dummies from the main regression, and $\hat{V_d}$ is matrix of the estimated variance co-variance.

Season dummies are used to capture seasonality since antibiotic consumption varies across seasons. In cold seasons, virus-induced secondary bacterial infections are more common (Hendaus et al., 2015). We also include a time trend to control for time effect. Moreover, in the supply-side regression, we include firm dummies, molecule dummies, form dummies and time trend as controls because they are all expected to explain marginal cost in production and distribution.

Estimation algorithm. In each econometric specification, we assume that the unobserved term ξ_{0t} for the outside option is zero(which is not a problematic assumption, as we control for time dummies in the regressions) and the unobserved term ξ_{jt} is orthogonal to the observed products characteristics X. On the supply side, we

assume that ω_{jt} are orthogonal to supply side covariates. The orthogonality conditions can be used to generate moments restrictions for generalized method of moments (GMM) estimation. Berry et al. (1995) and Nevo (2000) provide details on the algorithm. In this work, the adjusted outside option slightly modifies the calculation,to ensure that the characteristics and price difference between inside and outside options are accounted for, but this does not change the computation of elasticities. Moreover, if we were to have the outside option offered by a unique firm, which differs from the firms in the inside market, then also mark-ups and therefore pricing equations would be unaffected by the adjusted outside option, due to the feature of the partitioned matrix displayed in equation 4.13.[3]

Instrumental variables and optimal instruments. Instrumental variables are used for price and (in the case of nested logit version) within group share variables. The price variable is believed to be endogenous because of its correlation with unobserved drug quality. The within group share variable is also endogenous because it is essentially calculated by using market shares and it is correlated with the error term in demand. In discrete choice models, the unobserved product quality enters into the mean utility δ_{jt}, which is used in calculating the shares.

Under the GMM framework, optimal instruments can be retrieved as the conditional (on exogenous variables)) expectation of the derivative of unobservables with respect to the parameters; minimizing in this way the asymptotic covariance matrix of parameters (Chamberlain, 1987). However, these instruments are difficult to compute because of the non-linearity of the model, as discussed in Berry et al. (1995). Thus, approximations of optimal instruments are normally used, though they are less efficient than actual ones. We first use the instruments suggested by Berry et al. (1995) (thereafter, BLP), which are one sets of approximates. They are the sum or average of other product characteristics produced by the same firm. Unfortunately, we do not have many continuous characteristics for each product, which posts limitations on the quality of BLP instrumental variables for the price variable. The only characteristic that changes over time is 'pack variety', which represents the number of different pack types for each product, and it can be seen as a proxy for 'broadness of usage' of the product. Next, we consider as instruments variables that capture the competitive structure of the market and firms' efficiency to identify prices and within group shares, following Ackerberg and Rysman (2005) and Verboven (1996). By combing these two types of instruments we have the initial sets of instrumental variables include wholesale price, product's own characteristics, average characteristics of other products produced by the same firm, and counts of products in the market (in the overall market and in each group). In addition, since the price of products and product characteristics of the inside good are subtracted by the price

[3]This assumption is adopted to simplify the computation, but it may not be true in reality. Companies that produce products for the outside option may also produce products for the inside market.

and characteristics of the outside option, all of our instruments incur the same adjustment.

In the random coefficients logit model, we additionally employ another set of optimal instruments, suggested in Berry et al. (1999) and Reynaert and Verboven (2014), which are better approximates of the GMM optimal instruments proposed by Chamberlain (1987) and help gaining efficiency. Although computing the expected value of the derivatives of the unobservables directly from data is infeasible because it requires us to know the true value of parameters, it is possible to compute the derivatives evaluated at the expected value of the unobservables (i.e. $E[\xi_{jt}] = E[\omega_{jt}] = 0$). It, therefore, implies that we can compute optimal instruments by taking such derivatives from predicted market equilibrium prices and shares estimated in a first stage of a GMM procedure.

Specifically, we first use all non-optimal instruments mentioned earlier to obtain the initial values of the parameters and then calculate new equilibrium prices and market shares from pricing equations at the expected mean utilities and marginal costs, conditional on the parameters. Optimal instruments are then Jacobian matrices, based on new prices and market shares and initially estimated parameters. See appendix in Berry et al. (1999) and Reynaert and Verboven (2014) for detailed explanation of the procedure.

5.3 Estimation results

Table 5.1 displays the demand and pricing equation (supply-side) estimates for key variables from several specifications (logit, nested logit and random coefficients logit). The top panel of the table refers to the demand-side, and the bottom panel to the supply-side.

The first two columns are logit-model estimates. Column (1) is an OLS estimator. The price coefficient there is unreasonable because of the bias from the aforementioned endogeneity. The second column is an IV version of column one. The instruments turn around the sign of the price coefficient. By adding instruments, the price coefficient turns to be negative, but still over 50% of the observations have negative marginal cost, which is counter-intuitive. The pricing equation in column (2) is estimated separately from the demand, and it is a (log) hedonic pricing regression. Column (3) is also a logit model, but differs from previous columns by jointly estimating demand and supply. Joint estimation of demand and supply is also common to columns (4-6). Going from column (1) to column (6) results improve, as the percentage of negative marginal costs decreases.

Column (4) is the nested logit model, where we use type of molecules as the nests. The within group parameter σ_g is 0.529 and is significantly different from 0 (and from 1), suggesting that drugs under same nests are more similar than drugs in other groups. The price coefficient is -10.283, which is smaller (in absolute value) than the one estimated with logit and random coefficients logit models. However,

TABLE 5.1: Estimated demand and supply parameters.

	L	L DS[b]	L DS	NL DS	RCL DS		RCL DS opt	
	(1)	(2)	(3)	(4)	(5)		(6)	
				Demand side parameters				
					β	σ	β	σ
Price	0.024	-1.162	-6.499	-10.283	-9.989	5.256	-9.995	5.263
	(0.016)	(0.162)	(0.135)	(0.123)	(0.368)	(0.243)	(0.353)	(0.189)
$ln(s_{j\|g,t})$				0.529				
				(0.043)				
[a]*Cons*	-8.585	-7.951	-2.651	-1.430	-3.978	0.743	-3.213	1.160
	(0.332)	(0.234)	(0.502)	(0.406)	(1.191)	(3.061)	(1.144)	(0.826)
Packs	0.419	0.397	0.306	-0.057	0.219	0.447	0.252	0.447
	(0.02)	(0.017)	(0.011)	(0.019)	(0.040)	(0.419)	(0.022)	(0.064)
[a]*Spectrum*			0.013	-0.003	-0.010	0.818	-0.027	0.817
			(0.012)	(0.010)	(0.036)	(0.226)	(0.035)	(0.039)
Time	-0.006	-0.014	-0.051	-0.079	-0.049		-0.048	
	(0.0004)	(0.001)	(0.001)	(0.001)	(0.008)		(0.002)	
Spring	0.049	0.061	0.066	0.048	0.688		0.680	
	(0.027)	(0.033)	(0.026)	(0.026)	(0.315)		(0.044)	
Fall	0.057	0.085	0.228	0.301	0.389		0.286	
	(0.027)	(0.034)	(0.026)	(0.026)	(0.093)		(0.030)	
Winter	0.146	0.178	0.298	0.396	1.459		1.410	
	(0.028)	(0.034)	(0.026)	(0.026)	(0.662)		(0.076)	
[a]*Generics*			2.184	0.223	1.290		1.281	
			(0.289)	(0.246)	(0.326)		(0.328)	
[a]*Liquid*			-0.748	0.099	-1.095		-1.072	
			(0.342)	(0.241)	(0.348)		(0.353)	
				Supply side parameters				
Cons		-0.583	0.567	-0.148	0.572		0.576	
		(0.059)	(0.051)	(0.035)	(1.660)		(0.229)	
Packs		-0.094	-0.063	-0.160	-0.053		-0.053	
		(0.003)	(0.011)	(0.008)	(0.463)		(0.025)	
Time		-0.008	-0.003	-0.012	-0.003		-0.003	
		(0.0001)	(0.0004)	(0.0003)	(0.0125)		(0.0026)	
Statistics								
Obs	11417	11417	11417	11417	11417		11417	
% $mc < 0$		> 50	5.3	1.9	3.5		3.5	

Note: Robust standard errors are in parentheses. There are few observations with negative marginal cost and we restrict them to be slightly more than £0.00. [a] Coefficients βs are retrieved from minimum distance method, as product dummies are included. [b] Separate estimate of the supply, using hedonic price equation ($ln(price)$). IVs are used in regressions (2-6). Column (3-6) jointly estimate the demand and supply. Column (6) includes optimal instruments. Form *Liquid* is reported on the demand side. Other forms do not show significant difference from the base *Tablet*. Forms on the supply side are not reported as they are all insignificant.

this number is not directly compatible with those obtained in other columns, because of the presence of the within-group market share parameter σ_g. It is worth stressing that the absolute values of most parameters in the demand side in column (4) are smaller than those we obtain from other specifications. An explanation could be that the within group parameter is correlated both with the price and characteristics. The result suggests that grouping might be an important component in this market and we keep this column as a comparison for our final results.

The fifth column presents the results from the random coefficients logit (thereafter RCL) models and the last column (column (6)) adopts optimal instruments. Both of them give similar results, and it can be seen that optimal instruments significantly reduce standard errors, especially for the non-linear parameters. We choose the last column as main set of results, which will be used to generate price-cost margins and counter-factual scenarios.

To simulate the distribution of individual taste as shown in the model discussed in the previous chapter, we take 100 draws from Halton sequence and convert those to normal distribution for each selected characteristic of the drugs. This procedure is preferred to pseudo random draws (Train, 2009).[4] We use nested fixed points (NFP) algorithm as in BLP with tight convergence criterion (10^{-12}) for the inner loop as the method to minimise he general method of moments function.[5] We recalculated the optimum under several starting points as the fixed points algorithm may sometimes only give the local minima, as illustrated by Knittel and Metaxoglou (2014). Our results are quite robust to the starting points especially when the optimal instruments are used. Robust standard errors are listed in parentheses. Less than 5% observations present negative marginal costs and we restrict those to be positive and tiny in the marginal cost estimation.

