Department of Economics

An Economic Analysis of the Regulation of Pharmaceutical Markets

Lluís Saurí

Thesis submitted for assessment with a view to obtaining the degree of Doctor of Economics of the European University Institute

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Abstract

Regulation in pharmaceutical markets is pervasive in most countries, especially in Europe. The nature of existing regulations is diverse, as they serve a number of purposes: guaranteeing safety, efficacy and security of drug usage; but also ensuring patients access to treatment, preserving affordability and fostering pharmaceutical innovation.

A number of regulatory interventions are purposely designed to bring about more efficient pharmaceutical markets. These interventions are ultimately intended to increase welfare for patients today and patients tomorrow. Welfare today requires ensuring patients access to existing pharmacological treatment at an affordable cost. Welfare tomorrow requires ensuring a continued effort on research and development to produce pharmaceutical innovations that respond to currently unmet medical needs.

The chapters of this thesis focus on a number of regulatory interventions that attract notable attention due to their effect on access, affordability and innovation. These include the regulation of pharmaceutical parallel trade, direct-to-consumer advertising of prescription drugs and off-patent pharmaceutical markets. By assessing the impact of public interventions on market outcomes and patients welfare, this thesis aims at contributing to the debate about optimal regulation of pharmaceutical markets.

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Lluís Saurí

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" The apothecary may derive the following profits from his sales: Such extracts and simples as he need not keep in stock for more than a year, before they may be employed, may be charged for at the rate of three tarrenes an ounce. Other medicines, however, which in consequence of the special conditions required for their preparation or for any other reason, the apothecary has to have in stock for more than a year, he may charge for at the rate of six tarrenes an ounce. "

Frederick II of Hohenstaufen
Medical Law of 1240 in the Kingdom of the Two Sicilies

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Preface

Regulation in pharmaceutical markets is pervasive in most countries, especially in Europe. The nature of existing regulations is diverse, as they serve a number of purposes: guaranteeing safety, efficacy and security of drug usage; but also ensuring patients access to treatment, preserving affordability and fostering pharmaceutical innovation.

Most types of regulation have an economic impact, as they often modify the incentives given to the relevant stakeholders in the pharmaceutical markets and shape the normative framework within which stakeholders operate. Even regulations intended mainly to set scientific and technological standards are relevant from an economic perspective, as they typically have an impact both on the value delivered by medicines and the costs of development, production and provision to patients.

A number of regulatory interventions are purposely designed to bring about more efficient pharmaceutical markets. These interventions are ultimately intended to increase welfare for patients today and patients tomorrow. Welfare today requires ensuring patients access to existing pharmacological treatment at an affordable cost. Welfare tomorrow requires ensuring a continued effort on research and development to produce pharmaceutical innovations that respond to currently unmet medical needs.

The chapters of this thesis focus on a number of regulatory interventions that attract notable attention due to their effect on access, affordability and innovation. By assessing their impact on market outcomes and patients welfare, this thesis aims at contributing to the debate about optimal regulation of pharmaceutical markets.

Chapter 1

Parallel trade and incentives to innovate when governments regulate prices

Chapter 1 looks at how parallel trade of pharmaceuticals may contribute to the availability of cheaper drugs in certain markets at the expense of those drugs being more expensive in other countries. Parallel trade may as a consequence have an impact on patients access to medicines in exporting and importing markets, while distorting incentives to innovation by affecting returns to R&D investment.

Parallel trade limits the capacity of the manufacturer to price discriminate across customers in different geographic markets. In chapter 1 we assess the welfare effects of parallel trade when decisions on prices are not taken unilaterally by firms, as it is the case for instance in the pharmaceutical sector. We develop a model where governments impose price ceilings to show that the welfare implications of parallel trade depend crucially on who is the price setter. When firms unilaterally set prices, parallel trade

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tends to be welfare detrimental because it prevents firms from optimally discriminating in prices. When governments impose price ceilings, parallel trade is welfare enhancing because it mitigates the incentives to free-ride on other countries contribution to innovation. In both cases, the higher are the differences in demand across countries, the worse are the welfare properties of parallel trade.

Chapter 2

Direct-to-consumer advertising of prescription drugs: informing patients or persuading physicians?

In chapter 2 we discuss the impact of direct-to-consumer advertising (DTCA) on patients access to appropriate pharmacological treatment. DTCA increases the availability of information to patients about diseases, symptoms and available treatments, thus contributing to reduce under-diagnosis and increase access to treatment. It may however convey persuasive information that in certain circumstances could distort prescription decisions if the incentives of prescribers make them vulnerable to patients' demands.

DTCA may give patients the ability of better learning their needs, both regarding physician consultations and available treatments. DTCA may consequently reduce information asymmetries in the relation between the patient and the physician. Persuasive advertising may induce consumer demand not based on therapeutic grounds, eventually exacerbating informational problems. The purpose of chapter 2 is to analyse the welfare properties of DTCA, taking into account both its informative and persuasive effects. In our model, physicians are assumed to face some harassment costs when contradicting the preferences of their patients over the drugs prescribed, what creates an agency problem between the patient and the physician. We analyse the welfare properties of DTCA under the scenarios of perfect and imperfect agency. In the first case, DTCA can only have an informative effect on consumers. In the second case, it can have also a persuasive effect. We show that DTCA tends to be welfare enhancing when physicians are perfect agents. On the contrary, when they are imperfect agents, DTCA welfare effects are ambiguous. In particular, it can be detrimental to consumer welfare when harassment costs are relatively high.

Chapter 3

A theoretical framework for the analysis of branded-generic competition in off-patent pharmaceutical markets

In chapter 3 we study the impact of generic competition in off-patent pharmaceutical markets when patients perceive the branded product as being of higher quality than the generics and are allowed to pay a co-payment to consume the branded product. We

show that while generic competition always reduces prices, under certain circumstances branded and generic firms are able to coordinate around high-price equilibria with a detrimental impact on welfare. This is the case when the branded firm can commit to a certain preferred price before generics choose the quantities they produce. We argue that price regulation and authorised generics may facilitate this type of coordination. We also show that policy interventions that seek to increase generic market share by distorting patients choices may have the unintended effect of softening generic competition and lead to higher generic prices.

Chapter 4

Patterns of generic entry: number of entrants and time to entry

Generic entry is the main source of competition in off-patent pharmaceutical markets. However, generic entry does not occur in every market and it often tends to occur with a significant delay with respect to the date of loss of exclusivity by the patent holder. In chapter 4 we look at the patterns of generic entry in a number of European countries and identify the main factors that attract early generic entry. In particular, we are interested in the impact that pervasive regulation of European pharmaceutical markets has on the occurrence and pattern of generic entry. We show that patterns of generic entry differ significantly across European countries and types of drugs, and identify some factors that explain this heterogeneity. We observe that early entry is more likely in larger markets, when price regulation is less strict and where regulatory incentives for generic prescription and dispensation are in place.

Chapter 5

Effects of generic entry on market structure and prices

Generic competition is considered to be the main mechanism to erode the market power that patent-holders enjoy during the period of market exclusivity. However, generics do not appear to be always equally effective at driving market prices down and at gaining market share. In chapter 5 we look at the development of prices and market structure after loss of exclusivity and in presence of generic entry in a number of European countries. In particular, we are interested in the impact that pervasive regulation of European pharmaceutical markets has on the competitive landscape of off-patent pharmaceutical markets. We show that prices and market shares behave differently across European countries and types of drugs, and identify some factors that explain this heterogeneity. Price competition and generic uptake are positively correlated with the value of the market, the number of generic entrants, the absence of price controls, and the existence of regulatory incentives for the prescription and dispensation of generics.

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Part I

Welfare analysis of parallel trade and direct-to-consumer advertising of prescription drugs

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Chapter 1

Parallel trade and incentives to innovate when governments regulate prices

Abstract

Parallel trade limits the capacity of the manufacturer to price discriminate across customers in different geographic markets. In this paper we assess the welfare effects of parallel trade when decisions on prices are not taken unilaterally by firms, as it happens for instance in the pharmaceutical sector. We develop a model where governments may impose price ceilings to show that the welfare implications of parallel trade depend crucially on who is the price setter. When firms unilaterally set prices, parallel trade tends to be welfare detrimental because it prevents firms from optimally discriminating in prices. When governments impose price ceilings, parallel trade is welfare enhancing because it mitigates the incentives to free-ride on other countries' contribution to innovation. In both cases, the higher are the differences in demand across countries, the worse are the welfare properties of parallel trade.

Key words: Pharmaceuticals, Parallel trade, Price discrimination, Innovation
JEL Classifications: I11; K21; L41; L51

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1.1 Introduction

1.1.1 Policy and case law

Parallel trade is the resale of a product by a wholesaler in a market other than that intended by the manufacturer. When a manufacturer sells the same product in different markets at different prices, then parallel trade is simply arbitrage. Parallel trade limits the capacity of the manufacturer to price discriminate across customers in different geographic markets. Competition policy in the European Union tends to foster parallel trade as a means to integrate markets and enhance competition. Increased competition is thought to provide efficiency gains, but may also erode firms' incentives to innovate. The convenience of allowing parallel trade to take place or not is closely related to the welfare effects of price discrimination.

Price discrimination across countries is a typical feature of many industries, and in particular of those industries that are intensive in the use of knowledge under protection of intellectual property rights. Differences in prices create an incentive to buy the product in a low-price market and resell it at a higher price in another market, that is, price differentials create room for arbitraging through parallel trade. Allowing this practice may conflict with intellectual property law, because recognizing the right of buyers to freely trade with any good they buy may erode the right of owners of intellectual property rights to be the sole sellers of a given good.

Intellectual property rights usually give their holder the right to price discriminate between countries, while prohibiting at the same time parallel imports through contractual means. This is a consequence of the 'national-exhaustion' interpretation of patent law, which considers that by selling a product in one market the patent holder does not lose the right to be the only seller of that product in any other market. This view has been increasingly challenged, on the grounds of what has been called the 'international-exhaustion' interpretation of patent law. According to the latter, the patent holder would lose all property rights over a product once it has been sold in one market, what includes losing the right to prevent the buyer from reselling the product in any other market. The implications of moving from one interpretation to the other are evident, as one leads to the prohibition of parallel trade without the consent of the patent holder while the other leads to its legalization.

This was a contentious issue in the negotiation of the WTO's agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs). Developing countries argued

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that their licensees should be able to export their products to developed countries without restrictions based on intellectual property rights. The final agreement did not endorse any particular interpretation of property rights exhaustion, thus allowing countries to continue prohibiting international parallel imports on the grounds of patent law. One exception is the compulsory licensing of pharmaceuticals that any country can impose to deal with national health crises. Pharmaceuticals produced under compulsory licensing could be reexported to other markets without infringing any patent law or contractual agreement, because even if they are intended to satisfy domestic needs, there is no formal limitation to their exportation, other than those imposed by the destination country.

The convenience of allowing parallel trade has been an issue of debate also within developed countries due to the observed differences in pharmaceutical prices. These differences in prices are often the consequence of the variety of national regulatory regimes affecting the pharmaceutical industry. Typically, prices are lower in countries where governments participate in the price-setting process than they are in countries where prices are unilaterally set by firms. Canada is an example of the former and the United States are an example of the latter. Proximity and differences in prices have led to a substantial amount of cross border purchases by US buyers (Szymanski and Valletti [9]).

While parallel trade of pharmaceuticals remains illegal in most countries, it is allowed and even favoured within the European Union. The 'national-exhaustion' interpretation of intellectual property law is not recognized by European legislation as far as parallel trade within the EU is concerned. The Treaty of Rome eliminates any right to bar unauthorized trade between member States. The primacy of free trade over patent protection has been upheld by the European Court of Justice's ruling in *Merck v. Primecrown*[1], which held that a manufacturer's patent rights are internationally exhausted within the EU once a product is placed on the market in any member country. However, this initial interpretation has recently been complemented by the ruling of the European Court of First Instance in *GlaxoSmithKline v. EC Commission*[2], according to which price discrimination may have to be preserved if it gave rise to an economic advantage by contributing to promote innovation. It does not appear to be clear yet, hence, how this conflict should be solved.

As a consequence of market integration in Europe, parallel imports of pharmaceuticals have increasingly undermined price differentials across European countries. Kanavos and Costa-Font [5] provide evidence of the significative amount of parallel trade in the EU (the United Kingdom and the Netherlands are the countries with higher share of

[1] Case C-267-268/95. *Merck & Co. Inc. v. Primecrown Limited*. Court of Justice of the European Communities. Press Release No 58/96, 5 December 1996.

[2] Case T-168/01. *GlaxoSmithKline v. EC Commission*. Court of First Instance of the European Communities. Press Release No 79/06, 27 September 2006.

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imported pharmaceuticals, which represent 20% and 14% of the their markets respectively) and comment on its effects in terms of price convergence of pharmaceuticals in Europe. In fact, the European Commission has fostered parallel trade with the aim of effectively creating a single European market for pharmaceuticals and with the conviction that free trade would yield efficiency gains. However, parallel trade in pharmaceuticals may reduce economic welfare partly because countries achieve low pharmaceutical prices by regulation that could potentially undermine patients' access to medicines and partly because of the effects that parallel trade may have on incentives to innovate. The trade off between uniform pricing and innovation is at the base of the CFI's ruling in *GlaxoSmithKline v. EC Commission*.

1.1.2 Economic Analysis

Even without considering incentives to innovate, allowing firms to price discriminate may be controversial because the effects of third-degree price discrimination on aggregate welfare are ambiguous. Varian (1985) shows that price discrimination enhances social welfare only if it leads to an increase in output. Price uniformity is welfare enhancing when it does not imply the exclusion of any market from being served, but as soon as price uniformity leads to the closure of markets, then price discrimination is shown to be preferable.

Given that parallel trade limits the scope for price discrimination, we can follow the same line of reasoning as Varian [11] to conclude that the effects of parallel trade on social welfare may be ambiguous. Malueg and Schwartz [7] show that parallel trade between markets enjoying different prices is welfare enhancing only when it does not lead to the closure of any market. If the willingness to pay in one market were sufficiently low in relation to others, parallel imports would lead to its closure and aggregate welfare be reduced. They conclude that parallel trade benefits consumers in high-price markets, which see their price reduced, and punishes consumers in low-price markets, whose price is raised and who may even get their market closed. Depending on the size of these effects, parallel trade can turn out to be either beneficial or detrimental to welfare. The larger the differences in demand across countries, the higher the chance that parallel trade reduces welfare.

Other works introduce in the analysis some specific characteristics of the pharmaceutical industry. Bordoy and Jelovac [1] propose a model that accounts for the distortion on demand elasticities caused by copayments to finance the purchase of pharmaceuticals. They find that parallel trade is detrimental to welfare when it is motivated essentially by

differences in the public health systems, rather than by differences in demands. Ganslandt and Maskus [2] highlight the importance that problems of vertical control may have when parallel imports are permitted. In the presence of vertical-control problems, the manufacturer may use its ability to price discriminate in order to disincentivize parallel trade and to limit its pro-competitive effects in the import market. The main limitation of these works is that none of them studies the relation between price-discrimination and incentives to innovate. They just look at the static effects of parallel trade, but not at its dynamic effects on innovation.

The more innovation-based an industry is, the greater the importance of intellectual property rights tends to be. Incentives to invest in R&D depend on the ex-post capacity by the manufacturer to enjoy some market power to sell at prices above marginal cost. The ability to price discriminate reinforces manufacturer's ex-post capacity to extract rents from innovative goods, thus increasing incentives to spend in R&D. It is crucial to understand the interplay between price discrimination and incentives to innovate in order to determine whether and under what circumstances parallel trade is or not welfare enhancing. Szymanski and Valletti [9] address this issue by endogenizing the quality of the good sold. By doing so, they make quality decisions by the manufacturer depend on the prices at which it will be able to sell the product in each market. In that setup, higher prices foster R&D spending and parallel imports may have detrimental effects on quality decisions if they lead to a sufficiently low uniform price. Li and Maskus [6] get similar results through a different model in which the manufacturer decides how to invest in cost-reducing innovation. Again, parallel trade has a potential to damage social welfare by inhibiting R&D spending. Valletti [10] considers the case for imposing uniform pricing through parallel trade in a framework in which markets are different on two dimensions: marginal costs and consumer demands. The model leads to the conclusion that parallel trade produces lower investment in R&D when differential pricing is based on differences in countries' demands, while it fosters investment when the differences in prices are due to differences in costs of production.