The random coefficients logit model (with optimal instruments) improves the estimation of the price parameter as it goes down from -6.499 in logit to -9.995. The heterogeneity of the taste of price σ_x is around 5.263 and is significantly different from zero, which indicates that consumers react differently to price changes. Some are very price sensitive, while others are not. This is intuitive and reasonable. Heterogeneity in price tastes stems from the fact that practitioners have uneven professional experience, and react differently to national media and guidelines on cost saving (Scoggins et al., 2006). The distribution of price sensitivity is plotted in Figure 5.1.

The same logic applies to the taste for pack-variety, which is positive in most models and with significant variations in RCL (0.447). By contrast it is negative

[4] In general, all characteristics can have its own standard deviation, while we only select some important ones.

[5] We also considered the Mathematical Programming with Equilibrium Constraints (MPEC) algorithm suggested by Dubé et al. (2012), where the contracting mapping in NFP is replaced by constrained minimization based on the market share conditions. However, since we have many products, the MPEC is difficult to handle. But rely on Reynaert and Verboven (2014)), they show that both algorithms give, in principle, identical results when a tight inner loop is used, we are confident with our estimations with NFP.

FIGURE 5.1: Histogram of the distribution of taste on price

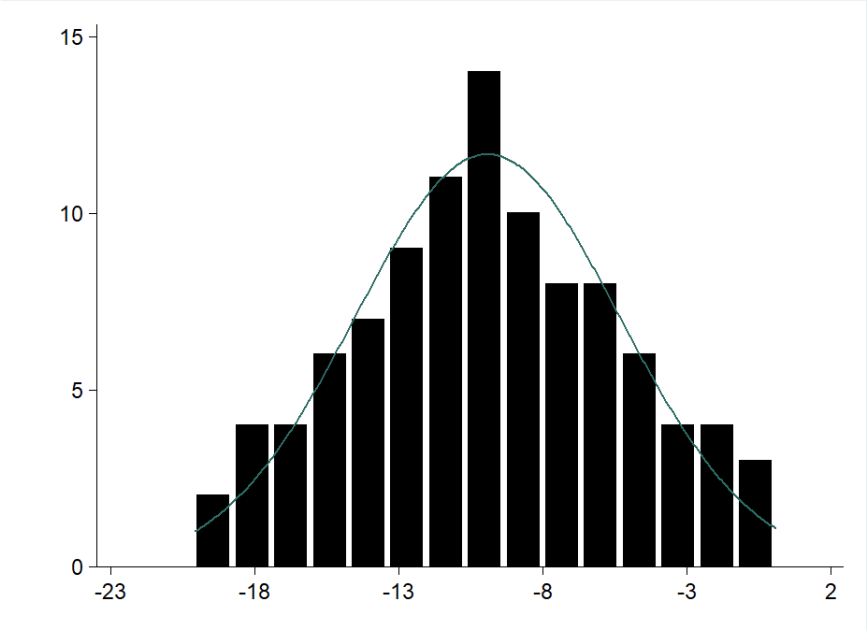
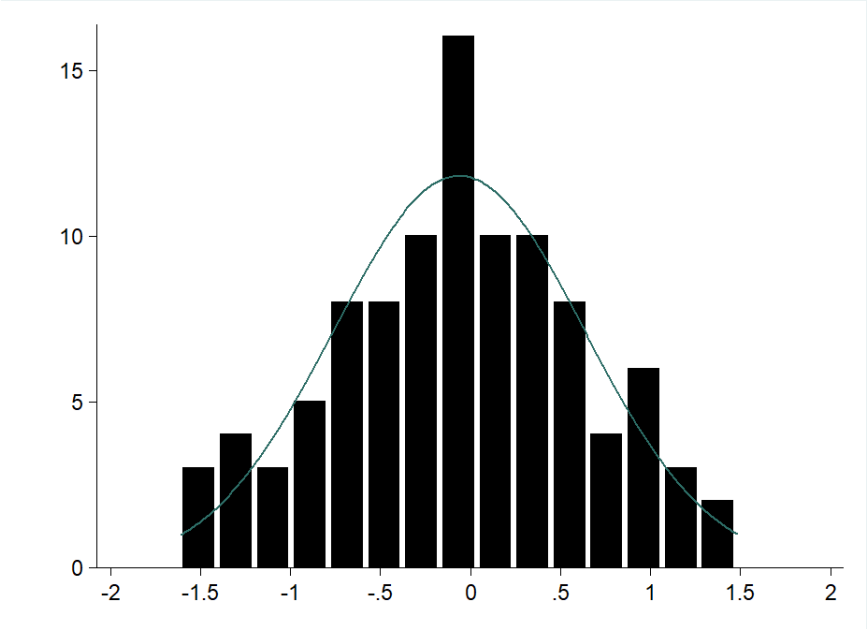


FIGURE 5.2: Histogram of the distribution of taste on spectrum



in the nested logit model as it may be correlated with within group shares. The random coefficient on pack variety suggests that most consumers prefer drugs with more pack varieties, because they would be able to use in broader conditions, while others may favour drugs with fewer pack types. Time trend is negative across all estimations, which gives evidence that the utility of consuming common antibiotics is reducing over time compared to uncommon antibiotics, which may be induced by increasing resistance level. Moreover, the utility of consuming antibiotic in other seasons, especially in winter, is significantly higher than in summer. It might relate to the high preference of using antibiotics to treat respiratory tract infections, and virus-induced secondary bacterial infection in cold seasons (Hendaus et al., 2015; Suda et al., 2014).

We also retrieve some important product characteristics applying the minimum distance method. The main figure that draws attention is the taste of the molecule spectrum. Although the mean taste of molecule spectrum is non-significantly different from zero, the RCL model reveals that the taste has substantial heterogeneity. Intuitively, it suggests that although on average consumers do not have special preferences over broad- or narrow-spectrum antibiotics, some consumers do prefer broad-spectrum antibiotics. Figure 5.2 plots the distribution of the taste on the spectrum of antibiotics.

Moreover, liquid drug seems to have lower preference than tablets, while other formulations do not have clear influence on the demand. As expected, the group of unidentified generic firms turn to have higher market share.

The supply side estimation shows the factors that affect the marginal cost of production. With the exception of column (2), all equations have joint estimation of supply and demand. Column (2) is separately estimated with $ln(price)$ as dependent variable and it shows the case of perfect competition where the mark-up is zero ($price = mc$). All estimations show similar results and all coefficients are of the expected sign. Because of economic of scale, if a product has more pack varieties, its marginal cost tends to be lower. Evidences from other industries also support this finding, see for example Kekre and Srinivasan (1990) and Moreno and Terwiesch (2016). Furthermore, the marginal cost is not significantly affected by formulations. Over time, the marginal cost of producing antibiotics is decreasing.

5.4 Profitability of antibiotics market

Profitability of the antibiotic market can then be derived from the estimated parameters and the assumption of Nash-Bertrand price competition. It is determined by the price elasticity of demand, which we will discuss in the next section. The implied margin is between the retail price and the marginal cost production. Therefore, it contains margins earned by manufacture, wholesalers and retailers. We aggregate the estimated price-cost margin of each product into the molecule-level, to give an overall picture. The aggregation is weighted by market shares in volume, and results

are shown in Table 5.2. The second column lists share-weighted price-cost margins estimated from the nested logit model, and in the third column are margins estimated from the random coefficients logit model. The rest of the columns show three selected years of margins of products obtained from the RCL model by product-type, i.e. branded and generics. The average for the whole market is also listed.[6]

Price-cost margin estimated by nested logit model is around 22.9%, which is slightly lower than the estimation from RCL model. This may be due to the functional form of the nested logit model, where the cross-price elasticity from products in other groups may be systematically underestimated. If products in different groups are close substitutes, the nested logit model would not be able to capture the true cross-price elasticity, leading to a downward biased price-cost margin. In comparison with the margin estimated by nested logit model, the one estimated by RCL model is slightly higher. Over the period of our study, price-cost margin for antibiotics industry is 35.2% on average, rising from 26.3% in 2004 to 46.2% in 2012.

Margins also vary across molecule groups and differ by brand types (branded or generics). Generally, narrow-spectrum antibiotics have relatively smaller margins than broad-spectrum ones, though the gap shrank in recent years. In 2012, the average margin for broad-spectrum molecules is 49.0%, and 44.1% for narrow-spectrum agents. To familiarize with the price-cost margin for each molecule group, we take amoxicillin as an example, but similar patterns hold for other molecule groups. Amoxicillin has a relatively high margin (81.6%), which increases over time to reach 94% in 2012. It is not surprising that the margin between retail price and manufactuer cost can be high. In fact, the estimated margin at retail level alone can be as high as 76.6% (Kanavos, 2007). On the other side, branded amoxicillins have significantly lower margins (less than 20%), while their generic counterparts have much higher ones.

Generic drugs are on average much more profitable than branded ones. Although their margins are similar for some molecule groups (e.g., cefalexin), the difference is dramatic in others (e.g. ciprofloxacin), where unbranded drugs are much more profitable than branded ones. This difference is mainly driven by the fact that unbranded drugs have lower prices, and also much lower marginal costs. Interestingly, similar findings are reported in the U.S. market. Investigation from journalisms finds that although prices of generics are generally lower than their branded counterparts, price-cost margins can be higher for generics (Freudenheim, 2002; Tanouye, 1998), especially at the pharmacy level.[7] Due to consolidation in generic markets, margins earned by large generic manufacturers can surpass that

[6]The total market in this exercise, and the analysis that will follow, relies on the whole 'inside market'. Since the models do not estimate the profits for the outside market, we exclude them from further analysis.

[7]They find that pharmacies can mark up 1000% more than purchasing cost on generics, comparing to 10-30% on branded drugs. It roughly equals to 90% margins for generics or 9-23% for branded drugs if retail price is used as the base.

TABLE 5.2: Estimated average price-cost margin of drugs

	Margin		Margin by year and type from RCL								
	NL	RCL	2004			2008			2012		
			All	Branded	Generics	All	Branded	Generics	All	Branded	Generics
Broad-spectrum	30.2	38.3	28.1	5.8	35.5	41.0	9.6	55.7	49.0	14.4	61.8
Amoxicillin	63.3	81.6	71.8	9.7	82.5	84.9	12.3	88.2	94.0	15.6	94.9
Co-amoxiclav	8.3	10.7	5.3	4.8	5.4	11.6	11.5	11.8	21.5	16.7	30.5
Cefalexin	13.1	15.9	11.9	12.8	11.8	18.0	19.8	17.2	28.0	31.5	26.3
Ciprofloxacin	11.6	11.4	5.4	2.5	6.1	26.1	2.8	49.2	29.6	3.4	41.7
Doxycycline	56.1	70.9	63.7	10.3	75.5	85.5	8.1	98.8	89.3	11.2	98.5
Levofloxacin	4.2	3.0	3.4	3.4	-	2.8	2.8	-	3.7	3.4	3.9
Ofloxacin	4.7	4.4	3.1	3.2	2.9	6.3	4.7	7.6	4.6	6.0	3.7
Tetracycline	14.2	9.2	45.5	-	45.5	5.9	-	5.9	6.1	-	6.1
Narrow-spectrum	16.0	32.3	24.2	17.6	29.0	29.9	22.7	32.5	44.1	21.0	48.8
Azithromycin	4.2	8.1	5.3	5.3	-	6.8	6.7	7.1	11.1	10.0	11.6
Clarithromycin	9.8	18.3	9.5	9.5	9.5	19.0	15.9	25.4	35.0	22.3	45.6
Clindamycin	1.4	3.6	4.3	4.7	3.8	2.6	4.4	2.4	6.1	4.7	8.1
Erythromycin	16.7	28.1	21.0	16.0	23.3	30.0	19.2	35.8	44.2	25.4	52.1
Flucloxacillin	12.5	47.9	37.8	51.8	32.8	43.6	64.9	40.7	60.3	24.1	60.3
Penicillin V	17.2	20.1	19.7	-	19.7	22.0	-	22.0	21.0	-	21.0
Trimethoprim	68.2	82.5	79.7	30.3	82.2	80.5	36.6	83.2	83.5	43.7	83.5
W. Mean	22.9	35.2	26.3	12.7	33.0	35.1	16.0	43.0	46.2	17.4	53.9

Note: This table uses cruder classification of broad- or narrow-spectrum of antibiotics. Penicillin V is considered to have a narrower spectrum than amoxicillin and we list it under narrow-spectrum group.

TABLE 5.3: Revenue, estimated profits and margins for selected firms

(£.m)	2004			2008			2012		
	Revenue	Profit	Margin	Revenue	Profit	Margin	Revenue	Profit	Margin
Abbott	22.01	2.59	11.30	7.54	1.37	16.23	5.47	1.43	22.32
Bayer	3.81	0.10	2.47	1.56	0.05	2.83	0.65	0.03	3.45
GSK	14.63	3.30	21.66	7.43	0.96	11.56	6.02	1.17	16.64
Novartis	2.51	0.35	13.47	3.10	0.34	9.63	1.87	0.56	25.82
Pfizer	5.37	0.35	6.33	4.85	0.37	6.74	3.72	0.39	9.05
Sanofi	3.45	0.12	3.47	1.71	0.06	3.28	0.72	0.04	5.17
Generic	3.98	1.36	22.11	3.30	1.58	27.96	2.97	1.85	30.68
Total	159.30	41.81	-	112.06	39.31	-	95.80	44.26	-

Note: Total presents the total market sales and profits in million pounds with CPI adjustment. The sales and profits figures for each firms are measured in millions of pounds. Price-cost margin is the quantity weighted average margin for each firm. A typical generics firm represents all generic firms. The margin we estimates include profitability of manufacturer, wholesalers and retailers (pharmacies). Therefore, the margin reported here is the overall margin of drugs produces by one manufacturer along the distribution channel, which is not necessary all obtained by that manufacturer.

of many big brand-name companies as well. In addition, the slower rise of price-cost margin of branded products may link to the aspect that branded drugs were required to cut price in 2005 (7%) and 2009 (3.9%) by the Pharmaceutical Price Regulation Scheme (PPRS) in the UK.

Firm profitability Estimated profitability of producing antibiotics by selected manufacturer is presented in Table 5.3. Though price-cost margins for many molecules are high as shown in Table 5.2, research-oriented firms may not necessarily benefit from the market profitability, but generic manufactures can. This may be one of the reasons why firms are reluctant in undertaking antibiotic research. As discussed before, the margins we estimate include profitability of manufacturer, wholesalers and retailers (pharmacies). Therefore, the margin reported here (Table 5.3) is the overall margin of drugs produces by one manufacturer along the distribution channel, which is not necessary all obtained by that manufacturer.

In Table 5.3, firms are grouped into two categories: research-led big international corporates and a grand generic firm, which includes all other manufacturers (identifiable or not) who produce branded or unbranded generic products.[8] GlaxoSmithKline (GSK) covers products produced by Beecham, which produces branded antibiotics. Most products sold under Novartis are manufactured under its generic manufacturer Sandoz. Products under Sanofi are produced by Zentiva (unbranded drugs) and Aventis (branded drugs). It is worth noticing that the branded-generic classification (of the drug) is not equal to the firm classification, as research-led firms also produce generic drugs and generic manufacturer may produce 'branded generics'. Therefore, we mainly discuss the different profitability between R&D firms and generic manufacturers.

[8]We follow Spellberg et al. (2004) for the definition of reasearch-led big pharmaceutical companies. We only list the ones that have relatively significant sales in antibiotics market.

Revenue and estimated profits of most research-oriented firms are negligible, and their trend decreased over the study period. For instance, Abbott has the highest revenue among all R&D firms, which however, drops from £22 million in 2004 to 5.47 in 2012 after CPI adjustment. The estimated profit of Abbott also reduces from £2.59 million to 1.43. The revenue of GSK decreases from £14.63 million to 6.02, and its profit declines from 3.3 to £1.17 million. Competition from generic drugs mainly drives down the profit of GSK, i.e., the price of 'Augmentin' halves between 2004 and 2008, substantially reducing profitability. On the other hand, generic manufacturers may enjoy higher share of market sales and profit. Furthermore, the quantity weighted average price-cost margin also varies by firm, and generic firms can have higher margins. In 2012, Abbott and Novartis had the highest margins among research-led firms, which are 22.32% and 25.82% respectively, whereas the margin for Bayer is only 3.45%. However, the margins for research firms have increased over time, which may because they only continued to market profitable products, and withdrew unprofitable ones. By contrast, the price-cost margin of a typical generic firm is 30.68% in 2012, increased from 22.11% in 2004. Increasing margins in generic firms may be the consequence of market consolidation, as argued in Freudenheim (2002).

Marginal cost In order to understand the divergence of price-cost margin across molecules and firms, we turn to the estimated marginal cost. The average cost is weighted by volume. Figure 5.3 presents the analysis for branded and unbranded drugs. The marginal cost for both of them declined more than 50% over this period, on average, and branded drugs have higher estimated marginal costs than unbranded ones. This result is consistent with previous literature. Arcidiacono et al. (2013) find that marginal cost of generics tend to decrease faster than that of branded ones, although their costs are similar when the generic just entered. One recent study by Ball et al. (2018) provides further evidence. They find that in the US manufacturing recalls are higher for generic drugs, especially when competition is intense. They argue that generic manufacturers may be able to compensate for the quality of drugs in response to price competition. Even though those generics are still bio-equivalent to the originator, there have considerable leeway under current regulation. Generic firms intentionally seek to shave production costs to improve efficiency. For example, they can reduce labour costs, purchase cheaper ingredients from suppliers, find cheaper ways of making their products, replace expensive manufacturing process with lower cost substitutes and reduce non-value-added activities. Their findings support our result that generics may have lower marginal cost of production.