So far we have been considering that the manufacturer enjoying monopoly power, thanks to patent protection, determines both prices and quality. In the pharmaceutical industry, however, very often are governments to set prices, not firms. It may therefore not be adequate to look at price discrimination using the case with firms fixing prices as the benchmark case. We should try to understand the actual process of determination of pharmaceutical prices, in order to be able to evaluate the welfare effects of parallel trade. Rey [8] proposes a model where pharmaceutical prices are the result of a negotiation between governments and firms. The outcome of the negotiations depends on the objective function of the governments, who care for low prices and high quality at the same time. To the extent that parallel trade leads to price uniformity across markets,

it also limits the scope for negotiation, thus limiting the search for an efficient outcome from negotiations. Price uniformity prevents a country that is willing to pay high prices in order to promote R&D from doing so, because the price set in the low-demand country prevails as the unique price everywhere. The author concludes that parallel trade worsens the already non-efficient outcome obtained without parallel trade and leads to price uniformity at the lowest level of R&D.

An important limitation of these works is that they ignore how different trade regimes may create different incentives for governments setting price controls. In Rey [8], for example, the contribution of each country to the financing of innovation is independent from the contribution of each other. Even if the public-good nature of innovation is explicitly recognized, the author defines governments' objective functions in such a way that make them completely insensitive to other governments contributions to innovation. As shown in Grossman and Lai [3], national policies to foster innovation are strategic substitutes in a two-country or many-country policy-setting game. This means that the greater willingness to pay for quality in some countries create incentives for other countries to free-ride on the contribution to innovation granted by the former ones. This reasoning has been applied to parallel trade in Grossman and Lai [4], where they develop a model for a world economy with ongoing innovation and trade and show that parallel trade can mitigate free-riding in the financing of innovation when governments unilaterally set price controls.

In this paper we develop a model where governments may impose price ceilings to firms. Even though the approach is similar to the one in Szymanski and Valletti [9], by introducing price regulation we account for the fact that prices of pharmaceuticals are only exceptionally set by firms. In contrast with Rey [8], here governments take into consideration other governments' policies when taking their own decisions on prices, what creates incentives to free-ride as in Grossman and Lai [4]. In this model, the welfare effects of parallel trade depend crucially on two factors: who leads the price setting process, governments or firms, and the degree of demand dispersion across countries. We show that depending on whether governments regulate prices or not, parallel trade may have different welfare implications. When firms unilaterally set prices, parallel trade tends to be welfare detrimental because prevents firms from optimally discriminate in prices, what reduces their profits as well as their incentive to innovate and to improve quality. When governments impose price ceilings, the possibility of sustaining price differentials across markets creates incentives for governments in low-demand markets to force their prices down in an attempt to free-ride on other governments' higher willingness to pay for quality. In that case, parallel trade is welfare enhancing because it

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disciplines governments in low-demand markets by making them responsible for the uniform price that will prevail in all markets. In both cases, the higher are the differences in demand across countries, the worse are the welfare properties of parallel trade.

This Section has been devoted to explain the policy debate on the convenience of allowing parallel trade and to briefly summarize previous economic analysis on that topic. In Section 2, we develop a model where prices are the result of the interaction between governments and firms. We derive this model under two different regimes of exhaustion of intellectual property rights: a national-exhaustion regime preventing parallel trade and an international-exhaustion regime allowing parallel trade to take place. We present the analytical results, show some numerical solutions and discuss their main implications. Section 3 summarizes the conclusions of our analysis.

1.2 The model

1.2.1 Setup and Timing

To formalize the effects of parallel trade on prices, consider the following timing of a game played by two governments, H and L, and an innovative firm F foreign to both countries:

1. Governments H and L establish price ceilings $\bar{p}_H$ and $\bar{p}_L$.
2. Firm F invests on R&D to produce a unique good of quality s and sets prices in markets H and L, eventually constrained by the price ceilings established in the first stage.
3. If parallel trade is allowed, buyers decide whether they engage or not in parallel trade.

The sequence of stages two and three are the same as in Valletti [10], where firms first invest on quality and set prices, and then buyers decide whether to engage on parallel trade. However, by contrast here firms are constrained by the price ceilings set by governments in a previous stage. Our timing leads us to assume full commitment by governments to maintain their price ceilings once firm F has invested in quality. We will see that in our model governments are willing to accept positive prices only to promote innovation. Unless full commitment is assumed, once innovation has been done,

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governments have the incentive to cut price ceilings. For our purposes, the assumption of full commitment is necessary to acknowledge the effects that the pricing policies by governments have on the investment decisions taken by the monopolist. By giving governments the ability to commit to certain pricing policies in the first stage and then letting the firm F decide on quality in the second stage, we can represent how governments take into account the consequences of their pricing policies in terms of quality. We could interpret it as if the history of pricing policies adopted by governments allowed firms to forecast next-period's price ceilings.

Marginal cost of production for the good is assumed to be zero. To produce quality, firm F has to invest in R&D at a quadratic cost $C(s) = \frac{s^2}{2}$. Quality in the pharmaceutical industry should be interpreted here as the outcome of an innovative process conducted by the manufacturer and oriented to the synthetization of a new active ingredient or to the indication of new uses for an already existing active ingredient. Both results tend to provide new treatments, thus widening the variety of treatments for a certain disease or offering pharmaceutical treatment for diseases for which no medicine was indicated before. Investments in R&D that provide this kind of quality improvements allow firm F to expand the number of its potential final customers. In this model the demand for the good is specific to each country and expands with quality.

$$D_i(p, s) = s\left(1 - \frac{1}{a_i}p_i\right) \tag{1.1}$$

We assume that $a_i \in (0, 1]$ for $i = H, L$ and $a_H \geq a_L$, where H and L stand for high and low demand respectively. All agents are assumed to have perfect knowledge about demand and cost characteristics.

1.2.2 Firm's decision on quality

In our model, governments and firm may have to take decisions under two alternative regimes. Under the first regime, NPT, parallel trade is prohibited and buyers are not allowed to export from one market to the other anything they may buy from firm F. Under the second possible regime, PT, parallel trade is authorized and buyers are allowed to decide whether or not they export products bought to firm F. The price that buyers pay to firm F acts as their marginal cost, so even if products can be exported at no cost, parallel trade can only occur from the low-price to the high-price market.

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Let us start by looking at what happens under these two alternative regimes in the third stage and how it affects quality decisions taken by firm F in the second stage of the game. Under NPT, in the third stage of the game buyers in one market are prevented from reselling in the other market and price differentials between countries do not give rise to arbitrage. Firm F is able to sell in each market at a different price and has no incentive to refuse supplying any market. We can characterize firm F's quality decision in the second stage for given prices by solving the following profit-maximization problem:

$$\max_{s} \pi\left(s, p_H, p_L\right) = s\left[p_H\left(1 - \frac{1}{a_H}p_H\right) + p_L\left(1 - \frac{1}{a_L}p_L\right)\right] - \frac{s^2}{2} \tag{1.2}$$

which implies that the level of quality chosen by firm F as a function of prices is:

$$s^{npt}\left(p_H, p_L\right) = p_H\left(1 - \frac{1}{a_H}p_H\right) + p_L\left(1 - \frac{1}{a_L}p_L\right) \tag{1.3}$$

where s^{npt} stands for firm F's optimal level of quality under NPT and depends on the price in each market. Quality depends positively on prices just up to a certain level of prices and negatively onwards, thus reflecting the fact that high prices may destroy incentives to innovate by restraining demand.

Let us now look at what happens under PT. In the third stage of the game buyers in the low-price market are allowed to resell in the high-price market. Assume that firm F and buyers from the low-price market compete à la Bertrand when they meet in the high-price market and that the exportation cost is zero. Then parallel trade makes price differentials unsustainable. As we will see in Section 2.3, when demands in both countries are close enough, firm F has no incentive to refuse supplying any market and sells in both markets at the same uniform price. Attempting to raise the price in one market, firm F would immediately trigger parallel trade by buyers from the other market, which would undercut it. The threat of parallel trade is sufficient to impose a uniform price and no parallel trade occurs in equilibrium. Under these circumstances, firm F's decision on quality can be characterized by imposing a uniform price for both countries in equation (1.3), which means that firm F anticipates that a uniform price is imposed by the threat of arbitrage in the third stage:

$$s^{pt}\left(p_U\right) = p_U\left(2 - \frac{a_H + a_L}{a_H a_L}p_U\right) \tag{1.4}$$

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where s^{pt} stands for firm F's optimal level of quality under PT when no market is excluded by firm F and p_U is the uniform price. Again, quality depends positively on price up to a certain price level.

However, as we will see, firm F may have incentive to exclude the low-price market if demand in the two markets are sufficiently different. That is, firm F may have incentives to refuse supplying the low-price market and concentrate on selling just in the other market at a higher price, rather than serving both countries at a low uniform price. When this is the case, firm F's decision of quality will be driven only by the incentives from the non-excluded market i:

$$s^{exc}(p_i) = p_i\left(1 - \frac{1}{a_i}p_i\right) \tag{1.5}$$

where s^{exc} stands for the firm F's optimal level of quality under PT when the market other than i is excluded by firm F. Again, quality depends positively on prices just up to a certain price.

1.2.3 Firm unilaterally sets prices

We turn now to the pricing decisions taken by firm F if no price ceilings have been established by governments in the first stage, and look at these pricing decisions under the two alternative trade regimes. Focus first on the NPT regime. Firm F is free to set a different price in each country in order to maximize profits, anticipating its own decision on quality. The fact that firm F decides on both quality and prices in the same stage, makes irrelevant the question of whether we solve first for quality, for prices or simultaneously. Substituting for the equilibrium level of quality we obtain firm F's profits just as a function of prices:

$$\max_{p_H,p_L} \pi(p_H,p_L) = \frac{1}{2}\left[p_H\left(1 - \frac{1}{a_H}p_H\right) + p_L\left(1 - \frac{1}{a_L}p_L\right)\right]^2 \tag{1.6}$$

and we use the first and second order conditions of this problem to solve for equilibrium prices:

$$\begin{aligned} p_H^{npt} &= \frac{a_H}{2} \\ p_L^{npt} &= \frac{a_L}{2} \end{aligned} \tag{1.7}$$

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where p_i^{npt} stands for the equilibrium price in market i under NPT. The optimal price in one market depends only on the characteristics of demand in that market and not surprisingly price is higher in the more inelastic market. Under NPT, firm F is able to discriminate in prices across markets and to charge a higher price in the low-elasticity market H without any threat of arbitrage by retailers from the high-elasticity market L.

Let us now look at what happens under PT, when price differentials across markets are unsustainable due to the threat of arbitrage. In this case, firm F must choose between serving both countries at a uniform price and excluding the low-price market L to sell only in market H at a higher price. In the former case of uniform pricing, firm F unilaterally sets the uniform price in order to maximize profits, anticipating its own decision on quality. Firm F's problem becomes the following:

$$\max_{p_U} \pi\left(p_U\right) = \frac{1}{2}\left[p_U\left(2 - \frac{a_H + a_L}{a_H a_L} p_U\right)\right]^2 \tag{1.8}$$

We find the first and second order conditions of this problem and solve for equilibrium price:

$$p_U^{pt} = \frac{a_H a_L}{a_H + a_L} \tag{1.9}$$

where p_U^{pt} stands for the equilibrium uniform price under PT when both markets are served. Firm F will sell in both markets at this uniform price only if it cannot enjoy higher profits by excluding market L. In the latter case of exclusion, firm F will charge in market H the same price as if under NPT, which we already saw that depends just on the characteristics of demand in H:

$$p_H^{exc} = \frac{a_H}{2} \tag{1.10}$$

where p_H^{exc} stands for the equilibrium price in market H when market L is excluded by firm F.

This allows us to write down the following incentive compatibility constraint, which says that no market is excluded if firm F's profits from serving both countries at uniform price p_U^{pt} are higher than its profits from selling only in market H at price p_H^{exc}:

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$$\frac{1}{2}\left(\frac{a_H a_L}{a_H + a_L}\right)^2 > \frac{a_H^2}{32} \tag{1.11}$$

which implies that firm F excludes market L whenever $3a_L < a_H$, that is, when demands in the two markets are different enough.

These results can be summarized in the following table:

TABLE 1.1: Firms' unilateral prices

No Parallel Trade	Market H	Market L
$\forall a_H, a_L$	$p_H^{npt} = \frac{a_H}{2}$	$p_L^{npt} = \frac{a_L}{2}$

Parallel Trade	Market H	Market L
$a_L \geq \frac{a_H}{3}$	$p_U^{pt} = \frac{a_H a_L}{a_H + a_L}$	
$a_L < \frac{a_H}{3}$	$p_H^{exc} = \frac{a_H}{2}$	Excluded

Proposition 1.1. *When firm F unilaterally decides on prices and $a_L \geq \frac{a_H}{3}$, allowing parallel trade leads firm F to charge an intermediate uniform price between the prices that it would charge if parallel trade were prohibited: $p_H^{npt} > p_U^{pt} > p_L^{npt}$.*

When firm F unilaterally decides on prices but $a_L < \frac{a_H}{3}$, allowing parallel trade leads firm F to exclude market L and to sell only in market H at a price equal to the price it would charge in that market had parallel trade been prohibited: $p_H^{exc} = p_H^{npt}$.

1.2.4 Governments establish price ceilings

Up to now, we have just analyzed the situation in which firm F can unilaterally set prices because prices are not regulated. In this section we derive equilibrium prices when governments establish price ceilings in the first stage. As we will see, price ceilings are binding for all values of the parameters and restrict the ability of firm F to set prices.

Let us start by the NPT regime. In the first stage, each government sets the maximum price in its country in order to maximize consumer surplus, anticipating firm F's decision on quality in the second stage. Government i's problem can be written as follows:

$$\max_{p_i} CS_i(p_i, p_j) = \frac{a_i}{2} s^{npt}\left(1 - \frac{1}{a_i} p_i\right)^2 \tag{1.12}$$

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Substituting for the equilibrium level of quality we can express it just as a function of prices:

$$\max_{p_i} CS_i\left(p_i, p_j\right) = \frac{a_i}{2}\left[p_i\left(1-\frac{1}{a_i}p_i\right)+p_j\left(1-\frac{1}{a_j}p_j\right)\right]\left(1-\frac{1}{a_i}p_i\right)^2 \tag{1.13}$$

We find the first order conditions of this problem for government i, which leads us to the following set of conditions:

$$a_i\left(1-\frac{4}{a_i}\bar{p}_i^{npt}\right)\left(1-\frac{1}{a_i}\bar{p}_i^{npt}\right) = 2\bar{p}_j^{npt}\left(1-\frac{1}{a_j}\bar{p}_j^{npt}\right) \tag{1.14}$$

with $i, j = H, L$ and $i \neq j$, and where $\bar{p}_i^{npt}$ stands for the optimal price ceiling set by government i under NPT. By looking at the condition above, we observe that any pair of price ceilings $\left(\bar{p}_H^{npt}, \bar{p}_L^{npt}\right)$ that maximize consumer surpluses while guaranteeing positive prices and demands must satisfy that:

$$\bar{p}_i^{npt} < \frac{a_i}{4} \tag{1.15}$$

which ensures that second order conditions for maximization are satisfied and that price ceilings are binding in both markets, given that they are lower than the optimal prices that firm F would unilaterally set if prices were not regulated.