Figure 5.4 plots the estimated marginal cost for broad-spectrum against narrow-spectrum antibiotics. The marginal cost for both narrow- and broad-spectrum antibiotics declines over the period. Though they start at the same level in 2003 the marginal cost of producing broad-spectrum drugs turns out to be much lower than that of producing narrow-spectrum ones in later years. Lower marginal cost of

FIGURE 5.3: Estimated marginal cost by branded/generics

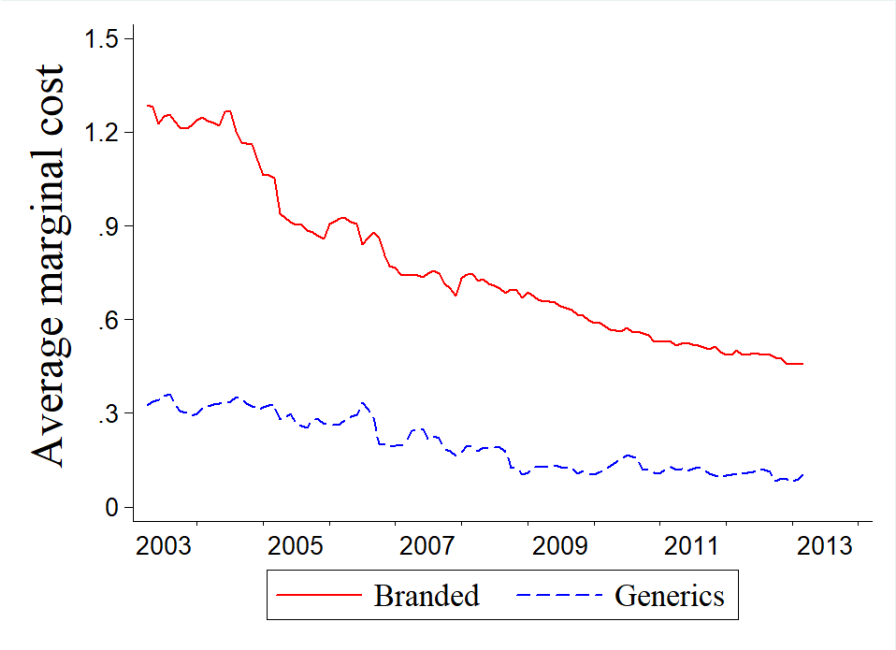
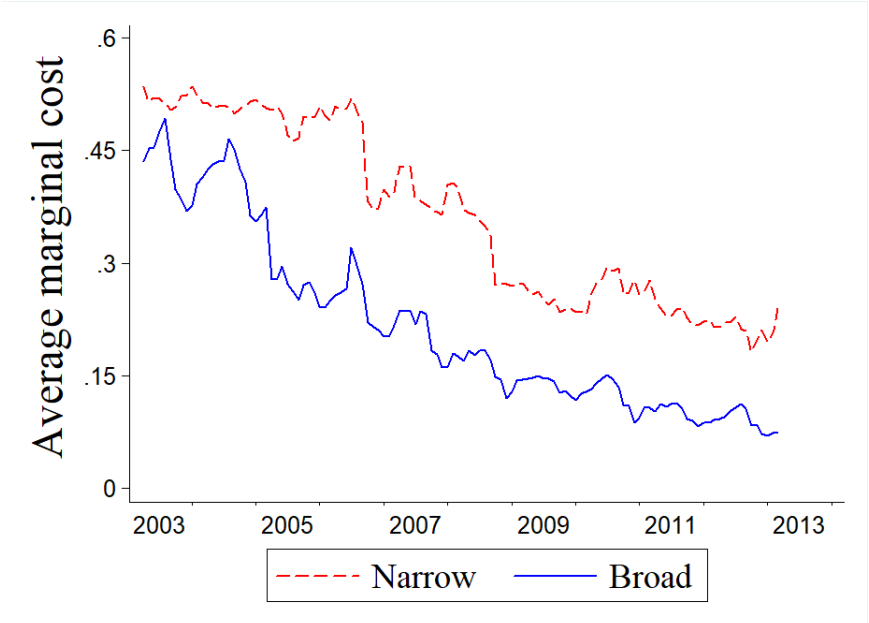


FIGURE 5.4: Estimated marginal cost by spectrum range



broad-spectrum drugs may give some ideas for possible policy interventions, as overuse of broad-spectrum antibiotics remains an issue. Since resistance can be considered as 'negative externality', the real cost of using broad-spectrum drugs should be higher. In the following sections we assess the possibility of switching consumption from broad- to narrow-spectrum drugs if their production cost were the same.

5.5 Price elasticity of demand

Based on the estimates, we present elasticities inferred by the random coefficients logit model (the last column in Table 5.1) in this section. The elasticity of demand not only determines the price-cost margins as presented in the last section, it also determines the successfulness of the cost-side interventions, which we will discuss in the next section.

The formula for computing price elasticity of market share in the random coefficient logit model of product j with respect to price change of product k in market t is the following:

$$\eta_{jkt} = \frac{\partial s_{jt}/s_{jt}}{\partial p_{kt}/p_{kt}} = \begin{cases} -\frac{p_{jt}}{s_{jt}} \frac{1}{ns} \sum_{i=1}^{ns} \alpha_i s_{ijt}(1 - s_{ijt}) & \text{if} \quad j = k \\ \frac{p_{kt}}{s_{jt}} \frac{1}{ns} \sum_{i=1}^{ns} \alpha_i s_{ijt} s_{ikt} & \text{if} \quad j \neq k \end{cases} \tag{5.1}$$

where α_i is individual taste on price and

$$s_{ijt} = \frac{\exp(\delta_{jt} + [p_{jt}, x_{jt}]Hv_i)}{\exp(\delta_{0t}) + \sum_{l=1}^{J_t} \exp(\delta_{lt} + [p_{jt}, x_{jt}]Hv_i)},$$

which is the purchasing probability of drug j by individual i in market t. In practice, we compute price elasticity for each individual and use Monte Carlo simulation to integrate it to product level.

For 131 drugs in our analysis, we have 131 own-price elasticities and 131×130 cross-price elasticities for each market, and over 120 markets (months). We summarize the price elasticities of demand in Table 5.4. All averages and standard deviations of price elasticities are weighted by product market shares. Specifically, for own-price elasticities, we first weight them by their market share in each market to obtain the average value for each market. We then give a weight to that market to compute the overall value, which equals to the proportion of the total volume of antibiotics consumed in that market over 10 years (120 markets). For cross-price elasticities, since shares of all other 130 products will change if the price of a single product changes, we do the following for summation. For each product, we aggregate 130 cross-price elasticities to one value by weighting each cross-price elasticity by the market shares of other products, which is the *weighted cross-elasticity* of the product. We next use the same steps in computing average own-price elasticities to summarize weighted cross-elasticity. On average, own-price elasticity at product

level is -3.31, with standard deviation (SD) of 4.835. Mean cross-price elasticities of all drugs is 0.172 with standard deviation of 0.308.

TABLE 5.4: Share weighted average price elasticities of demand with standard deviation

	η	SD
Own-price	-3.310	4.835
Cross-price	0.172	0.308
Share of broad-spec v.s. Price of broad-spec	0.288	0.471
Share of narrow-spec v.s. Price of broad-spec	0.148	0.199
Share of broad-spec v.s. Price of narrow-spec	0.058	0.113
Share of narrow-spec v.s. Price of narrow-spec	0.166	0.171

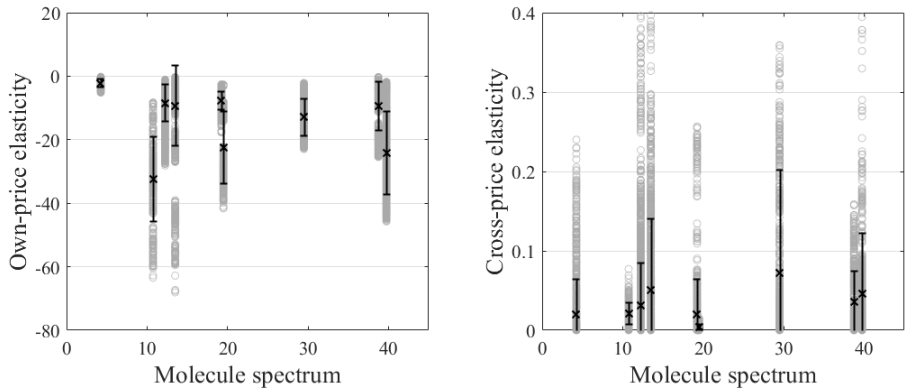
Note: Price elasticities are weighted by market share for both mean and standard deviation.

Most importantly, we partition cross-price elasticities by spectrum group of drugs, which gives information on how the price change of a drug in one group affects the market share change of another drug in and out of the same group. For instance, if the price of a broad-spectrum antibiotic increases by 1%, the share of another broad-spectrum drug will increase by 0.288%, whereas the share of a narrow-spectrum drug will only increase by 0.148%. Such elasticities suggest that two broad-spectrum drugs are closer substitutes than drugs belonging to different groups. The underline reason might be that broad-spectrum molecules may have larger overlapping in indications, as one family of bacteria may be susceptible to many of them. In contrast, drugs with narrow-spectrum molecules have smaller cross-price elasticities, and share of broad-spectrum drugs is less affected by price changes of narrow-spectrum ones.

Figure 5.5 and 5.6 plot detail own-price and weighted cross-price elasticities at product level by spectrum of molecules. Each circle represents the elasticity of a product. Figures also indicate unweighted means with crosses and standard deviations by error bars. Since more than one molecule may have an identical spectrum score, we may have many concentration points at one spectrum.

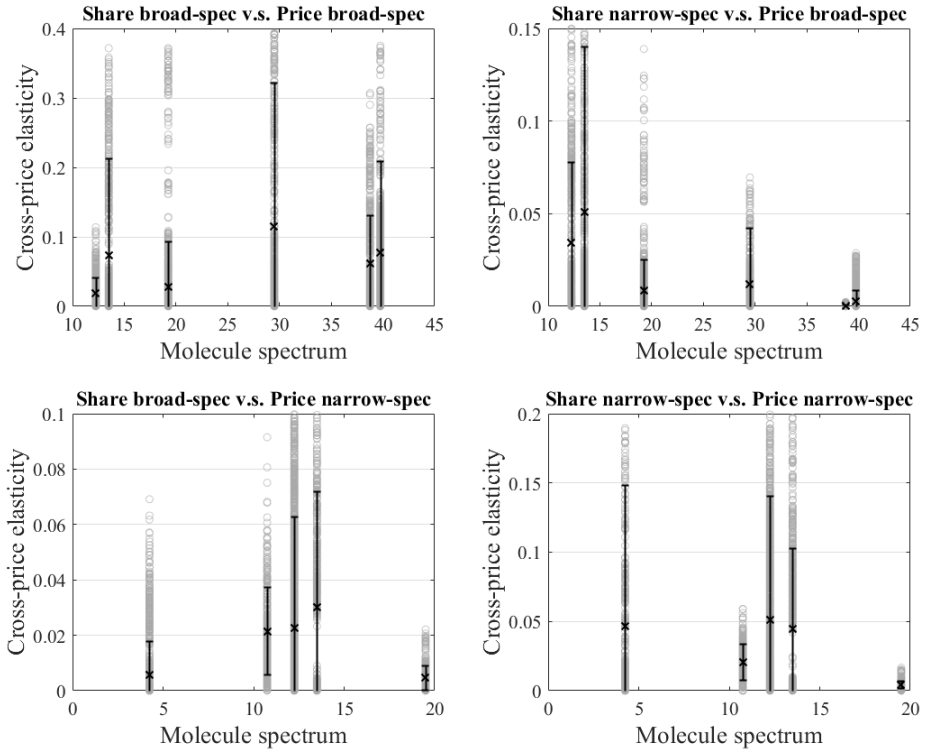
Our estimated elasticities have similar ranges of other studies. We are aware of two papers that have estimated demand for antibiotics and reported the elasticities, though those are for groups of drugs rather than for individual brands. In the context of how new drugs impact the calculations for a price index, Ellison et al. (1997) use sales data from the US for the cephalosporins and estimate a AIDS demand model. They report group wide elasticities by brand and generic groups, where each group consists of elasticities of drugs averaged over different manufacturers and forms within the same molecule. The own-price elasticities range between -4.34 and +1.06. Then, in the context of impact of TRIPS on welfare, Chaudhuri et al. (2006) use data on quinolones from India and also estimate AIDS demand by product groups. Their focus is on foreign versus domestic manufactures and so they

FIGURE 5.5: Estimated product level own-price elasticities and weighted average of cross-price elasticities by molecule spectrum



Note: A grey circle indicates the elasticity of a product, and unweighted mean and standard deviation are indicated by solid crosses and error bars.

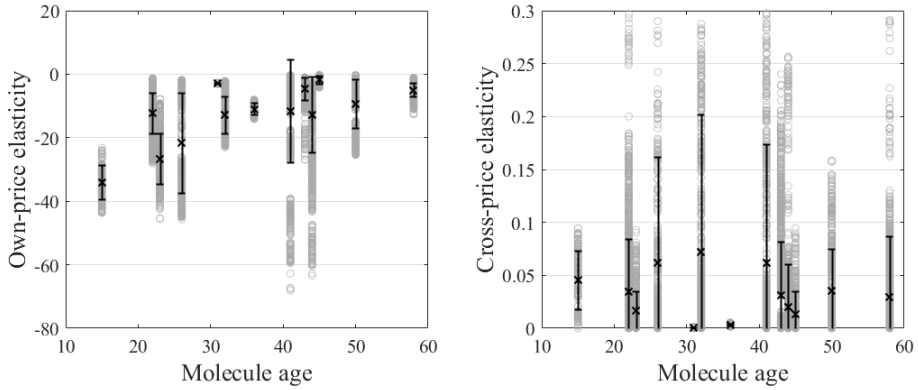
FIGURE 5.6: Estimated product level weighted average of cross-price elasticities by spectrum group



Note: A grey circle indicates the elasticity of a product, and unweighted mean and standard deviation are indicated by solid crosses and error bars.

provide for each molecule group elasticities by domestic and foreign status of manufacturers. Most of the own-price elasticities are below -2, and the range is between -5.94 and -0.08. While these estimates are at group level, there are examples of estimates at brand level as well, albeit not for antibiotics, which are more in line with our estimates. For instance, Duso et al. (2014) estimate nested logit models at brand level for anti-diabetic drugs from Germany, and report a range between -37.349 to -0.991 with a mean value of -6.65. Similarly, Björnerstedt and Verboven (2016) estimate nested-logit and random coefficients logit models using brand-level data from the Swedish analgesics market and report an average own-elasticity of -3.61 from the random coefficients logit models.

FIGURE 5.7: Estimated product level own-price elasticities and weighted average of cross-price elasticities by molecule age



Note: Age of a molecule is the difference between 2003 and the earliest launching year of a molecule. A grey circle indicates the elasticity of a product, and unweighted mean and standard deviation are indicated by solid crosses and error bars.

Finally, it is important to investigate whether price elasticity changes by the age of molecule. As discussed in the previous chapter, the antibiotics market is in urgent need of new molecules as bacteria develop resistance to old ones. However, if newly launched molecules are more sensitive to price changes, meaning they are less profitable than old products, firms may hesitate to invest further. Figure 5.7 plots own- and cross-price elasticities at product level over molecule age. The age of a molecules is computed as the difference between 2003 and the earliest launching year of a molecule anywhere in the world.[9] This figure shows that newer molecules tend be more elastic to their own price changes, signalling that they may be less profitable relative to older ones.

5.6 Demand shifting and welfare change

Recalling that the marginal cost of broad-spectrum molecules is below that of narrow spectrum molecules, in this section, we evaluate the counterfactual scenario of what would have happened if the marginal costs of producing broad-spectrum antibiotics

[9]The first launch country or area of a novel molecule is generally UK, US or EU.

were as high as those of producing narrow-spectrum agencies. One can think of this experiment as a policy intervention that aims to increase the cost of using broad-spectrum antibiotics as they are more likely to drive resistance problems, and thus, their social optimal price should be higher. As the total market in our model is defined as the sales of all antibiotics, our counter-factual scenarios do not allow us to study the shift from antibiotics to non-antibiotic drugs but rather, the shift from one kind of antibiotic to another.

Technically, we set the hypothetical marginal cost of producing broad-spectrum molecules to the same level as that of producing narrow-spectrum antibiotics. We then calculate new equilibrium prices and market shares in each period based on the hypothetical marginal cost according to the new pricing equations:

$$\tilde{p}_{jt} - \tilde{m}_{jt}(\tilde{p}_{jt}, \tilde{s}_{jt}(\tilde{p}_t; \theta); \theta) - \tilde{c}_{jt} \equiv 0 \tag{5.2}$$

where θ is the set of estimated parameters and $\tilde{c}_{jt}$ is the hypothetical marginal cost. $\tilde{p}_{jt}$ is the new market price. $\tilde{m}_{jt}$ and $\tilde{s}_{jt}$ are the recalculated market-ups and market shares from share equation and market-up equation. We solve the equation with respect to price to find new equilibrium price $\tilde{p}^*_{jt}$ and share $\tilde{s}^*_{jt}$.

We plot over time the average new market equilibrium price for broad- and narrow-spectrum molecules in Figure 5.8, weighted by the original market shares. To avoid unnecessary fluctuations, we smooth seasonal price spikes by using yearly data points. When the marginal costs were the same, broad-spectrum drugs would have higher prices than in the factual scenario, while the price of narrow-spectrum drugs would not change much. Under this new scenario, our results predict that (Figure 5.9), demand for broad-spectrum antibiotics will be reduced effectively if their production cost would be higher. On average, their demand will reduce by 27%. On the other side, the demand for narrow-spectrum agencies will be 42% higher. We also find that, it will only affect the share of the outside option at minimum, which may be supported by the fact that molecules in the outside option are not generally considered as substitutes for drugs in the inside market.

Changes in social welfare We finally calculate the associated welfare changes. Producer welfare is the monetary value of profits of all products sold in the market. Consumer welfare is defined by monetary utility, which is the individual indirect utility U_{ijt} divided by α_i, since $\alpha_i = \partial U_{ijt}/\partial y_{it}$ is the marginal utility of income. In case of logit and nested logit models, $\alpha_i = \alpha$. Consumer welfare cw_{it} is formulated as:

$$cw_{it} = \frac{1}{\alpha_i} \max_{j \in J_t} U_{ijt}, \tag{5.3}$$

as each consumer buys at most one drug to maximize his utility. cw_{it} varies across consumers in each market and an expectation should be taken to calculate the expected consumer welfare. Small and Rosen (1981) have shown that there is a closed

FIGURE 5.8: Estimated new market equilibrium price for broad- and narrow-spectrum molecules

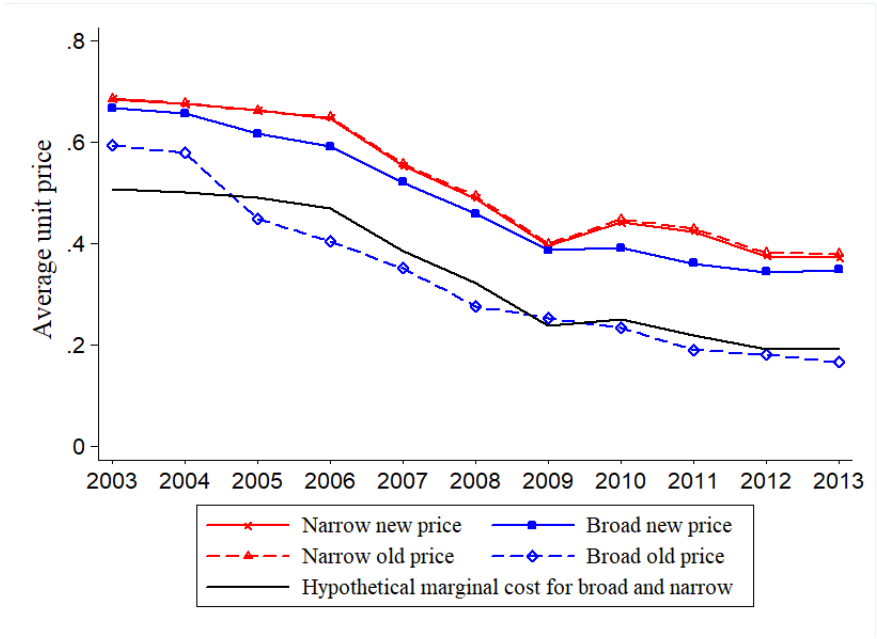
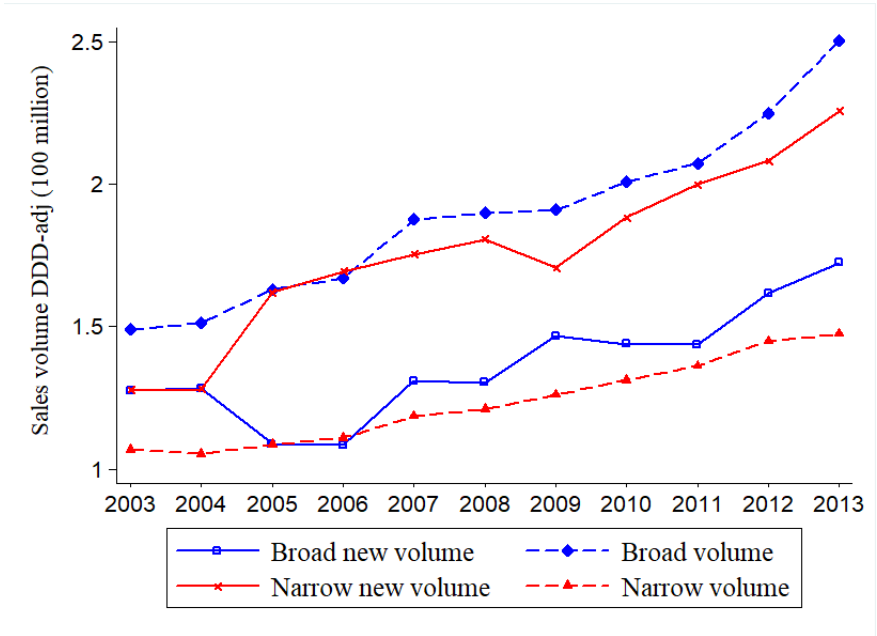