Moreover, the optimal price ceiling in one market depends on the price ceiling established in the other market, which denotes that governments strategically interact with each other when setting their pricing policies. In fact, we observe that the cross-derivatives of consumer surpluses with respect to the price ceilings in both markets are negative:

$$\frac{\partial^2 CS_i\left(p_i, p_j\right)}{\partial p_i \partial p_j} = \left(1-\frac{1}{a_i}p_i\right)\left(\frac{2}{a_j}p_j - 1\right) < 0 \tag{1.16}$$

This means that governments regard price ceilings as strategic substitutes. The higher is the optimal price ceiling for one government, the lower is the optimal price ceiling for the other. This result is coherent with the view of innovation as a global public good. In our model, governments are willing to set positive price ceilings in order to incentivize firm F to invest on innovation, but they have incentives to free ride on the other government's willingness to pay for innovation.

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For the values of the parameters a_H and a_L for which these interior solutions hold, it can be shown that the optimal price ceiling is higher in the market with a lower elasticity of demand. It may be however the case that for some values of the parameters a_H and a_L, this maximization problem leads to non-interior solutions. It can be shown that $\bar{p}_L^{npt}$ increases with a_L, that is, the more price inelastic is the demand in L, the higher is the optimal price ceiling in market L[3]. Knowing that, it is easy to see that for $a_L < \frac{3}{8}a_H$ the first order conditions give negative values for $\bar{p}_L^{npt}$. For these values of the elasticity parameters the problem of the government has a corner solution with the optimal price ceilings in markets H and L given by

$$\begin{aligned} \bar{p}_H^{npt} &= \frac{a_H}{4} \\ \bar{p}_L^{npt} &= 0 \end{aligned} \tag{1.17}$$

where the solution to $\bar{p}_H^{npt}$ comes from substituting $\bar{p}_L^{npt}$ by zero in equation (1.14). Zero price means that the price ceiling is set at the level of marginal cost, hence compatible with non-negative profits.

Lemma 1.2. *Under NPT, the price ceiling set by government H is higher than the price ceiling set by government L:* $\bar{p}_H^{npt} > \bar{p}_L^{npt}$.

We proceed now to look at the alternative trade regime PT. Let us assume for the moment that firm F has no incentive to exclude any market. Governments anticipate firm F's decision on quality in the second stage and the fact that the same price ceiling will prevail in both markets in the third stage due to the threat of arbitrage. Government i's preferred uniform price ceiling is the solution to the following maximization problem:

$$\max_{p_i} CS_i\left(p_i\right) = \frac{a_i}{2}\left[p_i\left(2 - \frac{a_H + a_L}{a_H a_L}p_i\right)\right]\left(1 - \frac{1}{a_i}p_i\right)^2 \tag{1.18}$$

with $i = H, L$. We find the first order conditions of this problem, which leads us to the following set of conditions:

[3] From the cross-derivatives of the consumer surpluses with respect to prices we know that $\frac{dp_H^{npt}}{dp_L^{npt}} < 0$, which implies that $\frac{dp_H^{npt}}{da_L}$ and $\frac{dp_L^{npt}}{da_L}$ must be of opposite sign for every value of a_L. By totally differentiating the FOC of government L we obtain the following equality:

$$-\frac{d\bar{p}_H^{npt}}{a_L}\left[1 + a_H - \bar{p}_H^{npt}\left(1 + \frac{4}{a_H}\right)\right] = 2\frac{d\bar{p}_L^{npt}}{a_L}\left(1 - \frac{2}{a_L}\bar{p}_L^{npt}\right) + \frac{2}{a_L^2}\left(\bar{p}_L^{npt}\right)^2$$

which together with the previous conclusion shows that the sign of $\frac{dp_L^{npt}}{da_L}$ must be the same for every value of a_L. We can evaluate the equation above for the symmetric case in which $a_L = a_H$, to obtain that $\frac{dp_L^{npt}}{da_L} > 0$ for all $a_L \in (0, a_H]$.

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$$a_i\left(1-\frac{1}{a_i}\bar{p}_i^{pt}\right)\left(1-\frac{a_H+a_L}{a_Ha_L}\bar{p}_i^{pt}\right)=\bar{p}_i^{pt}\left(2-\frac{a_H+a_L}{a_Ha_L}\bar{p}_i^{pt}\right) \tag{1.19}$$

where $\bar{p}_i^{pt}$ stands for the optimal price ceiling set by government i when the threat of parallel trade imposes a uniform price ceiling for both markets. From these conditions, we obtain that the price ceiling $\bar{p}_i^{pt}$ that maximizes consumer surplus in market i while guaranteeing positive prices and demand is given by the following expression:

$$\bar{p}_i^{pt}=\frac{a_ia_j}{a_i+a_j}+\frac{a_i^2-a_i\sqrt{8a_j^2+a_i^2}}{4\left(a_i+a_j\right)} \tag{1.20}$$

which satisfies that $\bar{p}_i^{pt}<p_i^{pt}$ and therefore is binding for firm F. In the third stage, due to the threat of arbitrage, the lowest price ceiling $\bar{p}_i^{pt}$ will prevail in both markets. It can be shown that the lowest price ceiling is the one set by government L and that government H has no incentive to set a price ceiling below $\bar{p}_L^{pt}$, as stated in the following lemma.

Lemma 1.3. *Under PT, government L sets a price ceiling* $\bar{p}_L^{pt}$ *that prevails in both markets as the uniform price ceiling:* $\bar{p}_U^{pt}=\bar{p}_L^{pt}$. *This is the only subgame perfect Nash equilibrium of the game because* $\bar{p}_H^{pt}>\bar{p}_L^{pt}$ *and there is no price ceiling* $\bar{p}$ *such that* $\bar{p}<\bar{p}_L^{pt}$ *and* $CS_H\left(\bar{p}\right)>CS_H\left(\bar{p}_L^{pt}\right)$.

Let's look now at the possibility of exclusion of market L. Firm F has incentive to exclude market L if its profits when selling only in market H are higher than its profits when serving both markets at the uniform price ceiling $\bar{p}_U^{pt}$. The fact that firm F has incentives to exclude market L does not immediately lead to its effective exclusion. Provided that at the price ceiling $\bar{p}_U^{pt}$ the consumer surplus in market L is positive, government L may have room to rise its price ceiling to avoid exclusion while maintaining a positive consumer surplus. The lowest possible uniform price at which firm F has no incentive to exclude market L is the price at which firm F enjoys the same amount of profits irrespectively of whether market L is excluded or not. This price is given by the following expression:

$$\bar{p}_U^{av}=\frac{a_Ha_L}{\left(a_H+a_L\right)}-\frac{\sqrt{-a_L\left(3a_H-13a_L\right)}}{4\left(a_H+a_L\right)} \tag{1.21}$$

obtained from equating firm F's profits with and without exclusion of market L. Government L will set $\bar{p}_U^{av}$ as price ceiling to avoid being excluded by firm F if two requirements

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are met: first, if firm F had incentive to exclude market L in case the price ceiling $\bar{p}_U^{pt}$ were imposed; and second, if at the alternative price ceiling $\bar{p}_U^{av}$ the consumer surplus in L were positive. This means that government L will be able to avoid exclusion by setting price ceiling $\bar{p}_U^{av}$ for the following interval of values of the parameter a_L:

$$\frac{3}{13}a_H \leq a_L < \left(\frac{16}{39} + \varepsilon\right) a_H \tag{1.22}$$

where $\varepsilon \sim 0.0142$ is a scalar[4]. For lower values of a_L, willingness to pay in market L is too low for the government to be able of setting a price ceiling high enough to convince firm F not to exclude its market and low enough to produce a positive consumer surplus in market L. The first inequality in expression (1.22) can be conceived as the incentive compatibility constraint that guarantees no exclusion when governments regulate prices. For lower values of a_L, firm F will exclude market L and concentrate on selling in market H at the following price:

$$\bar{p}_H^{exc} = \frac{a_H}{4} \tag{1.23}$$

which is the optimal price ceiling for governments H when market L is excluded.

These results can be summarized in the following table:

TABLE 1.2: Governments' price ceilings

No Parallel Trade	Market H	Market L
$a_L \geq \frac{3}{8}a_H$	$\bar{p}_H^{npt} < \frac{a_H}{4}$	$\bar{p}_L^{npt} > 0$
$a_L < \frac{3}{8}a_H$	$\bar{p}_H^{npt} = \frac{a_H}{4}$	$\bar{p}_L^{npt} = 0$

Parallel Trade	Market H	Market L
$a_L \geq \left(\frac{16}{39} + \varepsilon\right) a_H$	$\bar{p}_U^{pt} = \frac{a_H a_L}{a_L + a_H} + \frac{a_L^2 - a_L\sqrt{8a_H^2 + a_L^2}}{4(a_L + a_H)}$	
$\left(\frac{16}{39} + \varepsilon\right) a_H > a_L \geq \frac{3}{13}a_H$	$\bar{p}_U^{av} = \frac{a_H a_L}{(a_H + a_L)} - \frac{\sqrt{-a_L(3a_H - 13a_L)}}{4(a_H + a_L)}$	
$a_L < \frac{3}{13}a_H$	$\bar{p}_{FL}^{exc} = \frac{a_H}{4}$	Excluded

Before proceeding to the welfare analysis of parallel trade, it is necessary to understand whether the uniform price ceiling prevailing under PT is higher or lower than the price ceilings that each government sets under NPT. It can be shown that for all values of a_H and a_L, the price ceiling $\bar{p}_U^{pt}$ set by government L under PT is strictly higher than the price ceiling $\bar{p}_L^{npt}$ set by the same government L under NPT. Moreover as we show

[4] The exact expression for the scalar ε is the following:
$\varepsilon = \frac{1}{78}\left(827 + 351\sqrt{1002}\right)^{-\frac{1}{3}}\left(\left(827 + 351\sqrt{1002}\right)^{\frac{2}{3}} - 497\right)$

below, for values of a_L sufficiently close to a_H, the uniform price ceiling $\bar{p}_U^{pt}$ under PT is even higher than the price ceiling $\bar{p}_H^{npt}$ set by government H under NPT.

This result contrasts with the prediction in Rey [8], namely that parallel trade produces a uniform regulated price equal to the lowest regulated price when no parallel trade is allowed. As we have already argued above when commenting on the cross-derivatives of consumer surpluses, in our model innovation is a global public good. When no parallel trade is allowed, each government tends to free ride on the other government's willingness to pay for innovation, leading to low price ceilings and underfinancing of innovation. By allowing parallel trade, a uniform price is imposed, what eliminates any possibility of free riding and forces government L to set a uniform price ceiling for both markets taking into account that this will be the only source of incentives for firm F to innovate. This is stated formally in the following proposition:

Proposition 1.4. *(Free-riding) The uniform price ceiling under parallel trade is higher than the lowest price ceiling when no parallel trade is permitted:* $\bar{p}_U^{pt} > \bar{p}_L^{npt}$*, which means that parallel trade does not lead to a convergence of prices to the lowest price ceiling.*

When demands in markets H and L are close enough, the uniform price ceiling under parallel trade is higher than the highest price ceiling observed when no parallel trade is permitted: $\bar{p}_U^{pt} > \bar{p}_H^{npt}$ *for α_L sufficiently close to a_H, what exemplifies that parallel trade corrects the free-riding problem faced by governments when no parallel trade is allowed.*

1.2.5 Welfare analysis of parallel trade

When governments do not regulate prices and firm F is able to freely set its pricing policy subject to the parallel trade regime under which it is operating, then allowing parallel trade to take place tends to be detrimental to aggregate welfare. It can be inferred from the table below, which summarizes the level of profits, consumer surpluses and welfare in each of the equilibrium situations defined in Section 2.3.

TABLE 1.3: No price ceilings

	Profits	CS_H	CS_L	Welfare
No Parallel Trade	$\frac{(a_H+a_L)^2}{32}$	$\frac{a_H(a_H+a_L)}{32}$	$\frac{a_L(a_H+a_L)}{32}$	$\frac{(a_H+a_L)^2}{16}$
Parallel Trade and no exclusion	$\frac{a_H^2 a_L^2}{2(a_H+a_L)^2}$	$\frac{a_H^4 a_L}{2(a_H+a_L)^3}$	$\frac{a_H a_L^4}{2(a_H+a_L)^3}$	$\frac{a_H a_L}{2} - \left(\frac{a_H a_L}{a_H+a_L}\right)^2$
Parallel Trade and exclusion	$\frac{a_H^2}{32}$	$\frac{a_H^2}{32}$	0	$\frac{a_H^2}{16}$

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Start by looking at the situation in which demands in both markets are relatively similar (a_L close to a_H), parallel trade imposes a uniform price in both markets and no market is excluded. This prevents firm F from maximizing profits by optimally discriminating in prices across markets. Given that quality is an increasing function of profits, the fact that under parallel trade profits are lower implies that also the level of quality provided by firm F is lower when parallel trade is allowed. Consumer surplus in market H is higher under parallel trade because the negative effects of the decrease in quality are offset by the positive effects of the reduction in the price faced by its consumers. On the contrary, consumer surplus in market L is lower under parallel trade as a result of both the decrease in quality and the increase in the price paid by consumers in L. The overall effect of parallel trade on aggregate welfare, defined as the sum of profits and consumer surpluses, is negative when no market is excluded by firm F.

Let us turn now to the case in which the price elasticity of demand is substantially higher in market L than in market H (low values of a_L), and firm F has incentive to exclude market L and concentrate on selling in market H at a higher price. When this happens, the contribution of market L to the financing of innovation disappears and consumers in market H must finance on their own the level of quality they desire to consume. This repercutes negatively on the consumer surplus in market H, while consumers in market L lose all their surplus as a result of being excluded from buying the product produced by firm F. As a results, parallel trade turns out to be particularly harmful for consumer surpluses and aggregate welfare when it leads to the exclusion of market L.

These results coincide with those in Valletti [10], where it is argued that parallel trade can be welfare detrimental because it may erode incentives to innovate by preventing firms from optimally discriminating in prices across markets. However, as we show below, these results may change considerably if price regulation by governments prevents firms from optimally discriminating in prices even when no parallel trade can take place.

Let us start by looking at the extreme symmetric case in which both markets are identical, i.e., $a_H = a_L$ and price elasticities are hence the same. We can obtain without difficulty the equilibrium values for profits, consumer surpluses and aggregate welfare for that case:

TABLE 1.4: Price ceilings and equal demands

	Profits	CS_H	CS_L	Welfare
No Parallel Trade and $a_L = a_H$	$\frac{25}{648}a_H^2$	$\frac{125}{1296}a_H^2$	$\frac{125}{1296}a_H^2$	$\frac{25}{108}a_H^2$
Parallel Trade and $a_L = a_H$	$\frac{9}{128}a_H^2$	$\frac{27}{256}a_H^2$	$\frac{27}{256}a_H^2$	$\frac{9}{32}a_H^2$

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It shows that in the symmetric case with equal demands, allowing parallel trade increases firm F's profits, consumer surpluses in both markets and hence also aggregate welfare. As we have already seen in the previous section, for values of a_L sufficiently close to a_H the uniform price ceiling imposed by government L under parallel trade is higher than the price ceilings imposed by any of the governments when parallel trade is forbidden. This is so because in the first stage both governments anticipate that the threat of parallel trade will impose a uniform price ceiling and therefore there is no possibility for any government to free-ride on others willingness to pay for quality. Allowing parallel trade eliminates incentives to free-ride and may lead to higher uniform prices, quality (that is an increasing function of profits) and welfare. As we will see in Section 2.6, where we complete the analysis by computing numerical solutions, when governments establish price ceilings and for α_L sufficiently close to a_H, aggregate welfare is higher when parallel trade is allowed than when it is prohibited.

On the other hand, when $a_L < \frac{3}{13}a_H$ and market L is excluded, aggregate welfare is higher if parallel trade is prohibited. Exclusion of market L eliminates any consumer surplus from this market, while not contributing to rise neither firm F's profits nor the consumer surplus in market H that are realized when parallel trade is prohibited:

TABLE 1.5: Price ceilings and exclusion

	Profits	CS_H	CS_L	Welfare
No Parallel Trade and $a_L < \frac{3}{8}a_H$	$\frac{9a_H}{512}$	$\frac{27a_H^2}{512}$	$\frac{3a_H^2}{32}$	$\frac{9a_H+75a_H^2}{512}$
Parallel Trade and $a_L < \frac{3}{8}a_H$	$\frac{9a_H}{512}$	$\frac{27a_H^2}{512}$	0	$\frac{9a_H+27a_H^2}{512}$

For intermediate values of a_L, we cannot reach any conclusive analytical results on the welfare effects of parallel trade. In the following Section we present a numerical example illustrating the results presented so far and complementing this welfare analysis.