FIGURE 5.9: Estimated sales volume for broad- and narrow-spectrum molecules



form solution for discrete choice model and we follow Mariuzzo et al. (2010) to determine the welfare for the following three logit specifications:

Logit:

$$E(cw_{it}) = \frac{1}{\alpha} \ln \left[\exp(\delta_{0t}) + \sum_{l=1}^{J_t} \exp(\delta_{lt}) \right] + K_{1t}. \tag{5.4}$$

Nested logit:

$$E(cw_{it}) = \frac{1}{\alpha} \ln \left\{ \exp(\delta_{0t}) + \sum_{g=1}^{G_t} \left[\sum_{j \in \mathcal{J}_{gt}} \exp\left(\frac{\delta_{jt}}{1-\sigma} \right) \right]^{1-\sigma} \right\} + K_{2t}. \tag{5.5}$$

Random coefficients logit:

$$E(cw_{it}) = \frac{1}{ns} \sum_{i=1}^{ns} \frac{1}{\alpha_i} \ln \left[\exp(\delta_{0t}) + \sum_{l=1}^{J_t} \exp(\delta_{lt} + [p_{lt}, x_{lt}] H v_i) \right] + K_{3t}. \tag{5.6}$$

Note from the formula that K_{1t}, K_{2t}, and K_{3t} are unknown period-specific constants that are assumed the same for different scenarios and specifications in period t. Due to these unknown constants, we cannot calculate the level of consumer welfare. However, we can still generate the consumer welfare change between factual and counterfactual for each period for the total society if a baseline situation is selected.

The change in social welfare is shown in Table 5.5. Our results are adjusted for 1000 capita based on the total UK population of each year. Social welfare loss would be considered as the price paid for interventions because it distorts the market. On average, the estimated loss of social welfare is £565 per 1000 capita each year, of which the loss of consumer surplus is £412 and the loss of pharmaceutical companies is £152. Loss of welfare is larger in later years as larger proportion of demand would be shifted from broad- to narrow-spectrum drugs. In year 2012, the total loss of social welfare would be £723.8 per 1000 capita, which is equivalent to around £46 million loss for the UK in total.

TABLE 5.5: Estimated changes in social welfare

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	Mean
Consumer welfare	-183.3	-442.7	-470.9	-452.3	-450.1	-341.0	-401.9	-465.2	-503.4	-412.3
Producer welfare	-61.3	-109.8	-130.1	-147.4	-176.7	-144.5	-185.7	-199.8	-220.4	-152.9
Social welfare	-244.7	-552.5	-601.0	-599.6	-626.9	-485.4	-587.6	-665.0	-723.8	-565.2

Note: Consumer, producer and total welfare changes are the monetary changes per 1000 capita based on UK population in that year.

5.7 Tax evaluation

In the previous section, we have found significant switching behaviour if the cost of producing broad-spectrum antibiotics had almost doubled. In this section, we consider the effect of tax rates of the order: 5-20%. Since prices can vary largely for different drugs, *ad valorem* tax is considered. By contrast, unit tax may induce too large effects for some drugs and be almost ineffective for others. Technically, we rewrite the pricing equation as the following:

$$\tilde{p}_{jt}/(1+\tau) - \tilde{m}_{jt}(\tilde{p}_{jt}, \tilde{s}_{jt}(\tilde{p}_{jt};\theta);\theta) - c_{jt} \equiv 0 \tag{5.7}$$

where θ and c_{jt} represents estimated parameters and marginal cost, which are assumed to be unchanged. τ is tax rate. $\tilde{p}_{jt}$ is the new market price after the tax. $\tilde{m}_{jt}$ and $\tilde{s}_{jt}$ are the recalculated market-ups and market shares from share equation and market-up equation. We solve the equation with respect to price to find new equilibrium price $\tilde{p}^*_{jt}$ and share $\tilde{s}^*_{jt}$. We run the simulation for year 2012. Table 5.6 summarises the simulated change of prices, shares and outside share for each targeting drug group. Three tax levels are compared: 5%, 10% and 20%. In 'Scenario One', the tax is imposed only on the most worrying broad-spectrum antibiotic molecules (co-amoxiclav, quinolones and cephalosporins) in the UK (PHE, 2015a), while in 'Scenario Two', the tax base is expanded to all broad-spectrum antibiotics. The left-hand panel displays percentage changes of prices, sales volumes and the share of outside option, relatively to the factual scenario. As taxes affect welfare, we evaluate the effect of this counterfactual on consumer surplus, producer surplus, tax revenue and total surplus. The results are presented for each scenario on the right half of the table. Numbers are adjusted for 1000 capita, based on the total population of the UK in 2012, which was 63.7 million.

Scenario one (in Table 5.6) distinguishes the most problematic broad-spectrum *group* (group_g) from *other* broad-spectrum antibiotics (group_o). Co-amoxiclav, quinolones and cephalosporins together take 9% of the total market share in volume and their average price (£0.36) is higher than other broad-spectrum antibiotics. Demand for this group may drop significantly if the cost of production rises. For instance, a tax rate of 5% would reduce the demand by 9.83%. This leads consumers to switch to other drugs, where the sales volume of other broad-spectrum antibiotics will increase 1.39%, and that of narrow-spectrum agents will inflate 0.96%. The share of outside option will not change much (-0.03%). Switching behaviour would be fiercer when the tax rate is higher. A 20% tax would be enough to induce 33.34% reduction of demand for this problematic group. On the other hand, most tax would be passed to consumers. The pass-on rate is more than 90% in all cases. The average price of other broad-spectrum antibiotics increases more than narrow-spectrum drugs, as they are closer substitutes to this group.[10]

[10]In single product firm case, price increase on some products will also induce price increase on other products since they are strategic complement under Bertrand price competition. However, this

TABLE 5.6: Estimated market changes and welfare changes

		Market change			Monitory welfare change			
		% Price	% Volume	% Outside	CS	PS	Tax	TS
Scenario One								
5%	$Broad_g$	4.74	-9.83	-0.03	-34.9	15.4	10.0	-9.5
	$Broad_o$	2.46	1.39					
	Narrow	-0.05	0.96					
10%	$Broad_g$	9.47	-18.56	-0.05	-67.3	30.0	17.9	-19.4
	$Broad_o$	4.84	2.57					
	Narrow	-0.10	1.88					
20%	$Broad_g$	18.90	-33.34	-0.07	-126.1	57.0	29.3	-39.9
	$Broad_o$	9.33	4.44					
	Narrow	-0.20	3.61					
Scenario Two								
5%	Broad	5.61	-1.33	0.09	-48.7	7.6	30.9	-10.2
	Narrow	-0.05	2.02					
10%	Broad	11.19	-2.58	0.17	-93.5	14.1	60.4	-19.1
	Narrow	-0.10	3.91					
20%	Broad	22.18	-4.86	0.26	-173.8	23.8	117.7	-32.4
	Narrow	-0.21	7.41					

Note: $Broad_g$ include molecule: co-amoxiclav, quinolones (ciprofloxacin, levofloxacin and ofloxacin) and cephalosporins (cefalexin). $Broad_o$ covers all other broad-spectrum antibiotics. The table displays percentage changes of prices, volumes and the share of outside option. Welfare changes in consumer surplus, producer surplus and total surplus are monitory changes per 1000 capita based on the UK population in 2012.

The change in consumer surplus is always negative because of the price increase. The loss is £34.9 per 1000 residents when tax is at 5% level and it would increase to £126.1 when tax rate is 20%. The sign of producer surplus change is not easy to predict. It can be positive when patients switch molecules that are more profitable and benefit exceeds the loss from cost increase. Since the average price-cost margin for this group is lower than other molecule groups, producer surplus changes are positive in all cases. The loss of total surplus may serve as a monetary measure of the 'price' the society has to bear to reduce the consumption of broad-spectrum antibiotics in this group, which are small if cost increases are moderate, and larger when the tax rates are high. It would cost the market £9.5 per 1000 residents if we wanted to reduce the demand for this group by 9.83% and, could surge to £39.9 if we wanted to reduce the demand by a third.

However, price increase via tax may not be sufficient to restrict the demand for all broad-spectrum antibiotics. Although it may induce some switching behaviour from broad- to narrow-spectrum antibiotics, its overall effect may not be considerable. As shown in scenario two, with 20% tax rate, the consumption of broad-spectrum antibiotic only reduces by 4.86%, of which the majority of consumption is shifted to narrow-spectrum drugs. The pass-on rate is above unity in all cases, which creates large loss in consumer surplus. Comparing these new results with the first scenario, price increase may be sufficient to reduce the demand for some specific molecules

may not be true in multi-product firms situation, where firms may reduce the price of products that are exempting from tax, and thus making the prediction unclear.

while it may not be effective to control the demand for all broad-spectrum antibiotics. This result is intuitive. Most substitution happens within broad-spectrum antibiotic molecules, while them as a whole lack of substitutes from molecules in narrow-spectrum group. As a result, doctors can succeed in finding a better alternative available only if some molecules bear price increases but not all of them.

5.8 Conclusions

In the second part of the thesis, we estimate the demand of antibiotics market in the UK. Logit, nested logit and random coefficients logit models have been used to jointly estimate the demand and supply. Our findings give further support to the existing literature on why pharmaceutical companies are reluctant to invest in new molecules in the antibiotic market. In general, this market is still profitable with an average 35.2% price-cost margin and increasing profitability over time due to fast declining marginal cost. However, generic products do not only dominate market sales, but also siphon most of the market profitability. The marginalization of research-led pharmaceutical companies harms R&D in antibiotics. Besides, although broad-spectrum antibiotics are not recommended as first-line treatment, they produce higher margins than narrow-spectrum drugs, which may be a warning sign of inappropriate demand pattern (from a societal point of view).

Since the entry of new molecules to tackle antibiotic crisis is unlikely, 'making the most of existing antimicrobials' is the second-best option (Davies, 2013). As broad-spectrum antibiotics are more likely to exacerbate resistance, we consider whether it is possible to switch consumption from broad- to narrow-spectrum drugs with interventions. Based on the demand estimation, we provide quantitative evidence of the effectiveness of several cost-side interventions aimed at switching consumption from broad- to narrow-spectrum antibiotics and then evaluate the welfare losses. The results suggest that, cost increase may be quite an effective way to stop people from using broad-spectrum drugs, if it is sufficiently large. If the marginal cost of producing broad-spectrum antibiotics would be as high as that of narrow-spectrum drugs (almost doubled), the demand would be significantly shifted from the former to the latter. This result may shed light on the debate of using economic interventions (such as applying Pigouvian 'tax' on human antibiotic drugs) to restrict the demand. Low tax rate would only work if it were selectively imposed on the most worrying broad-spectrum molecules, however, it may not be sufficient to restrict the use on all broad-spectrum molecules.

The divergence of individual taste for the spectrum of antibiotics estimated, could be exploited to modify individual tastes and, in this way, to reduce consumption. Currently, such interventions are mainly educational campaigns, including raising awareness of antibiotics resistance to the public, professional education to prescribers as well as stewardship of preferred prescription in primary care and in hospitals (Davies and Gibbens, 2013; Scoggins et al., 2006). However, such campaigns may

not be sufficient. Since part of the preference over broad-spectrum antibiotics stems from the fear of treatment failure, especially in primary care when there is no clear clue of the specific type of bacterial pathogen, quick and cheap diagnosis test may completely solve the puzzle. Although those tests are expensive, time consuming (Shah et al., 2013) and rarely used in primary care now, scientists have made huge progress in reducing the cost and time in diagnostic method. For example, Schmidt et al. (2017) have successfully reduced the time of testing pathogens to four hours by direct DNA sequencing. If the uncertainty of bacteria type or level of susceptibility could be reduced by widely used accurate diagnosis, the inappropriate consumption of antibiotics would be calibrated.

Chapter 6

Concluding remarks

This thesis applied methods from Industrial Organization to study entry barriers and profitability of pharmaceutical markets in the UK. The first part of the thesis focused on the possibility of using product proliferation as barrier to deter or delay entry by competitors. It used the non-monotonicity test between number of products and market size, as proposed in Ellison and Ellison (2011), to detect incumbents' entry-deterrence incentive. It then used a hazard rate model to estimate the effectiveness of product varieties by incumbents on entry probability of a competitor. The first part terminates with a regression, where we investigated whether more varieties hold by incumbents prior to entry can shield their market share post entry.

Our results suggest that product proliferation has potential to be a barrier to entry in the UK. Product proliferation reduces entry probability overall, and this effect is strongest in middle-sized markets and is not significant in small-sized market. Furthermore, a large number of drug varieties hold by incumbents prior to entry can help them to preserve market share post entry. The non-monotonicity tests, however, failed to give much credit to the idea that incumbents strategically employ this strategy.

The second part of the thesis focused on antibiotic market. We used logit, nested logit and random coefficients logit model to estimate the demand of antibiotics. Based on the estimates, we assessed the profitability of the market. We found that price-cost margin is 35.2% on average, but with large variation across molecule groups and between brand/generic types. We also found that generic firms capture most of the profit in the market, while research firms earn much less. Inspired by policy discussion of using cost interventions to promote proper use of antibiotics, we estimated the price elasticity of demand between drugs, and assessed the success of shifting consumption away from broad-spectrum molecules, that cause larger resistance, to narrow-spectrum drugs. The results suggest such intervention can be effective but under certain conditions.

Apart from the topics we have studied in this thesis, there are other issues that can affect entry and market profitability in the pharmaceutical market, for instance, cartels and vertical agreements, which are recorded in other industries to have great impact on market structure and performance. The Vitamin cartels are leading cases.[1]

[1] Case COMP/E-1/37.512 — Vitamins.

They operated in the 1990s and were investigated by European Commission (EC) in 1999 and fined in 2001. EC describes them as the most damaging series of cartels that it has ever investigated. These cartels fixed prices and allocated sales quotas of their bulk vitamins sold to downstream firms who produce animal feed, human nutrition, food and pharmaceuticals, hence, damaging the profitability of downstream firms. Vertical agreements are set along the distributions line between manufacturers, wholesalers and pharmacies. One ongoing changing of the distribution model in the UK is the direct to pharmacy (DTP) agreement, which sets the rule that manufactures no longer sell their products to wholesalers, but use wholesalers only as logistic service provider. The Office of Fair Trading (OFT) report in 2007 concludes that DTP might give manufactures the ability to increase prices in the UK (OFT, 2007). However, the impacts of cartels and vertical agreements on the UK pharmaceutical markets are not fully documented in literature, and thus further studies are needed.

Appendix A

Appendix for chapter 1 and 2

TABLE A.1: Effect of product proliferation on originators' market share post-entry by market size. Interaction with time.

Variables	(1)	(2) S	(3) M	(4) L
Drugs_f	0.080	-0.395	0.107*	0.133**
	(0.050)	(0.408)	(0.062)	(0.058)
Year=2	-0.101***	0.011	-0.153**	-0.093**
	(0.039)	(0.138)	(0.075)	(0.047)
Year=3	-0.162**	-0.618*	-0.034	-0.138*
	(0.075)	(0.357)	(0.104)	(0.076)
Year=2 $\times$ Drugs_f	0.010	-0.053	0.019	0.012
	(0.031)	(0.110)	(0.054)	(0.038)
Year=3 $\times$ Drugs_f	0.021	0.414	-0.157**	0.019
	(0.065)	(0.288)	(0.067)	(0.064)
Sales_f	-0.011	-0.075*	-0.020	-0.010
	(0.009)	(0.042)	(0.045)	(0.020)
MonoYear	0.010**	0.029	0.013**	0.004
	(0.004)	(0.025)	(0.006)	(0.007)
Chronic	0.017	0.352	0.101	-0.068
	(0.054)	(0.230)	(0.082)	(0.072)
EMEA	0.037	0.000	-0.141	0.089
	(0.090)	(0.000)	(0.277)	(0.086)
Constant	0.716***	1.394***	0.761	0.789**
	(0.158)	(0.511)	(0.600)	(0.352)
Observations	515	37	112	366
# markets	182	14	40	128
R^2 within	0.254	0.274	0.446	0.230
R^2 between	0.0377	0.198	0.136	0.0509
R^2 overall	0.0687	0.111	0.212	0.0666

Note. Robust standard errors are in parentheses. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$. Since the main variable is market specific, we cluster our errors at market level. 8+2(+1) is dropped because markets experienced entry are all older than the implementation of the new rule.

TABLE A.2: Effect of product proliferation on entry probability.
C-loglog regressions. Dependent variable: $\log\left(-\log(1-\lambda_{kt})\right)$
Actual number of formulation veriaties.