1.2.6 Numerical example

In the analysis presented so far, we were unable to present closed-form solutions of prices for all possible equilibria. Even though this has not prevented us from offering a series of analytical results that characterize the equilibria, it is worth to devote some attention to comment on the numerical results of our model.

Let us normalize the parameter of demand in market H, a_H, to one. Qualitative results are the same for any alternative value of $a_H \in (0, 1]$. We have looked for equilibrium

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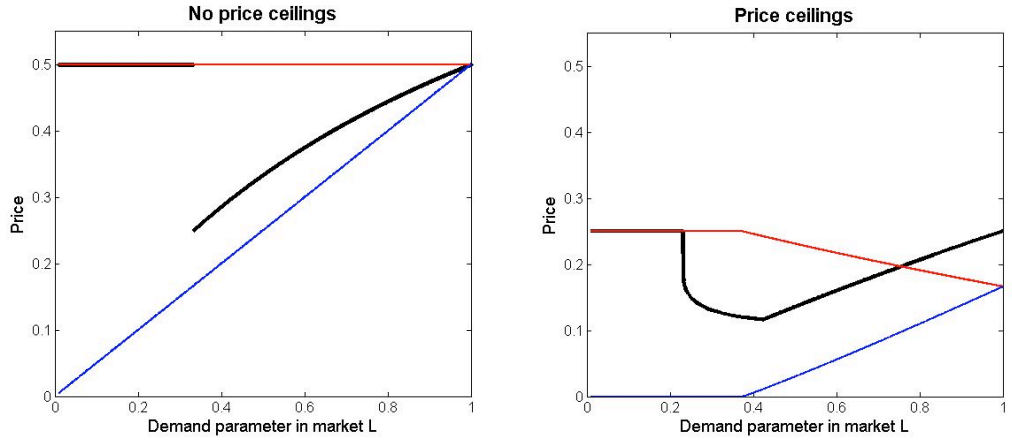
FIGURE 1.1: Equilibrium prices



prices under each regulatory and trade regime for different values of $a_L \in (0, a_H]$. The figures below show graphically the numerical results obtained from performing iterations for one thousand evenly distributed different values of a_L.

Figure 1.1 shows how equilibrium prices vary with α_L. Thin lines represent equilibrium prices under NPT and thick lines represent equilibrium prices under PT. The figure on the left shows prices when governments do not impose price ceilings. When prices are set unilaterally by a profit-maximizing firm, parallel trade imposes an intermediate uniform price between the lower and the higher prices that prevail locally when markets are segmented. Under parallel trade and for values of the demand parameter such that $\alpha_L < \frac{1}{3}$, firm F prefers to exclude market L and to sell only in market H at a higher price.

Giving local governments the possibility of establishing price ceilings constitutes a kind of decentralization of pricing decisions that creates a public-good problem when no parallel trade is allowed. A price increase in any of the two markets raises the level of quality available in both markets, but may eventually erode consumer surplus just in the market that has raised prices. The greater taste for quality in market H leads its government to be willing to set a higher price in order to incentivate high levels of quality. The government in L, whose preferred level of quality is lower, sets a lower price than it would be willing to set otherwise and lets government H to be the one who mainly pays for quality. That is, government L has incentive to free-ride and let government H be the only one to finance innovation, what leads to inefficiently low prices. Innovation

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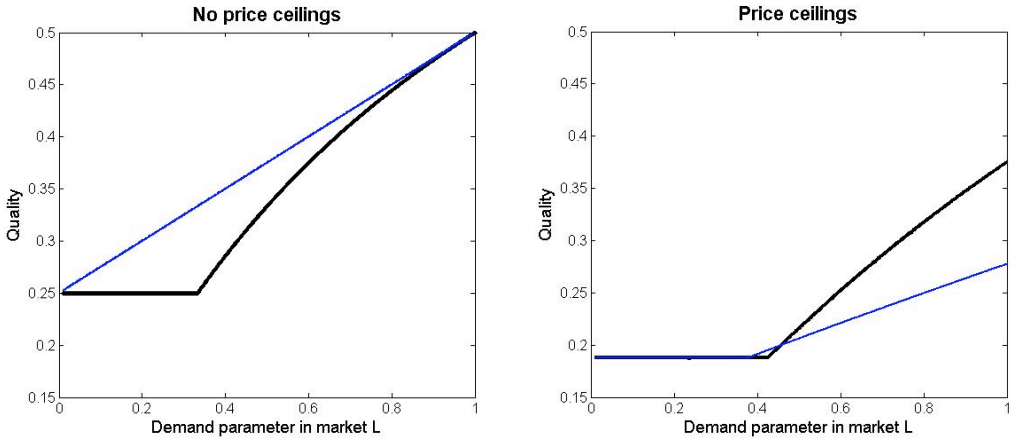
FIGURE 1.2: Quality



behaves as a global public good and gets underfinanced when governments set prices and no parallel trade is permitted.

Allowing parallel trade to take place partially solves the public-good problem by making government L responsible for the uniform price that will prevail in both markets, and therefore eliminating any possibility of free-riding. Again, for sufficiently low values of the demand parameter α_L, firm F chooses to exclude market L in order to avoid government L imposing an excessively low price in both markets. In the figure on the right, which shows equilibrium prices when price ceilings are imposed by governments, we identify two regions. For $\alpha_L < \frac{3}{13}$, there is no price that guarantees a non-negative consumer surplus in market L, while avoiding incentives for firm F to exclude that market. Therefore, in this region firm F sells only in market H at a constant price that does not depend on the parameter α_L. For $\alpha_L > \frac{3}{13}$, firm F does not exclude market L and serves both markets at the uniform price ceiling imposed by government L.

Figures 1.2 and 1.5 show how quality and aggregate welfare vary with α_L (figures for profits and cosnumer surpluses are included in Appendix II). When firm F sets prices unilaterally, both quality and aggregate welfare are lower under parallel trade than without it. Parallel trade does not allow firm F to optimally discriminate in prices according to the demand in each market. This implies that under parallel trade firm F's profits are lower than they are when no parallel trade can take place. This in turn results into lower quality and aggregate welfare for any value of the demand parameter α_L below 1. When governments establish price ceilings, then parallel trade helps to prevent government L from free-riding on government H's willingness to pay for quality.

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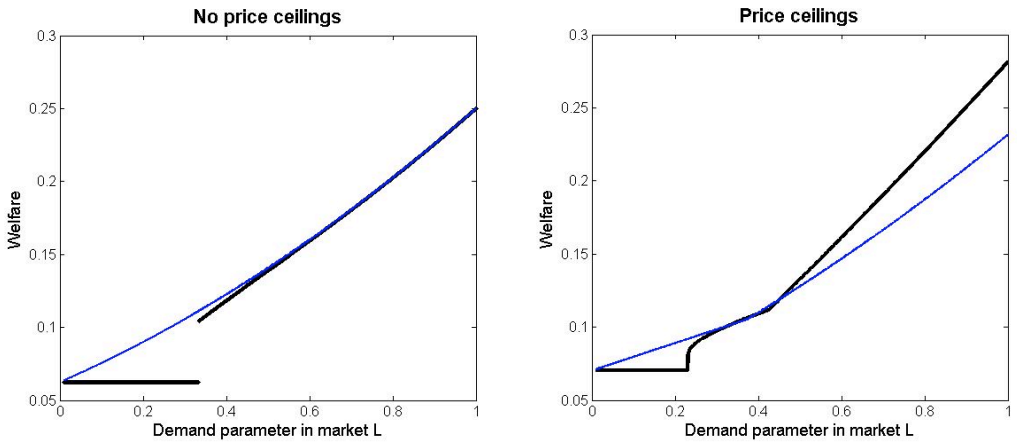
FIGURE 1.3: Aggregate welfare



We observe that for values of α_L sufficiently close to 1, quality and aggregate welfare are higher under parallel trade than they are when parallel trade is not permitted. On the contrary, for intermediate values of α_L the effects of parallel trade on quality and aggregate welfare are less clear-cut. There is a trade off between addressing the public good problem to finance quality and optimally discriminating in prices across markets. For values of α_L close to 1, the loss of profits and quality associated to price uniformity is relatively low compared with the gains of solving the public-good problem through arbitrage. Therefore, aggregate welfare is higher under parallel trade for high values of α_L. The inefficiency of price uniformity grows with the dispersion of the demands, and for low values of α_L this inefficiency outweighs any gain from arbitrage. That is the reason why parallel trade is detrimental to welfare for low values of α_L.

The discussion on the welfare effects of parallel trade is driven by the trade-off between the positive effect of price discrimination on profits and quality and the negative effect on quality of the miscoordination of governments' pricing policies when price differentials are sustainable. The intensity of the price discrimination inefficiency depends on the value of the parameter α_L. The larger is the difference between demands in the two countries, the more inefficient is price uniformity in terms of profit maximization. Consequently, parallel trade tends to be welfare enhancing when governments set price ceilings and markets have similar demands (α_L close to 1). On the contrary, price discrimination is always preferable either when firm unilaterally sets prices or when governments set price ceilings but markets have sufficiently different demands (α_L far from 1).

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1.3 Extensions: F as a domestic firm and supply constraints

In the previous sections we have assumed that firm F is located neither in country H nor L, but in a third country. Consequently, governments H and L set price ceilings to maximise just their countries' consumer surpluses. In this section we discuss how equlibria change when firm F is located either in H or L.

1.3.1 Governments' decisions on price ceilings when F is a domestic firm

Let's assume that firm F is located in country H. A government L that maximises consumer surplus would not change its policy with respect to the case analysed above, where firm F is located in a third country. A welfare-maximising government in H would have to set price ceilings taking into account their impact on both consumer surplus in H and profits of firm F. Under the NPT regime, government H must solve the following maximisation problem:

$$\max_{p_H} W_H(p_H, p_L) = CS_H(p_H, p_L) + \pi(p_H, p_L) \tag{1.24}$$

We know from 1.15 that the price p_H^{npt} that maximises $\pi(p_H, p_L)$ is higher than the price ceiling $\overline{p}_H^{not}$ maximising $CS_H(p_H, p_L)$. Hence, the welfare-maximising price ceiling under NPT, $\hat{p}_H$ must lie in-between the price ceiling that maximises consumer surplus and the price that maximises firm F's profits.

$$\hat{p}_H^{npt} \in (\overline{p}_H^{npt}, p_H^{npt}) \tag{1.25}$$

While the maximisation problem of government L does not vary, we know from 1.16 that governments H and L view their respective price ceilings as strategic substitutes. Therefore, when firm F is located in H, then the price ceiling imposed by government L under the NPT regime is lower than when firm F is located in a third country.

$$\hat{p}_L^{npt} < \overline{p}_L^{npt} \tag{1.26}$$

Under the NPT regime, consumers in H face a higher equilibrium price and consumers in L face a lower equilibrium price when firm F is located in H. Firm F's profits in H are

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higher when it is located in H than when it is in a third country, as the new equilibrium is the result from incorporating profits into government H's objective function. Firm F's profits in L are instead lower.

Under the PT regime, it is irrelevant whether firm F is located in H or in a third country. Government L establishes a price ceiling to maximise the same consumer-surplus function and its price ceiling becomes the prevalent price both in H and L.

$$\hat{p}_L^{pt} = \overline{p}_U^{pt} \tag{1.27}$$

If firm F is located in H, the difference between price ceilings in H and L tends to be larger. The higher willingness to pay of government H is likely to exacerbate the incentive for government L to free-ride by further lowering its price ceiling.

Let's assume conversely that firm F is located in country L. Government H establishes a price ceiling to maximise the same consumer-surplus function irrespectively of whether firm F is located in L or in a third country. A government H that maximises consumer surplus would not change its policy with respect to the case where firm F is located in a third country. Conversely, a welfare-maximising government in L would have to set a price ceiling taking into account its impact on both consumer surplus in L and profits of firm F. Under the NPT regime, government L must solve the following maximisation problem:

$$\max_{p_L} W_L(p_H, p_L) = CS_L(p_H, p_L) + \pi(p_H, p_L) \tag{1.28}$$

Again, we know from 1.15 that the price p_L^{npt} that maximises $\pi(p_H, p_L)$ is higher than the price ceiling $\overline{p}_L$ maximising $CS_L(p_H, p_L)$. Hence, the welfare-maximising price ceiling under NPT, $\hat{\hat{p}}_L^{npt}$ must lie in-between the price ceiling that maximises consumer surplus and the price that maximises firm F 's profits.

$$\hat{\hat{p}}_L^{npt} \in (\overline{p}_L^{npt}, p_L^{npt}) \tag{1.29}$$

While the maximisation problem of government H does not vary, we know from 1.16 that governments H and L view their respective price ceilings as strategic substitutes. Therefore, when firm F is located in L, then the price ceiling imposed by government H under the NPT regime is lower than when firm F is located in a third country.

$$\hat{\hat{p}}_H^{npt} < \overline{p}_H^{npt} \tag{1.30}$$

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Under NPT, consumers in H face a lower equilibrium price and consumers in L face a higher equilibrium price when firm F is located in L. Firm F's profits in L are higher when it is located in L than when it is located in a third country, as the new equilibrium is the result from incorporating profits into government L's objective function. Firm F 's profits in H are instead lower.

Under the PT regime, government L also establishes a price ceiling $\hat{\tilde{p}}_L^{pt}$ taking into account their impact on both consumer surplus in L and profits of firm F. As long as this price ceiling is lower than the price ceiling that maximises consumer surplus in H, $\hat{\tilde{p}}_H^{npt}$, it becomes the prevalent price both in H and L. This is the case when the difference in demand elasticities between countries is sufficiently large and firm's profits are sufficiently small compared to consumer surplus in L.

If firm F is located in L, the difference between price ceilings in H and L tends to be smaller. The higher willingness to pay of government L reduces its incentive to free-ride.

1.3.2 Sustainability of parallel trade in equilibrium when firm F has the ability to impose supply constraints

In the previous sections we have assumed that buyers face no constraint to their capacity to export unlimited quantities of product. It is reasonable to think that the manufacturer has some ability to impose capacity constraints on parallel traders by supplying limited quantities of product. While manufacturers are typically not allowed to refuse supplying, they may still be able to supply limited quantities of their product.

Let's assume that buyers can export a maximum quantity $\tau > 0$ from the low-price to the high-price market after having fully served the low-price market. We assume that buyers have a legal obligation to serve their domestic market and that they are only able to export exceeding quantities of pharmaceuticals. At the same time, we assume that the manufacturer can only imperfectly observe the quantities required to guarantee continued supply and reserve stocks in the low-price market and must therefore agree to supply an exceeding quantity of product. These exceeding quantity is the maximum exportable quantity τ.

In these circumstances, under the PT regime the manufacturer has two alternative strategies:

- To set a uniform price, as analysed above
- To discriminate prices, setting $\tilde{p}_H^{pt} > \tilde{p}_L^{pt}$

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We have already solved for the optimal uniform price in section 1.2.3. Let's solve for the optimal prices if the manufacturer choses to discriminate prices when buyers are constrained in their exporting capacity. In this case, buyers in L are able to export a limited quantity τ from L to H, while firm F serves the remaining fraction of the demand in H. Firm F maximises the following profit function:

$$\max_{p_H,p_L} = \frac{1}{2}\left[p_H\left(1-\frac{1}{a_H}p_H-\tau\right)+p_L\left(1-\frac{1}{a_L}p_L+\tau\right)\right]^2 \tag{1.31}$$

and we use the first and second order conditions of this problem to solve for equilibrium prices:

$$\tilde{p}_H^{pt} = (1-\tau)\frac{a_H}{2} \tag{1.32}$$
$$\tilde{p}_L^{pt} = (1+\tau)\frac{a_L}{2} \tag{1.33}$$

where $\tilde{p}_H^{pt} > \tilde{p}_L^{pt}$, as long as $\tau < \frac{a_H-a_L}{a_H+a_L}$. Firm F chooses to price discriminate if and only if it produces higher profits than setting a uniform price. It can be shown that this is the case when τ is sufficiently small.