	No early entry			1986-2006			Since 1986		
Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Drugs_{t-1}	0.086	0.095	-0.502	0.036	0.045	0.125	0.038	0.041	-0.183
	(0.091)	(0.091)	(0.835)	(0.086)	(0.086)	(0.594)	(0.086)	(0.086)	(0.681)
Middle		0.339	-0.378		0.404	0.647		-0.328	-0.361
		(0.467)	(1.133)		(0.351)	(0.901)		(0.352)	(0.961)
Large		0.380	-0.441		0.355	0.424		-0.094	-0.435
		(0.583)	(1.205)		(0.468)	(0.942)		(0.441)	(0.963)
Middle $\times$ Drugs_{t-1}			0.562			-0.174			0.052
			(0.851)			(0.633)			(0.726)
Large $\times$ Drugs_{t-1}			0.615			-0.059			0.255
			(0.844)			(0.605)			(0.689)
Sales_{t-1}	0.405***	0.395***	0.401***	0.331***	0.318***	0.317***	0.321***	0.311***	0.313***
	(0.044)	(0.070)	(0.071)	(0.036)	(0.064)	(0.064)	(0.033)	(0.052)	(0.052)
Chronic	0.248	0.274	0.291	0.201	0.243	0.243	0.239	0.287	0.287
	(0.229)	(0.230)	(0.233)	(0.199)	(0.202)	(0.203)	(0.197)	(0.202)	(0.202)
SPC	-0.284	-0.271	-0.272	0.130	0.155	0.151	0.137	0.125	0.128
	(0.366)	(0.384)	(0.386)	(0.302)	(0.315)	(0.316)	(0.303)	(0.315)	(0.317)
8+2(+1)	2.087***	2.154***	2.155***	0.020	0.065	0.066	0.194	0.279	0.259
	(0.785)	(0.794)	(0.792)	(0.568)	(0.578)	(0.581)	(0.445)	(0.452)	(0.454)
Constant	-11.179***	-10.536***	-9.910***	-9.656***	-9.685***	-9.762***	-8.889***	-8.471***	-8.203***
	(2.308)	(2.405)	(2.472)	(1.201)	(1.280)	(1.341)	(1.167)	(1.169)	(1.239)
Observations	2,670	2,523	2,523	5,460	5,199	5,199	6,345	6,071	6,071
Log Likelihood	-426.3	-407	-406.7	-605	-585.3	-585.2	-635.4	-615.6	-615.3
Entry events	138	135	135	171	168	168	176	173	173
Markets	460	402	402	498	440	440	691	632	632

Note. Robust standard errors are in parentheses. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$. Errors are clustered at market level. Variables are lagged one year if contemporaneous values are used. Duration dummies and calendar year dummies are included in all regressions. Observations and markets at risk have slightly smaller sample size because of missing observations when constructing market size group. MolFirm_{t-1} group dummies, Nearby_{t-1} dummy, EMEA dummy are not shown, and they are all insignificant.

TABLE A.3: Effect of product proliferation prior to entry on originators' market share post entry, excluding markets where competitor has no sales value.

Variables	(1)	(2)	(3)	(4) S	(5) M	(6) L
$Drugs_f$	0.110**	0.112**	0.023	0.037	0.090	0.157***
	(0.049)	(0.049)	(0.283)	(0.215)	(0.087)	(0.058)
Middle		0.052	-0.009			
		(0.118)	(0.379)			
Large		0.004	-0.120			
		(0.150)	(0.379)			
Middle $\times$ $Drugs_f$			0.052			
			(0.298)			
Large $\times$ $Drugs_f$			0.110			
			(0.290)			
$Sales_f$	-0.005	-0.001	-0.002	0.145*	0.010	-0.009
	(0.010)	(0.019)	(0.019)	(0.086)	(0.052)	(0.020)
Year=2	-0.092***	-0.092***	-0.092***	-0.035	-0.129***	-0.083***
	(0.011)	(0.011)	(0.011)	(0.046)	(0.026)	(0.013)
Year=3	-0.149***	-0.149***	-0.149***	-0.162	-0.216***	-0.127***
	(0.018)	(0.018)	(0.018)	(0.136)	(0.034)	(0.020)
MonoYear	0.011**	0.011**	0.011**	0.016	0.014**	0.006
	(0.005)	(0.005)	(0.005)	(0.024)	(0.006)	(0.007)
Chronic	0.036	0.047	0.047	0.294	0.133	-0.059
	(0.056)	(0.057)	(0.058)	(0.314)	(0.088)	(0.072)
EMEA	0.056	0.053	0.056	0.000	-0.109	0.109
	(0.090)	(0.090)	(0.092)	(0.000)	(0.288)	(0.086)
Constant	0.547***	0.460*	0.566	-1.244	0.322	0.685*
	(0.185)	(0.252)	(0.431)	(0.950)	(0.739)	(0.364)
Observations	476	476	476	31	103	342
# markets	175	175	175	12	40	123
R^2 within	0.280	0.280	0.280	0.161	0.524	0.248
R^2 between	0.0801	0.0849	0.0859	0.353	0.187	0.0882
R^2 overall	0.0935	0.0964	0.0987	0.323	0.228	0.0943

Note. Robust standard errors are in parentheses. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$. Since the main variable is market specific, we cluster our errors at market level. 8+2(+1) is dropped because markets that experienced entry are all older than the implementation of the new rule. Some markets are missing due to missing co-variates.

Appendix B

Appendix for chapter 3 and 4

Appendix 1.

Suppose there are K different products in the outside option, each is associated with mean utility δ_k and market share s_k. Under the logit model, the market share of drug l in the outside is expressed as $s_l = \exp(\delta_l)/(\sum_{l=1}^{K}\exp(\delta_l) + A_J)$, where A_J represents the term from the inside option:

$$A_J \equiv \begin{cases} \sum_{l=1}^{J_t}\exp(\delta_{lt}), & \text{if logit} \\ \sum_{G,t} D_{gt}^{(1-\sigma_g)}, & \text{if nested logit} \\ \sum_{l=1}^{J_t}\exp(\delta_{lt} + [-p_{jt}, x_{jt}](\Sigma v_i)), & \text{if rc logit} \end{cases} \tag{B.1}$$

Suppose there is a δ_0 that satisfies $s_0 = \exp(\delta_0)/(\sum_{l=1}^{K}\exp(\delta_0) + A_J)$. Since

$$s_0 = s_1 + s_2 + ... + s_K,$$

we have

$$s_0 = \sum_{l=1}^{K}\exp(\delta_l)/(\sum_{l=1}^{K}\exp(\delta_l) + A_J).$$

It implies $\delta_0 = \ln(\sum_{l=1}^{K}\exp(\delta_l))$. Take the feature of the LogSumExp function, we have δ_0 lies in the interval: $[\max(\delta_1, \delta_2, ..., \delta_K), \quad \max(\delta_1, \delta_2, ..., \delta_K) + \ln(K)]$.

Appendix 2.

In this appendix, we describe how to calculate share weighted own- and cross-price elasticities. We take one market for example, and in the data we have 120 such markets. To sum up over 120 markets, we use the DDD-adjusted quantity as weight.

For one market, suppose we have only 4 drugs: J_1, J_2, J_3 and J_4, of which J_1, J_2 are broad-spectrum and J_3, J_4 are narrow-spectrum. Their market shares are s_1, s_2, s_3 and s_4 respectively. Suppose s_0 is the share of the outside market, and thus, $1 \equiv s_0 + s_1 + s_2 + s_3 + s_4$. Let $\eta_j, j = 1, 2, 3, 4$ denote their own price elasticities and $\eta_{nk}, n = 1, 2, 3, 4$ and $k = 1, 2, 3, 4$ denote the cross-price elasticity between two product n and k, say change of share of product k with respect to the price change of product n. Table B.1 summarizes the setting.

TABLE B.1: An illustration of price elasticity of demand

Price-Share		B		N	
		J_1	J_2	J_3	J_4
B	J_1	η_1	η_{12}	η_{13}	η_{14}
	J_2	η_{21}	η_2	η_{23}	η_{24}
N	J_3	η_{31}	η_{32}	η_3	η_{34}
	J_4	η_{41}	η_{42}	η_{43}	η_4

The share weighted average own-price elasticity Γ^O for this market is easy to compute, which is

$$\Gamma^O = \frac{s_1\eta_1 + s_2\eta_2 + s_3\eta_3 + s_4\eta_4}{s_1 + s_2 + s_3 + s_4}.$$

If we only want to compute the weighted average own-price elasticity for broad-spectrum drugs Γ^O_B, we take only own-price elasticities of the first two drugs:

$$\Gamma^O_B = \frac{s_1\eta_1 + s_2\eta_2}{s_1 + s_2}.$$

Similarly, we can do it for narrow-spectrum drugs as well.

To compute the share weighted average cross-price elasticity of a market, we have an extra step at the beginning. Suppose, we want to compute the overall average of weighted cross-price elasticity, we do the following. In the first step, we compute the *weighted cross-price elasticity* w_j for each drug j. For instance, for drug 1, it is:

$$w_1 = \frac{s_2\eta_{12} + s_3\eta_{13} + s_4\eta_{14}}{s_2 + s_3 + s_4}$$

Second, we aggregate them to market level,

$$\Gamma^C = \frac{s_1w_1 + s_2w_2 + s_3w_3 + s_4w_4}{s_1 + s_2 + s_3 + s_4}.$$

where Γ^C is the share weighted average cross-price elasticity for the market.

In addition, if we want to compute the cross-price elasticity within broad-spectrum antibiotics, we can first compute the weighted cross-price elasticity of a drug to other broad-spectrum drugs only, and we aggregate them over all broad-spectrum drugs. We do the following. First, we compute the weighted cross-price elasticity to other broad-spectrum drugs: $w^B_1 = s_2\eta_{12}/s_2 = \eta_{12}$ and $w^B_2 = s_1\eta_{21}/s_1 = \eta_{21}$. Then the weighted average cross-price elasticity within broad-spectrum antibiotics $\Gamma^C_B B$ is

$$\Gamma^C_{BB} = \frac{s_1w^B_1 + s_2w^B_2}{s_1 + s_2}.$$

Similarly, the weighted average cross-price elasticities between broad- and narrow-spectrum drugs, i.e., the share change of narrow-spectrum w.r.t. the price change of broad-spectrum drugs, can be calculated in the following way. First compute the

weighted cross-price elasticity of a drug to other narrow-spectrum drugs:

$$w_1^N = \frac{s_3\eta_{13} + s_4\eta_{14}}{s_3 + s_4}$$

and

$$w_2^N = \frac{s_3\eta_{23} + s_4\eta_{24}}{s_3 + s_4}.$$

Then sum up over all broad-spectrum antibiotics:

$$\Gamma_{BN}^C = \frac{s_1 w_1^N + s_2 w_2^N}{s_1 + s_2}.$$

For all averages used in the main content, weighted standard deviations are computed accordingly.

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