Proposition 1.5. *When firm F is able to constrain buyers' capacity to export to a sufficient degree (τ is sufficiently low), then it is optimal for firm F to price discriminate across markets. In that case, buyers in L are able to serve a fraction of the demand in H at price $\tilde{p}_H^{pt}$ and make profits. Firm F serves the remaining demand in H at the same price $\tilde{p}_H^{pt}$.*

The greater is firm F's ability to impose constraints to buyers' exporting capacity, the stronger is the incentive for firm F to price discriminate, as shown by the first derivatives of the equilibrium prices with respect to τ:

$$\frac{\partial \tilde{p}_H^{pt}}{\partial \tau} = -\frac{a_H}{2} < 0 \tag{1.34}$$
$$\frac{\partial \tilde{p}_L^{pt}}{\partial \tau} = \frac{a_L}{2} > 0 \tag{1.35}$$

The lower is the exporting capacity of parallel traders (the lower is τ), the higher is $\tilde{p}_H^{pt}$ and the lower is $\tilde{p}_L^{pt}$. In the extreme case of $\tau \to 0$, the equilibrium under the PT regime approaches the equilibrium under the NPT regime.

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1.4 Conclusions

The debate on the convenience of allowing parallel trade of pharmaceuticals to take place has been substantial in the last years. Increasing pressure from developing countries, unsatisfaction of consumers in high-price countries or market integration in Europe have been some of the factors that have contributed to challenge the traditional national exhaustion interpretation of intellectual property rights. Even if it seems clear that parallel trade may be beneficial in some respects, especially in the short run, it is not easy to assess its welfare effects in a long run perspective. Parallel imports may help develop incipient pharmaceutical industries in developing countries, may provide medicines at lower prices to consumers in certain countries and may even enhance regional-wide competition in Europe. But it may also reduce profits of innovative pharmaceutical producers and undermine the incentives to spend in R&D that intellectual property rights are intended to create.

In this paper we have tried to assess incentives to invest and welfare effects of parallel trade taking into account all these considerations and, particularly, focusing on the fact that decisions on prices in the pharmaceutical industry are only exceptionally taken by firms on a unilateral basis. The pharmaceutical industry is a highly regulated industry and in most countries governments actively participate in the price-setting of medicines. When evaluating the welfare implications of parallel trade, it is convenient to take into account how prices are determined.

We have used a model where governments and firms interact on setting prices to show that parallel trade may be either beneficial or detrimental to welfare, depending on who is deciding on prices and on the degree of demand dispersion across countries. When firms unilaterally set prices, parallel trade tends to be welfare detrimental because prevents firms from optimally discriminating in prices, what reduces their profits as well as their incentive to innovate. When governments impose price ceilings, the possibility of sustaining price differentials across markets creates incentives for governments in low-demand markets to force their prices down in an attempt to free-ride on other governments' higher willingness to pay for quality. In that case, parallel trade is welfare enhancing because it disciplines governments in low-demand markets by making them responsible for the uniform price that will prevail in all markets. The higher are the differences in demand across countries, the worse are the welfare properties of parallel trade.

The results in this paper allow us to draw some policy implications. Allowing parallel trade to take place between countries with great differences of demand may have negative implications on welfare. It may either destroy incentives to innovate substantially by

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forcing an inefficiently low uniform price, or may even lead to the exclusion of low-demand countries. This may be the case of parallel imports from developing to developed countries. On the contrary, parallel trade between countries with similar demands may be a good instrument to discipline governments that actively participate in the price-setting processes and that may have the temptation of free-riding on others willingness to pay for quality. This could be the case in the European Union.

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1.5 Appendix I: Proofs

Proof. **of Lemma 2**

For the FOCs to be satisfied, it must be that $\left(1-\frac{4}{a_i}\bar{p}_i^{npt}\right)\geq 0$, which implies that $\bar{p}_i^{npt}\leq\frac{4}{a_i}$ and guarantees that any pair of prices satisfying the FOCs, satisfies also the SOCs.

We know that by definition $a_H > a_L$. Suppose that contrarily to the proposition $\bar{p}_H^{npt}\leq\bar{p}_L^{npt}$. Then we can say that $1-\frac{1}{a_H}\bar{p}_H^{npt}\geq 1-\frac{1}{a_L}\bar{p}_L^{npt}$. The FOCs can be restated as follows:

$$\begin{aligned}\left(1-\frac{4}{a_H}\bar{p}_H^{npt}\right)\left(1-\frac{1}{a_H}\bar{p}_H^{npt}\right) &= \frac{2}{a_H}\bar{p}_L^{npt}\left(1-\frac{1}{a_L}\bar{p}_L^{npt}\right)\\ \left(1-\frac{4}{a_L}\bar{p}_L^{npt}\right)\left(1-\frac{1}{a_L}\bar{p}_L^{npt}\right) &= \frac{2}{a_L}\bar{p}_H^{npt}\left(1-\frac{1}{a_H}\bar{p}_H^{npt}\right)\end{aligned}$$

which combined with the previous inequality allows us to say that:

$$\begin{aligned}1-\frac{4}{a_H}\bar{p}_H^{npt} &\leq \frac{2}{a_H}\bar{p}_L^{npt}\\ 1-\frac{4}{a_L}\bar{p}_L^{npt} &\geq \frac{2}{a_L}\bar{p}_H^{npt}\end{aligned}$$

Operating, we can reformulate this pair of inequalities to get the following:

$$\begin{aligned}a_H-2\bar{p}_H^{npt} &\leq 2\left(\bar{p}_H^{npt}+\bar{p}_L^{npt}\right)\\ a_L-2\bar{p}_L^{npt} &\geq 2\left(\bar{p}_H^{npt}+\bar{p}_L^{npt}\right)\end{aligned}$$

which allows us to restate them as a unique inequality:

$$a_H-2\bar{p}_H^{npt}\leq a_L-2\bar{p}_L^{npt}$$

or equivalently:

$$a_H-a_L\leq 2\left(\bar{p}_H^{npt}-\bar{p}_L^{npt}\right)$$

As we already said, by definition $a_H\geq a_L$, which implies that $\bar{p}_H^{npt}\geq\bar{p}_L^{npt}$. This is in contradiction with the initial guess. It proves by contradiction the statement in the proposition.

In the interval $p_i\in\left(0,\frac{a_i}{4}\right)$, function $CS_i\left(p_i,p_j\right)$ is continuous in p_i and its second derivative with respect to p_i is negative. The first derivative is positive if evaluated at the lower bound and negative if evaluated at the upper bound of the interval. Hence, for a given p_j, there is a unique $p_i\in\left(0,\frac{a_i}{4}\right)$ that maximizes $CS_i\left(p_i,p_j\right)$. □

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Proof. **of Lemma 3**

We know that by definition $a_H > a_L$. Suppose that contrarily to the proposition $\bar{p}_H^{pt} \leq \bar{p}_L^{pt}$. Then we can say that $1 - \frac{1}{a_H}\bar{p}_H^{pt} \geq 1 - \frac{1}{a_L}\bar{p}_L^{pt}$ and $1 - \frac{a_H+a_L}{a_H a_L}\bar{p}_H^{pt} \geq 1 - \frac{a_H+a_L}{a_H a_L}\bar{p}_L^{pt}$. The FOCs can be restated as follows:

$$\begin{aligned} a_H\left(1-\frac{1}{a_H}\bar{p}_H^{pt}\right)\left(1-\frac{a_H+a_L}{a_H a_L}\bar{p}_H^{pt}\right) &= \bar{p}_H^{pt}\left(2-\frac{a_H+a_L}{a_H a_L}\bar{p}_H^{pt}\right) \\ a_L\left(1-\frac{1}{a_L}\bar{p}_L^{pt}\right)\left(1-\frac{a_H+a_L}{a_H a_L}\bar{p}_L^{pt}\right) &= \bar{p}_L^{pt}\left(2-\frac{a_H+a_L}{a_H a_L}\bar{p}_L^{pt}\right) \end{aligned}$$

which combined with the previous inequalities allows us to say that:

$$\bar{p}_H^{pt}\left(2-\frac{a_H+a_L}{a_H a_L}\bar{p}_H^{pt}\right) \geq \bar{p}_L^{pt}\left(2-\frac{a_H+a_L}{a_H a_L}\bar{p}_L^{pt}\right)$$

Additionally, for the FOC in L to hold, it must be that either $2 - \frac{a_H+a_L}{a_H a_L}\bar{p}_L^{pt} \leq 0$ or $1 - \frac{a_H+a_L}{a_H a_L}\bar{p}_L^{pt} \geq 0$. However, we know that $2 - \frac{a_H+a_L}{a_H a_L}\bar{p}_L^{pt} \leq 0$ is not possible because it would imply $\bar{p}_L^{pt} \geq 2\frac{a_H a_L}{a_H+a_L} > a_L$, giving a negative demand in market L. Therefore we know that $\bar{p}_L^{pt} \leq \frac{a_H a_L}{a_H+a_L}$, which together with the inequality derived above implies that necessarily $\bar{p}_H^{pt} \geq \bar{p}_L^{pt}$. This is in contradiction with the initial guess. It proves by contradiction that $\bar{p}_H^{pt} > \bar{p}_L^{pt}$.

In the interval $p_i \in \left(0, \frac{a_i a_j}{a_i+a_j}\right)$, function $CS_i(p_i)$ is continuous and concave. The first derivative is positive if evaluated at the lower bound and negative if evaluated at the upper bound of the interval. Hence, there is a unique $p_i \in \left(0, \frac{a_i a_j}{a_i+a_j}\right)$ that maximizes $CS_i(p_i)$.

Consequently, the first derivative of $CS_H(p_H)$ evaluated at any positive price lower than $\bar{p}_H^{pt}$ is negative, and therefore there is no $\bar{p} < \bar{p}_L^{pt}$ such that $CS_H(\bar{p}) > CS_H\left(\bar{p}_L^{pt}\right)$. □

Proof. **of Proposition 4**

We know that by definition $a_H > a_L$. Suppose that contrarily to the proposition $\bar{p}_U^{pt} \leq \bar{p}_L^{npt}$. We know that the following inequality holds

$$\frac{1}{a_L}\bar{p}_U^{pt}\left(2-\frac{a_H+a_L}{a_H a_L}\bar{p}_U^{pt}\right) < \frac{2}{a_L}\bar{p}_U^{pt}\left(1-\frac{1}{a_H}\bar{p}_U^{pt}\right)$$

because $\frac{a_H+a_L}{a_H a_L} > \frac{2}{a_H}$. We can also say that

$$\frac{2}{a_L}\bar{p}_U^{pt}\left(1-\frac{1}{a_H}\bar{p}_U^{pt}\right) \leq \frac{2}{a_L}\bar{p}_H^{npt}\left(1-\frac{1}{a_H}\bar{p}_H^{npt}\right)$$

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because by assumption in this proof $\bar{p}_U^{pt} \leq \bar{p}_H^{npt} \leq \frac{a_L}{4}$. Combining both inequalities we get the following:

$$\frac{1}{a_L}\bar{p}_U^{pt}\left(2 - \frac{a_H + a_L}{a_H a_L}\bar{p}_U^{pt}\right) < \frac{2}{a_L}\bar{p}_H^{npt}\left(1 - \frac{1}{a_H}\bar{p}_H^{npt}\right)$$

which allows us to relate the FOCs in the NPT case and in the PT case through the expression that follows:

$$\left(1 - \frac{1}{a_L}\bar{p}_U^{pt}\right)\left(1 - \frac{a_H + a_L}{a_H a_L}\bar{p}_U^{pt}\right) < \left(1 - \frac{4}{a_L}\bar{p}_L^{npt}\right)\left(1 - \frac{1}{a_L}\bar{p}_L^{npt}\right)$$

Given that $\left(1 - \frac{1}{a_L}\bar{p}_U^{pt}\right) \geq \left(1 - \frac{1}{a_L}\bar{p}_L^{npt}\right)$, this can be reduced to:

$$\left(1 - \frac{a_H + a_L}{a_H a_L}\bar{p}_U^{pt}\right) < \left(1 - \frac{4}{a_L}\bar{p}_L^{npt}\right)$$

which implies that $a_L > 3a_H$. This is a contradiction and therefore it proves that $\bar{p}_U^{pt} > \bar{p}_L^{npt}$.

On the other hand, we know that $\bar{p}_H^{npt}$ decreases with a_L and we can show that $\bar{p}_U^{pt}$ decreases with a_L by differentiating:

$$\frac{\partial \bar{p}_U^{pt}}{\partial a_L} = \frac{(4a_H + 3a_L)\left(4a_H + a_L - \sqrt{8a_H^2 + a_L^2}\right)}{16\left(a_H + a_L\right)^2} + \frac{a_L\left(\sqrt{8a_H^2 + a_L^2} - a_L\right)}{4\left(a_H + a_L\right)\sqrt{8a_H^2 + a_L^2}} > 0$$

By evaluating equilibrium prices for $a_L = \frac{4}{5}a_H$, we obtain that $\bar{p}_H^{npt} \sim 0.1912$ and $\bar{p}_U^{pt} \sim 0.2067$. Hence, we can say that at least for $a_L > \frac{4}{5}a_H$ it is true that $\bar{p}_U^{pt} > \bar{p}_H^{npt}$. □

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1.6 Appendix II: Figures

In this Annex we enclose some complementary figures that show the behavior of profits and consumer surpluses with respect to variations in the parameter α_L and for $\alpha_H = 1$.

FIGURE 1.4: Profits

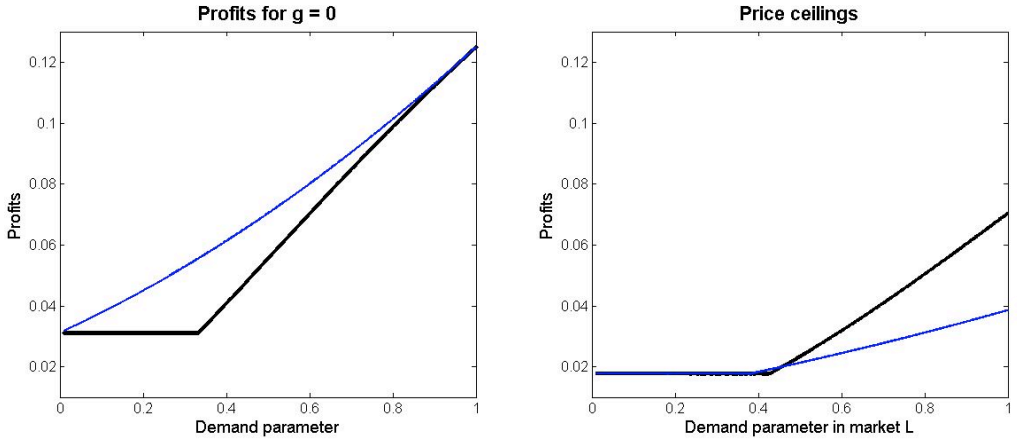
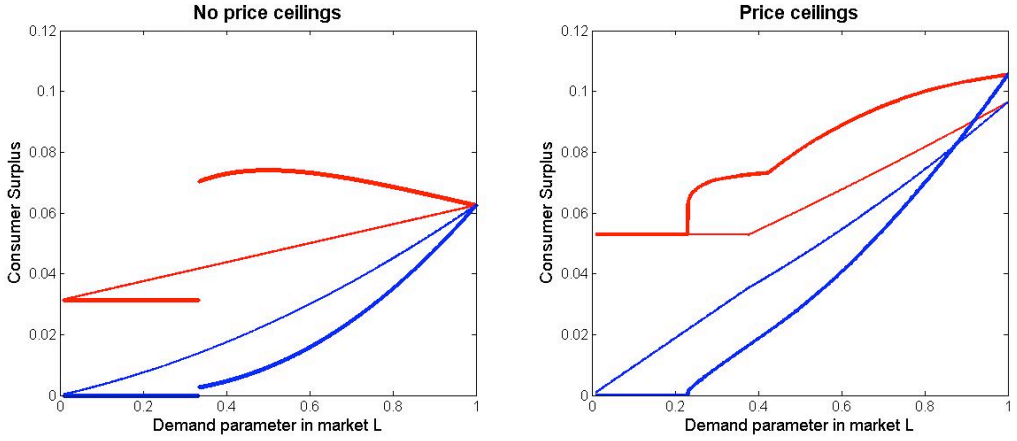


FIGURE 1.5: Consumer Surpluses



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Chapter 2

Direct-to-consumer advertising of prescription drugs: informing patients or persuading physicians?

Abstract

DTCA gives patients the ability of better learning their needs, both regarding physician consultations and available treatments, and may reduce information asymmetries in the relation between the patient and the physician. Persuasive advertising may induce consumer demand not based on therapeutic grounds, eventually exacerbating informational problems. The purpose of this chapter is to analyse the welfare properties of DTCA, taking into account both its informative and persuasive effects. In our model, physicians are assumed to face some harassment costs when contradicting the preferences of their patients over the drugs prescribed, what creates an agency problem between the patient and the physician. We analyse the welfare properties of DTCA under the scenarios of perfect and imperfect agency. We show that DTCA tends to be welfare enhancing when physicians are perfect agents. On the contrary, when they are imperfect agents, DTCA welfare effects are ambiguous. In particular, it can be detrimental to consumer welfare when harassment costs are relatively high.

Key words: Pharmaceuticals, Advertisement, Principal-agent, Regulation
JEL Classifications: I11; K23; L51; M38

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2.1 Introduction: The controversy on DTCA

Advertising activities in the pharmaceutical industry have traditionally been subject to strict regulation by national authorities in order to avoid potential negative effects related to the informational structure of the market for drugs. Specifically, DTCA is often prohibited on the grounds that it could induce consumers to ask for inappropriate treatments and it might undermine the patient protection that the health legislation seeks by requiring physicians to certify patients' need for prescription drugs.

There are a number of arguments in favor and against the allowance of DTCA for prescription drugs. The reasons in its favor focus on the informative role played by advertising, meaning that through DTCA the public may come to know about the existence of new treatments for their diseases and thus that the match between patient and drug can be improved by allowing pharmaceutical firms to advertise directly to consumers. Proponents argue that better informed patients reduce the level of under-diagnosis of some diseases by increasing physician visits. DTCA would be profitable for firms and beneficial for patients because of this market-expanding effect. On the other hand, opponents of DTCA fear that it may affect the choice of prescription and lead to the consumption of unnecessarily expensive or even inappropriate therapies. This business-stealing effect may be profitable for firms carrying on DTCA, while being harmful for patients and leading to unreasonably high pharmaceutical spending.

The persuasive or informative nature of advertising lies at the base of the distinction between these two potential effects of DTCA. Informative advertising may give patients the ability of better learning their needs, both about visiting the physician and about possible treatments, and may reduce information asymmetries in the relation between the patient and the physician. Persuasive advertising may induce consumer demand not based on therapeutic grounds, eventually exacerbating informational problems.

2.1.1 The regulation on pharmaceutical advertising

While advertising to physicians (so-called detailing) has been traditionally recognized as an acceptable practice in the pharmaceutical industry, even if subject to regulations aiming at guaranteeing its informative purpose; for a long time DTCA of pharmaceuticals has been considered as not convenient.

In the US, prescription drugs are subject to a specific marketing regulation since the 1962 Kefauver-Harris amendments that made the Food and Drug Administration (FDA) responsible for monitoring the promotion of prescription drugs. According to these amendments, promotional materials cannot be false or misleading; they must provide

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a fair-balance coverage of risks and benefits of using the drug; they must provide a summary of contraindications, side effects, and effectiveness; and they must also meet specific guidelines for readability and size of print [see 12, p. 694]. Restrictions on DTCA were relaxed in 1997 with the issue of new FDA guidelines, allowing producers to advertise drugs without having to enclose a summary of side effects and other risks. Since this regulatory reform, it can be considered that DTCA is a legal practice in the US.

In contrast, Europe has not yet changed its legislation to allow for DTCA, even though the issue is under debate and the reform is clearly in the agenda of the pharmaceutical industry. DTCA in Europe is prevented under the Council Directive 92/28/EEC, which requires the Member States to prohibit the advertising of prescription drugs to the general public [see 15]. However, the European Commission has launched in December 2007 a public consultation about the reform of the legislation on pharmaceutical information to patients. In the last months, several stakeholders in the pharmaceutical sector and notably the associations of the pharmaceutical industry have published a number of reports to inform the Commission about their positions. A complete permission of DTCA has been already excluded, but there is an interest in facilitating increased flows of information from firms directly to consumers.

2.1.2 The physician-patient relationship

It has been traditionally assumed that the decision of consuming prescription drugs corresponds to the physician acting as prescriber, while the patient just accepts the physicians decision. This peculiar feature of the demand for drugs arises from the presence of information asymmetries, the patient being incapable of performing a correct self-diagnosis and an appropriate self-medication and thus having to rely on the physician's advice. This perspective of the pharmaceutical markets has been gradually called into question, while there is an increasing interest on understanding what could be the role of an informed patient.

If we assume that DTCA plays just an informative role, then allowing pharmaceutical firms to advertise directly to consumers could mitigate this information asymmetry, and reduce under-diagnosis without affecting the choice of prescription. Any misleading or persuasive effect on patients associated to DTCA should not affect the prescription choice, provided that the final decision on medication is taken by the physician. One can however think that this could not be the case and that, to the extent that the patient is able to influence physicians' final prescription, the positive effects of DTCA on consumers welfare should be put under closer scrutiny.

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Nonetheless, it remains to be explained why a physician would change a choice of prescription according to the preferences of the patient. A first explanation refers to the physicians will of avoiding a conflictive relationship with the patient, that is, he would be willing to satisfy the prescription preferences of patients in order to avoid any harassment cost. Alternatively, we could think about remuneration mechanisms leading physicians to have strong incentives to satisfy patients requests. This would be, for instance, the case of private practitioners afraid of losing customers and of practitioners in the public sector being paid according to the number of patients treated or the number of visits performed. Understanding the features of the physician-patient relationship is essential in order to determine to which extent is there room for persuasive effects associated to DTCA. In this paper we propose a model that formalises this relationship to assess the welfare properties of DTCA.

2.1.3 Economic analysis on DTCA

There is not much theoretical work on the motivations and effects of DTCA, while a substantial amount of empirical research has been carried on lately, especially since the modification of the FDA guidelines in 1997. Rosenthal et al. [14] find that DTCA increases aggregate demand of drugs, without affecting market shares within each therapeutic class. Wosinska [17] shows that demand effects of DTCA are substantially smaller than those of detailing. Iizuka and Jin [10] find that DTCA increases visits to physicians by new patients, but does not affect the choice of prescription done by physicians. Iizuka [8] finds that firms are more likely to advertise new and high-quality drugs, that advertising is more intense when the number of potential rather than current patients is higher, and that firms advertise less as competition gets more intense. Iizuka and Jin [9] conclude that DTCA has mainly a market-expanding effect, while recognising that the weaknesses of their empirical work do not allow a comprehensive assessment of the welfare effects of DTCA. Berndt et al. [1] show that pharmaceutical marketing has not only a market-expanding effect, but also a business-stealing effect.

Despite the fact that theoretical work on DTCA is scarce, there are some recent works available. Brekke and Kuhn [2] study the interaction between DTCA and detailing, showing that these are complementary marketing strategies for pharmaceutical firms and that they have a positive impact on consumers' welfare. Their model reflects the informational asymmetries between physician and patient, and assumes that detailing has mainly a business-stealing effect, while DTCA has just a market-expanding effect. Thus, the assumptions in the model tend to match the findings of the empirical literature. Brekke and Straume [3] study the relation between DTCA and pharmaceutical R&D

and show that both tools can be used as strategic substitutes by an incumbent firm facing the entry of a potential competitor.

Brekke and Kuhn [2] discard by assumption any possible persuasive effect of DTCA. On the one hand, they assume that the only effect of DTCA on patients is to encourage them to visit their physician. On the other hand, physicians are assumed to be perfect agents that only care for their patients' health. Persuasive effects on patients and the view of physicians as imperfect agents are precisely the main line of reasoning against DTCA. In order to assess the welfare effects of DTCA, we try to formalize these considerations. To do that, we assume that physicians are not necessarily perfect agents for their patients. That physicians take into account a variety of considerations when taking their prescription decisions has been already shown in the literature. Gruber and Owings [7] show that in the face of negative income shocks, physicians may exploit their agency relationship with patients by providing excessive care. In particular, they show a relation between physicians financial incentives and cesarean delivery. Lundin [13] shows that patients tastes and costs matter when prescribing generic or branded versions of a drug.

In order to incorporate the potential persuasive effect of DTCA, we propose to analyze how the induced consumer demand may translate into prescriptions signed by physicians. This leads us to a principal-agent approach to represent the relationship between physicians and patients. Physicians can be assumed to have some interest on prescribing the appropriate medication to patients, but also to minimize conflict with patients or to maximize some financial incentives. Harassment costs or inadequate institutional frameworks could give physicians strong incentives to deviate from prescribing the most suitable treatment and to satisfy patient requests induced by DTCA.

In this paper, we propose a Hotelling-type model in the line of Brekke and Kuhn [2]. In our model, physicians are assumed to face some harassment costs when contradicting the preferences of their patients over the drugs prescribed. We take the notion of harassment cost, following Lindbeck and Snower [11] as our main reference, and we introduce it in the physician's utility function as to create a problem of agency between the patient and the physician. We analyse the welfare properties of DTCA under two scenarios: in the first one, harassment costs are zero and physicians behave as perfect agents; in the second one, harassment costs are positive and physicians act as imperfect agents. In the former case, DTCA can only have an informative effect on consumers. In the latter, it can also have a persuasive effect. We show that DTCA tends to be welfare enhancing when physicians are perfect agents. On the contrary, when they are imperfect agents, DTCA welfare effects are ambiguous. In particular, it can be detrimental to consumer welfare when harassment costs are relatively high.

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In Section 2.2.1 we present the setup of the model. Section 2.2.2 describes the problem faced by physicians when prescribing a treatment. Section 2.2.3 solves the firm's problem and characterizes the equilibria. In Section 2.2.4 we present the problem of the regulator and proceed to the welfare analysis of DTCA under each scenario. Section 2.3 concludes.

2.2 The model

2.2.1 Basic setup

We use a Hotelling-type model to describe the interaction between two pharmaceutical firms, each one selling a drug with similar therapeutic properties. We build on the framework proposed by Brekke and Kuhn [2], but we depart from their analysis to account for the persuasive effect of DTCA. Consider a pharmaceutical market with a continuum of individuals uniformly distributed on the line segment $[0,1]$ with mass 1. A fraction s of all the individuals are in need of medical treatment, while the rest are healthy. The location of an arbitrary individual, $x \in [0,1]$, is associated with his personal characteristics. There are two pharmaceutical firms, indexed by $i = 0, 1$, in this market, where firm i sells drug i at a uniform price p_i. The drugs are located at either end of the unit interval, reflecting their differing chemical compounds and associated side effects.

The gross utility derived by an individual in need of medical care from consuming one unit of either drug is given by v, where v represents the therapeutic value of the drug consumed and is assumed to be the same for both drugs. Alternatively, a healthy individual gets zero gross utility from consuming either drug. Individual's net utility from consuming drug i is obtained by subtracting to the value v, the proportion of the price paid by the individual and the negative side effects caused by the consumption of a given drug. These side-effects are assumed to depend on personal characteristics and are proportional to the distance between individuals' and drugs' locations. More formally:

$$U(x,i,p_i) = \begin{cases} v - t|x-i| - \tau p_i & \text{if } x \text{ is an ill patient,} \\ -t|x-i| - \tau p_i & \text{otherwise,} \end{cases} \tag{2.1}$$

where $v > 0$, $t > 0$, and $\tau \in (0,1]$. The parameter t captures the utility loss ('mismatch cost') per unit distance between drug i and a patient x. Finally, the parameter τ denotes the copayment rate, i.e., the fraction of the drug's price paid by the patient.

We assume that individuals ignore their health status and their location in the unit segment. They have to visit a physician to get a diagnostic and eventually a drug

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prescription. We let $z \in [0,1]$ be the fraction of individuals that attend the physician's practice either because they have developed some symptoms of their condition or as part of a regular check-up. The remaining fraction $(1-z)$ do not visit the physician as, for instance, they do not have developed any symptoms.

If allowed by health authorities, pharmaceutical firms can advertise directly to consumers. On one side, we assume that DTCA influences individuals' decisions on whether or not to seek medical advice by a physician, informing about the possible symptoms associated with the disease and about the existence of an indicated drug. On the other side, we assume that DTCA affects individual's preferences by informing just about one of the two pharmacological therapies available in the market. Let $\Phi_i \in [0,1]$ denote the fraction of patients who receive an ad from firm i. The informative effect of DTCA induces every individual who has seen at least one ad to visit a physician. Only the fraction of the individuals who have not been exposed to an ad do not seek medical advice, and this is given by $(1-z)(1-\Phi_0)(1-\Phi_1)$. The persuasive effect of DTCA determines individual's preferences over the two existing drugs. We assume that patients who have seen just one ad express a preference for the drug they have seen in the ad. On the contrary, patients exposed to both ads or to neither of them are indifferent between the two drugs. The expected fraction of individuals attending a physician for medical advice being indifferent between the two drugs is the following:

$$N_{01}(\mathbf{\Phi}) = \Phi_0\Phi_1 + z(1-\Phi_0)(1-\Phi_1), \tag{2.2}$$

where $\mathbf{\Phi} = (\Phi_0, \Phi_1)$. While the expected fractions of individuals that go to the physician and prefer drug 0 or 1 are respectively the following:

$$\begin{aligned} N_0(\mathbf{\Phi}) &= \Phi_0(1-\Phi_1), \\ N_1(\mathbf{\Phi}) &= (1-\Phi_0)\Phi_1, \end{aligned} \tag{2.3}$$

where $N(\mathbf{\Phi}) = N_{01}(\mathbf{\Phi}) + N_0(\mathbf{\Phi}) + N_1(\mathbf{\Phi})$ is the expected fraction of all the individuals seeking for medical advice. To ease the exposition, from now on we will refer to this expected fraction just as fraction or number of individuals. The number of individuals with a preference for drug i depends positively on the amount of advertising conducted by firm i and negatively on the amount of advertising by the other firm, while the overall number of individuals going to the physician depends on the amount of advertising done by either firm.

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Once the basic setup has been described, we can proceed to present the structure of the game. The following sequence of moves is considered and solved by backwards induction:

- *Stage 1*: The regulator decides on whether or not to allow DTCA.
- *Stage 2*: Pharmaceutical firms determine spending on DTCA and set prices.
- *Stage 3*: Some patients go to the physician, who prescribes either drug 0, drug 1 or no treatment at all.

2.2.2 The physician's problem

Physicians are identical and face the same distribution of patients. They have the skills to identify a patient's health status, healthy or ill, and his personal characteristics, i.e., the location $x \in [0, 1]$. Assume that physicians are imperfect agents for their patients. During the medical visits, patients with a preference for one of the drugs will suggest the physician to prescribe their preferred drug. When patients ask for the wrong drug, physicians who care only for the patient's health have to bear the cost of litigating with the patient about the drug to be prescribed. The same happens when a healthy individual insists on getting a drug prescription. That is, if physicians want to be perfect agents, they face a 'harassment cost' that may involve just a longer medical visit (to give the necessary explanations to change the patient's mind) or that may even imply the loss of the patient (and perhaps the corresponding retribution). When prescribing, physicians maximize patient's utility minus the harassment cost:

$$\max_i V(x, i, p_i) = U(x, i, p_i) - \phi(i) \cdot h, \tag{2.4}$$

where ϕ is an indicator function that takes value 1 when patient x has only received an ad from the firm other than i and value 0 otherwise, and h is a scalar indicating the magnitude of the harassment cost.

Let us look first at the prescription behavior that would maximize the utility $U(x, i, p_i)$ of an ill patient. Drug i should be prescribed to patient x if the following holds:

$$U(x, i, p_i) \geq 0 \tag{2.5}$$

If $U(x, i, p_i) < 0$, then the patient should not be given any treatment at all, as it is the case for healthy individuals. Letting $\hat{x}$ denote the patient who is indifferent between the two drugs, we have:

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$$\hat{x}(\mathbf{p}) = \frac{1}{2} - \frac{\tau(p_0 - p_1)}{2t}, \tag{2.6}$$

where $\mathbf{p} = (p_0, p_1)$. Let us assume that every ill patient is better off consuming a drug than getting no treatment. That is, $U(x, 0, p_0) > 0$ for any ill patient such that $x \leq \hat{x}(\mathbf{p})$ and $U(x, 1, p_1) > 0$ for any ill patient such that $x \geq \hat{x}(\mathbf{p})$. This guarantees that only healthy patients should not be prescribed to consume any drug. Physicians who only care for the utility of their patients should prescribe drug 0 to every ill patient in the interval $[0, \hat{x}]$ and drug 1 to every ill patient in $(\hat{x}, 1]$. No drug should be prescribed to healthy individuals.

In this model, however, physicians are imperfect agents whose prescription behavior is oriented to maximize their own utility rather than patients' utility. Let us look first at prescription decisions for the fraction s of the population that is in need of pharmacological treatment. Physician's utility $V(x, i, p_i)$ coincides with patient's utility $U(x, i, p_i)$ for every ill patient that is indifferent between the two drugs. In this case, the physician will act as a perfect agent for the patient, prescribing according to the criteria above.

On the contrary, for individuals with a preference towards a particular drug, the physician's utility function $V(x, i, p_i)$ differs from $U(x, i, p_i)$ because of the harassment cost h. Take an ill patient who has only seen an ad from firm 0 and therefore asks his physician to prescribe drug 1 to him. The physician prescribes drug 0 if the following inequality is satisfied:

$$V(x, 0, p_0) \geq V(x, 1, p_1) \Leftrightarrow v - tx - \tau p_0 \geq v - t(1 - x) - \tau p_1 - h \tag{2.7}$$

Rearranging this inequality and substituting for $\hat{x}$, we observe that a physician prescribes drug 0 to a patient x with a preference for drug 0 if and only if the following is true:

$$x \leq \hat{x}(\mathbf{p}) + \frac{h}{2t} \tag{2.8}$$

Otherwise, the physician prescribes drug 1. Physicians prescribe drug 0 to every ill patient with a preference for drug 0 in the interval $[0, \hat{x} + \frac{h}{2t}]$ and drug 1 to every ill patient with a preference for drug 0 in $(\hat{x} + \frac{h}{2t}, 1]$. The higher the harassment cost h and the lower the negative side effects t, the higher the number of patients who get drug 0, in spite of drug 1 being more suitable for them.

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Analogously, we know that an ill patient x with a preference for drug 1 will be prescribed drug 0 if and only if:

$$x \leq \hat{x}(\mathbf{p}) - \frac{h}{2t}, \tag{2.9}$$

and drug 1 otherwise. Physicians prescribe drug 0 to every ill patient with a preference for drug 1 in the interval $[0, \hat{x} - \frac{h}{2t}]$ and drug 1 to every ill patient with a preference for drug 1 in $(\hat{x} - \frac{h}{2t}, 1]$. Again, the higher the harassment cost h and the lower the negative side effects t, the higher the number of patients who get the less suitable drug.

Let us look now at prescription decisions for healthy individuals going to the physician. Some of them visit the physician for a regular check-up without having seen any advertisement and do not get any drug prescription. However, this is not the case for healthy individuals who have been exposed to advertising from one or both firms. Take either a healthy individual who asks for a prescription of drug 0 after having seen an ad from firm 0 or a healthy individual x such that $x \leq \hat{x}$ and who asks for a drug prescription, regardless of which is the precise drug prescribed, after having seen all ads. In both cases, the physician satisfies the patient's request if the physician's utility when prescribing drug 0 is higher than the harassment cost of convincing him of not taking any drug. The physician prescribes drug 0 to a healthy individual x asking specifically for drug 0 or generically for any drug, if and only if the following inequality is satisfied:

$$x < \frac{h - \tau p_0}{t} \tag{2.10}$$

Otherwise, no treatment is prescribed. Analogously, a healthy individual x asking specifically for drug 1 or generically for any drug gets a prescription for drug 1 if and only if the following is true:

$$x > 1 - \frac{h - \tau p_1}{t}, \tag{2.11}$$

while no treatment is prescribed otherwise. The lower the negative side effects t and the lower the monetary cost τp of drug 0 for the patient, the higher the probability that the physician accepts to prescribe it even if the patient does not really need it. The higher the harassment cost h, the higher the probability of the unnecessary prescription. Given that $x \in [0, 1]$, a positive number of healthy individuals will be prescribed drug i if the following inequality holds:

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$$h - \tau p_i > 0 \tag{2.12}$$

These prescription decisions lead to the following expected demands for drug 0 or 1, respectively:

$$\begin{aligned} Q_0(\mathbf{\Phi}, \mathbf{p}) &= s\hat{x}(\mathbf{p})N(\mathbf{\Phi}) \\ &\quad + s\frac{h}{2t}\left[N_0(\mathbf{\Phi}) - N_1(\mathbf{\Phi})\right] \\ &\quad + (1-s)\frac{h-\tau p_0}{t}\left[\Phi_0\Phi_1 + N_0(\mathbf{\Phi})\right] \\ Q_1(\mathbf{\Phi}, \mathbf{p}) &= s\left[1 - \hat{x}(\mathbf{p})\right]N(\mathbf{\Phi}) \\ &\quad - s\frac{h}{2t}\left[N_0(\mathbf{\Phi}) - N_1(\mathbf{\Phi})\right] \\ &\quad + (1-s)\frac{h-\tau p_1}{t}\left[\Phi_0\Phi_1 + N_1(\mathbf{\Phi})\right] \end{aligned} \tag{2.13}$$

The first term in the RHS of each equation accounts for the amount of prescriptions not distorted by the harassment cost as a consequence of the persuasive effect of DTCA. That is, these terms give the amount of patients for which the physicians have prescribed the best treatment available. The second term in the RHS of each equation gives the amount of prescriptions distorted by DTCA, i.e., the number of patients for whom a more suitable drug could have been prescribed. Finally, the third term in the RHS of each equation corresponds to the amount of healthy individuals to whom physicians end up prescribing a drug, although they would be better off without taking any pharmacological treatment at all.

2.2.3 The firm's problem

Now that we have already solved the physician's problem in the third stage and we have obtained the demand for each drug, we can proceed backwards to solve the firm's problem in the second stage. Pharmaceutical firms face identical and constant marginal production costs, which we normalize to zero. The R&D costs are considered sunk at the time marketing and price decisions are taken and play no role in the analysis. The cost of advertising is the same for both firms. This allows us to write down the expected profit function of firm i as follows:

$$\pi_i(\mathbf{\Phi}, \mathbf{p}) = p_i Q_i(\mathbf{\Phi}, \mathbf{p}) - K(\Phi_i) \tag{2.14}$$

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Brekke and Kuhn [2], building on the framework introduced by Butters [4], assume that the cost of reaching a fraction Φ_i of patients is given by the following general advertising cost function, $K(\Phi_i)$. The function $K(\cdot)$ is increasing and convex in the quantity of DTCA. In order to simplify exposition, we assume additionally that the cost function of DTCA is quadratic:

$$K(\Phi_i) = k\frac{\Phi_i^2}{2} \tag{2.15}$$

2.2.3.1 The benchmark case: no DTCA is allowed

Let us start by looking at the case in which DTCA is prohibited by the regulator. This situation corresponds to the current European regulation on DTCA and will be the benchmark case throughout the paper. In this case, levels of DTCA are *ex ante* set to be zero, $\Phi_i = 0$. Firm 0 maximizes profits only with respect to p_0, as no DTCA is allowed, anticipating the number of patients attending the physicians and the physicians prescription choices. This problem can be written as follows:

$$\max_{p_0} \pi_0(\mathbf{p}) = p_0 sz\hat{x}(\mathbf{p}), \tag{2.16}$$

and the first order condition with respect to p_0 is:

$$\frac{\partial \pi_0(\mathbf{p})}{\partial p_0} = sz\left[\hat{x}(\mathbf{p}) - \frac{\tau p_0}{2t}\right] = 0 \tag{2.17}$$

Firm 1 faces a symmetric problem and a symmetric set of first-order conditions. We therefore impose symmetry in order to derive the equilibrium price and level of DTCA. Symmetry implies that prices are equal, i.e., $p_0 = p_1 = p$. With identical prices, only the median patient is indifferent between the two drugs:

$$\hat{x} = 1 - \hat{x} = \frac{1}{2} \tag{2.18}$$

We have assumed above that every ill patient is better off consuming some drug than without being treated. In the symmetric equilibrium, this assumption implies that the following condition must hold:

$$\tau p < v - \frac{t}{2} \tag{2.19}$$

The symmetric equilibrium prices and DTCA levels in the benchmark case with DTCA prohibition are then the following:

$$\begin{aligned} p^b &= \frac{t}{\tau}, \\ \Phi^b &= 0, \end{aligned} \tag{2.20}$$

where the superscript b denotes the benchmark equilibrium. The equilibrium price comes from imposing symmetry in equation 2.17, while the level of DTCA has been determined *ex ante* by the regulator.

2.2.3.2 DTCA is allowed and physicians are perfect agents

Suppose now that the regulator allows pharmaceutical firms to advertise directly to consumers, but also that consumers are completely unable to distort prescription decisions taken by physicians. This is the case analyzed in Brekke and Kuhn [2], where DTCA is assumed to have only an informative effect. Under these circumstances, firms are able to choose positive levels of DTCA while anticipating that $h = 0$. Firm 0 faces now the following problem:

$$\max_{p_0, \Phi_0} \pi_0(\mathbf{\Phi}, \mathbf{p}) = p_0 s \hat{x}(\mathbf{p}) N(\mathbf{\Phi}) - K(\Phi_i) \tag{2.21}$$

where the first term in the RHS is the revenue from prescriptions to ill patients and the second term is the cost of advertising. Firm 0 gets no revenue from selling to healthy individuals because for $h = 0$ condition 2.12 is not satisfied and physicians do not write any unnecessary prescription to healthy patients. The solution to this problem is defined by the following set of first-order conditions:

$$\begin{aligned} \frac{\partial \pi_0(\mathbf{\Phi}, \mathbf{p})}{\partial p_0} &= s \left[\hat{x}(\mathbf{p}) - \frac{\tau p_0}{2t} \right] N(\mathbf{\Phi}) = 0, \\ \frac{\partial \pi_0(\mathbf{\Phi}, \mathbf{p})}{\partial \Phi_0} &= p_0 s \hat{x}(\mathbf{p})(1 - z)(1 - \Phi_1) - k\Phi_0 = 0 \end{aligned} \tag{2.22}$$

Firm 1 faces a symmetric problem and a symmetric set of first-order conditions. We therefore impose symmetry in order to derive the equilibrium prices and DTCA levels, which are given by

$$\begin{aligned} p^p &= \frac{t}{\tau}, \\ \Phi^p &= \frac{ts(1-z)}{ts(1-z)+2k\tau}, \end{aligned} \tag{2.23}$$

with the superscript p denoting equilibrium under perfect agency. Equilibrium prices are the same with and without DTCA, provided that physicians act as perfect agents for their patients. Positive DTCA equilibrium levels increase the number of ill patients who get access to a pharmacological treatment. Assuming that physicians are perfect agents, i.e., that $h = 0$, we find that allowing DTCA must have a positive effect on consumer surplus, while the effect on aggregate welfare will depend on how profits react. As expected, these results coincide with those in Brekke and Kuhn [2]. We will come back to this discussion in Section 2.2.4, where we present a welfare analysis to assess the regulator's decision on DTCA.

2.2.3.3 DTCA is allowed and physicians are imperfect agents

Let us now allow for positive values of h, which implies that harassment costs might now distort prescription choices by physicians in the way described in Section 2.2.2. Firm 0 maximizes profits with respect to Φ_0 and p_0, anticipating the number of patients attending the physicians and the effect of harassment costs on prescription choices. The problem faced by firm 0 can be written in the following manner:

$$\begin{aligned} \max_{p_0,\Phi_0} \pi_0(\mathbf{\Phi},\mathbf{p}) &= p_0 s\hat{x}(\mathbf{p})N(\mathbf{\Phi}) \\ &\quad + p_0 s\frac{h}{2t}(N_0(\mathbf{\Phi}) - N_1(\mathbf{\Phi})) \\ &\quad + p_0(1-s)\frac{h-\tau p_0}{t}(\Phi_0\Phi_1 + N_0(\mathbf{\Phi})) \\ &\quad - K(\Phi_i) \end{aligned} \tag{2.24}$$

The first term in the RHS accounts for the revenue from correct prescriptions that have not been distorted by the persuasive effect of DTCA. The second term represents the revenue from wrong prescriptions to patients that would be better of consuming the alternative drug. The third term corresponds to the revenue from unnecessary prescriptions to healthy people. The fourth term in the RHS is the cost of advertising.

The solution to this problem is defined by the following set of first-order conditions:

$$\begin{aligned}
\frac{\partial \pi_0(\mathbf{\Phi}, \mathbf{p})}{\partial p_0} &= s\left[\hat{x}(\mathbf{p}) - \frac{\tau p_0}{2t}\right] N(\mathbf{\Phi}) \\
&\quad + s\frac{h}{2t}(N_0(\mathbf{\Phi}) - N_1(\mathbf{\Phi})) \\
&\quad + (1-s)\frac{h - 2\tau p_0}{t}(\Phi_0\Phi_1 + N_0) \\
&= 0, \\
\frac{\partial \pi_0(\mathbf{\Phi}, \mathbf{p})}{\partial \Phi_0} &= p_0 s\hat{x}(\mathbf{p})(1-z)(1-\Phi_1) \\
&\quad + p_0 s\frac{h}{2t} \\
&\quad + p_0(1-s)\frac{h - \tau p_0}{t} \\
&\quad - k\Phi_0 \\
&= 0
\end{aligned} \tag{2.25}$$

Again, firm 1 faces a symmetric problem and a symmetric set of first-order conditions. Imposing symmetry, we obtain equilibrium prices and DTCA levels as implicitly given by the following system of equations:

$$\begin{aligned}
p^h &= \frac{t}{\tau} \cdot \frac{sN(\Phi^h) + (1-s)\Phi^h}{sN(\Phi^h) + 4(1-s)}, \\
\Phi^h &= \frac{p^h s(1-z)}{p^h s(1-z) + 2k} + \frac{p^h\left[sh + 2(1-s)(h - \tau p^h)\right]}{t\left[p^h s(1-z) + 2k\right]},
\end{aligned} \tag{2.26}$$

with the superscript h denoting equilibrium under imperfect agency. This system does not allow to find a closed-form explicit solution for p^h and Φ^h for the whole range of parameter values. We can however draw some conclusions. First, we observe now that price depends positively on the fraction s of patients that need some medical treatment. This result means that the higher is the fraction of healthy people, the more important are healthy customers for the firm. Given that these customers do not get any benefit from following a pharmacological treatment, physicians tend to be particularly reluctant to prescribe any drug to them, unless the secondary effects and the price are sufficiently low. While secondary effects are out of the firm's control, price can be adjusted downwards as the importance of the healthy customers increase. Second, even if everybody is healthy and nobody can benefit from any drug, i.e., $s = 0$, in equilibrium we observe a positive level of DTCA, provided that condition 2.12 is satisfied. This is so because in our model the persuasive effect of DTCA may lead some healthy individuals to ask for and obtain unnecessary prescriptions.

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Finally, let us compare system 2.26 with the results under perfect agency derived in the previous section shown in 2.23. It is easy to see that the second factor in the product at the RHS of the first equation in 2.26 cannot be higher than 1. Therefore, comparing this with the first equation in 2.23, we conclude that equilibrium prices are lower or equal under imperfect agency than they are under perfect agency. Moreover, the first term in the RHS of the second equation in 2.26 is higher or equal than the whole RHS of the second equation in 2.23, while the second term is positive. Hence, equilibrium levels of DTCA are higher under imperfect agency than they are under perfect agency. Let us sum up these comparative statics in the following pair of inequalities:

$$\begin{aligned} p^b = \quad & p^p \geq \quad p^h, \\ \Phi^b \leq \quad & \Phi^p \leq \quad \Phi^h, \end{aligned} \tag{2.27}$$

When physicians are imperfect agents, prices are lower and DTCA more intensive than when physicians are perfect agents. However, from these comparative statics, we can still not determine whether the positive effect on consumer welfare from the lower prices dominates or not the negative effect of inefficient prescription choices. We devote the next section to present a welfare analysis to answer this question.

2.2.4 The regulator's problem

In our game, the regulator decides in the first stage whether to allow or not pharmaceutical firms to advertise directly to consumers, anticipating the consequences of this decision in terms of welfare. As we show below, these consequences depend crucially on the incentives that determine prescription choices by physicians, while the regulator may take different decisions depending on whether he is aiming at maximising consumer welfare or aggregate welfare. In the exposition that follows we reproduce the structure of the analysis in the previous section. We start by look at the benchmark case with prohibition of DTCA, then we study what happens with DTCA under perfect agency, and finally we proceed to the case with DTCA under imperfect agency.

2.2.4.1 The benchmark case: DTCA is not allowed

Recall firm i's profits in the benchmark case from equation 2.16 and substitute for the equilibrium values to obtain profits in equilibrium:

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$$\pi_i^b = \frac{sz}{2} \cdot \frac{t}{\tau} \tag{2.28}$$

Profits depend positively on the fraction s of individuals in need of treatment, the fraction z of individuals seeking for medical advice and the mismatch cost t, and negatively on the copayment τ. On the other hand, expected consumer surplus can be expressed as follows:

$$CS(\Phi, p) = sN(\Phi) \left[\int_0^{\frac{1}{2}} (v - \tau p_0 - tx)dx + \int_{\frac{1}{2}}^1 [v - \tau p_1 - t(1-x)]dx \right] \tag{2.29}$$

We can distinguish two definite integrals between brackets in the RHS, the first corresponding to consumer surplus of patients consuming drug 0 and the second corresponding to consumer surplus of patients consuming drug 1. Substituting for the equilibrium values we obtain the following:

$$CS^b = sz \left(v - \frac{5t}{4} \right) \tag{2.30}$$

The positivity of this expression is ensured by condition 2.19. Consumer surplus depends positively on the fraction s of individuals in need of treatment, the fraction z of individuals seeking for medical advice and the beneficial effect v for an ill patient from consuming a drug, and negatively on the mismatch cost t.

Apart from profits and consumer surplus, we must also take into account public expenditure on pharmaceuticals, which depends on the level of copayment τ. This expected public expenditure equals the number of prescriptions times the part of the price paid by the regulator, and for the benchmark case can be expressed as follows:

$$X^b = tsz \tag{2.31}$$

In the discussion about the regulator's decision on whether to allow DTCA or not, we consider two possible objective functions. A 'consumer-oriented' regulator will be mainly concerned about consumer welfare. We assume that such a regulator seeks to maximize consumer surplus minus public expenditures (which are assumed to be indirectly paid by consumers through taxes). We will refer to this objective function as consumer welfare:

$$CW^b = CS^b - X^b \tag{2.32}$$

Alternatively, an 'industry-oriented' regulator may include in his objective function also profits and therefore maximize aggregate welfare, which can be written as follows when DTCA is prohibited:

$$AW^b = 2\pi_i^b + CS^b - X^b, \tag{2.33}$$

2.2.4.2 DTCA is allowed and physicians are perfect agents

When DTCA is allowed, firms obtain some additional revenue from individuals who visit the physician only after being exposed to some ad. To obtain the equilibrium level of profits of a single firm, we substitute in equation 2.21 for the equilibrium prices and levels of DTCA:

$$\pi_i^p = \frac{sz}{2} \cdot \frac{t}{\tau} + \frac{s(1-z)}{2}\left[1 - \left(\frac{2k\tau}{ts(1-z)+2k\tau}\right)^2\right]\frac{t}{\tau} - \frac{1}{2}\cdot\left[\frac{ts(1-z)}{ts(1-z)+2k\tau}\right]^2 \tag{2.34}$$

The first element in the RHS represents profits without the contribution of DTCA, and the second and third elements are the contribution to profits from the supplementary sales originated by DTCA and its cost, respectively.

If physicians are assumed to be perfect agents, DTCA increases the number of prescriptions without distorting prescription choices. Under these circumstances, consumer surplus can still be written as in equation 2.29. Substituting for equilibrium values we can rewrite it as follows:

$$CS^p = sz\left(v - \frac{5t}{4}\right) + s(1-z)\left[1 - \left(\frac{2k\tau}{ts(1-z)+2k\tau}\right)^2\right]\left(v - \frac{5t}{4}\right) \tag{2.35}$$

where we can distinguish two elements in the RHS, the first corresponding to the fraction of consumer surplus independent from DTCA and the second representing the contribution to consumer surplus of new patients treated thanks to the informative effect of DTCA.

Rearranging equations 2.34 and 2.35, it can be easily proved that both profits and consumer surpluses are higher with than without DTCA, provided that physicians are perfect agents. This is so because DTCA is assumed to have only an informative effect, leading to an expansion of the market just among individuals with the need of being treated, but without distorting prescriptions.

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Now, public expenditure on pharmaceuticals is higher because of the additional amount of prescriptions signed by physicians:

$$X^p = tsz + ts(1-z)\left[1 - \left(\frac{2k\tau}{ts(1-z)+2k\tau}\right)^2\right] \tag{2.36}$$

As before, we consider two alternative measures of welfare, consumer and aggregate welfare:

$$AW^p = 2\pi_i^p + CW^p = 2\pi_i^p + CS^p - X^p \tag{2.37}$$

2.2.4.3 DTCA is allowed and physicians are imperfect agents

We now turn our attention to the welfare implications of DTCA's persuasive potential. As shown in Section 2.2.3.3, it is not possible to find explicit closed-form solutions for prices and DTCA levels in equilibrium for the whole range of possible parameter values. Let us therefore restrict for the moment our attention to the particular case with $s = 1$, that is, suppose that the whole population is in need of pharmacological treatment. As we discuss further below, by restricting to this particular case we will be able to reach some analytical results, before relaxing this restriction when proceeding to the numerical welfare analysis.

As shown before, when DTCA is allowed firms obtain some additional revenue from individuals who visit the physician only after being exposed to some ad. They should also receive some revenues from unnecessary prescriptions to healthy individuals who have been persuaded by DTCA of being in need of treatment. The latter does not apply now, given that we have momentarily restricted our attention to the situation in which everybody is ill and needs treatment. To obtain the equilibrium level of profits of a single firm, we substitute in equation 2.24 for the equilibrium prices and levels of DTCA and for $s = 1$:

$$\pi_i^h = \frac{z}{2}\cdot\frac{t}{\tau} + \frac{(1-z)}{2}\left[1 - \left(\frac{2k\tau - h}{t(1-z)+2k\tau}\right)^2\right]\frac{t}{\tau} - \frac{1}{2}\cdot\left[\frac{t(1-z)+h}{t(1-z)+2k\tau}\right]^2 \tag{2.38}$$

On the other hand, consumer surplus of patients can now be expressed as follows:

$$\begin{aligned} CS(\Phi,p) &= sN_{01}(\Phi)\left[\int_0^{\frac{1}{2}}(v-\tau p_0-tx)dx+\int_{\frac{1}{2}}^1[v-\tau p_1-t(1-x)]dx\right] \\ &+s\left[\frac{t+h}{2t}N_0(\Phi)+\frac{t-h}{2t}N_1(\Phi)\right]\int_0^1(v-\tau p_0-tx)dx \\ &+s\left[\frac{t-h}{2t}N_0(\Phi)+\frac{t+h}{2t}N_1(\Phi)\right]\int_0^1[v-\tau p_1-t(1-x)]dx \end{aligned} \quad (2.39)$$

As before, in the first term in the RHS we can distinguish two definite integrals between brackets, the first corresponding to the consumer surplus of indifferent patients consuming drug 0 and the second corresponding to the consumer surplus of indifferent patients consuming drug 1. Now, we find two additional terms corresponding respectively to non-indifferent patients that consume drug 0 even if some of them would be better off consuming drug 1 and to non-indifferent patients that consume drug 1 even if some of them would be better off consuming drug. The symmetry of the equilibrium allows us to rewrite this as follows:

$$\begin{aligned} CS^h &= z\left(v-\frac{5t}{4}\right)+(1-z)\left[1-\left(\frac{2k\tau-h}{t(1-z)+2k\tau}\right)^2\right]\left(v-\frac{5t}{4}\right) \\ &-\frac{[t(1-z)+h]\,(2k\tau-h)}{[t(1-z)+2k\tau]^2}\frac{t}{2} \end{aligned} \quad (2.40)$$

The first term in the RHS is equal to the consumer surplus when DTCA is allowed. The second term reflects the positive impact that the informative effect of DTCA has on consumer surplus, by giving access to pharmacological treatment to some patients that otherwise would not be treated. The third term accounts for the negative impact of the persuasive effect of DTCA, which leads to suboptimal treatments for some patients. Public expenditure on pharmaceuticals is the same as in 2.36, i. e., $X^h = X^p$ because the number of prescriptions is the same under perfect and imperfect agency for $s = 1$. This will not be true for other values of s. Again, two alternative measures of welfare can be considered:

$$AW^h = 2\pi_i^h + CW^h = 2\pi_i^h + CS^h - X^h \quad (2.41)$$

When physicians are imperfect agents and $s = 1$, the overall effect of DTCA on profits and consumer surplus depends on the values of the parameters. Profits are higher with DTCA if the revenue from additional sales is higher than the cost of DTCA. This

could seem similar to what happened in the previous Section under perfect agency. The difference is that now firms advertise not only to increase the number of individuals attending the physician, but also to avoid patients being persuaded by the competing firm. This may lead firms to increase the amount of DTCA in equilibrium, accepting an increase in costs to avoid a loss of sales in favour of the competing firm. From equation 2.38, we know that profits are higher with DTCA if the following inequality is satisfied:

$$\frac{[t(1-z)+h]^2}{[t(1-z)+2k\tau]^2-(2k\tau-h)^2} < (1-z)\frac{t}{\tau} \tag{2.42}$$

Similarly, consumer surplus is higher when DTCA is allowed if the positive contribution from new prescriptions is higher than the loss associated to inefficient prescriptions. This is the case when the following inequality holds:

$$\frac{[t(1-z)+h]\,(2k\tau-h)}{[t(1-z)+2k\tau]-(2k\tau-h)} < (1-z)\frac{2}{t}\left(v-\frac{5t}{4}\right) \tag{2.43}$$

For values of z close to one, the RHS in both inequalities converges to zero and hence they are less likely to hold. This result is reasonable. High values of z indicate a well informed population with a high propensity to seek medical advice. Under these circumstances, the contribution of DTCA to consumer surplus in terms of informing population about their health status is relatively low in comparison with the losses from inefficient prescription practices induced by DTCA. Moreover, the moderate increase in sales may not even cover the costs of DTCA, thus leading to lower profits for the firms. Conversely, when z is low and hence a significant fraction of population does not go to the physician in spite of being ill, DTCA may positively contribute to consumer surplus and firms' profits by inducing a substantial increase in the number of ill people treated, which more than compensates the negative effect of potential distortions in prescription choices.

The results presented so far about the welfare effects of DTCA under imperfect agency have been derived assuming that $s = 1$. By relaxing this assumption, we introduce the possibility that DTCA leads to the unnecessary treatment of healthy individuals, which contributes negatively to consumer surplus. On the other hand, we have already seen that equilibrium prices depend positively on the fraction of individuals in need of treatment: lower values of s imply lower prices, which benefits consumers. The overall impact on consumer surplus will depend on which of the two effects dominates and remains ambiguous. In order to get a better picture of this trade-off, we must numerically solve for the equilibrium values.

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2.2.4.4 Numerical analysis

In this section we present some numerical results that allow us to better understand the welfare properties of DTCA in the two scenarios considered, perfect and imperfect agency. Even though we have computed the equilibrium values for a wide range of parameter values, here we present only some of them. In particular, we focus on how the welfare properties of DTCA depend on the magnitude of the harassment cost h. We have found a persistent tendency for DTCA to be less desirable for consumer welfare as h increases. This is what can be observed in the tables below, where the last two columns are the increments of consumer welfare and aggregate welfare when DTCA is allowed under a given regime j, where $j = p, h$, departing from the benchmark case b:

$$\triangle CW^j = CW^j - CW^b$$
$$\triangle AW^j = AW^j - AW^b$$

The first line in each able corresponds to the equilibrium values under perfect agency. In that case, physicians do not face any harassment cost and therefore results are invariable to h. The last lines in each table correspond to the equilibrium values under imperfect agency. In that case, results depend substantially on the value of h. The values of the parameters shown in the tables satisfy conditions 2.12 and 2.19.

Let us start by looking at the equilibrium prices and levels of DTCA. As stated in 2.27, when physicians are imperfect agents, firms tend to set lower prices and do more DTCA. This is reasonable, as under imperfect agency DTCA may be used to steal customers from the competing firm. Competition is then tougher and firms tend to behave more aggressively. However, this only translates into lower profits for high values of s, that is, when the fraction of people in need of medical treatment is high. To see that, note that each table shows results for a different value of s. Under perfect agency, a low value of s implies low sales, because healthy people do not get any prescription. On the contrary, under imperfect agency, DTCA may cause some healthy individuals to get prescriptions. The lower is s, the higher are the potential gains from DTCA for the firms in terms of sales under imperfect agency, in comparison with the potential gains under perfect agency.

DTCA tends to have a positive effect on consumer surplus if public expenditures are not taken into account. Even when physicians are imperfect agents, the positive impact of the informative effect of DTCA on consumer surplus through additional prescriptions seem to dominate the negative impact of the persuasive effect of DTCA through inefficient prescriptions. The higher is the fraction s of ill people, the more important is the informative role of DTCA.

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TABLE 2.1: Numerical analysis with a low fraction of ill population

$z = t = \tau = 0.5$, $v = k = 1$ and $s = 0.25$

	p^p	Φ^p	π_i^p	CS^p	X^p	$\triangle CW^p$	$\triangle AW^p$
	1.0000	0.0400	0.0662	0.1180	0.0674	0.0037	0.0111
h	p^h	Φ^h	π_i^h	CS^h	X^h	$\triangle CW^h$	$\triangle AW^h$
0.5	0.5375	0.1347	0.1485	0.1657	0.0671	0.0517	0.2236
0.6	0.6293	0.1911	0.2166	0.1687	0.1044	0.0174	0.3256
0.7	0.7212	0.2607	0.3063	0.1722	0.1612	-0.0359	0.4518
0.8	0.8135	0.3459	0.4248	0.1761	0.2459	-0.1167	0.6080
0.9	0.9063	0.4504	0.5830	0.1802	0.3698	-0.2365	0.8045

TABLE 2.2: Numerical analysis with an intermediate fraction of ill population

$z = t = \tau = 0.5$, $v = k = 1$ and $s = 0.5$

	p^p	Φ^p	π_i^p	CS^p	X^p	$\triangle CW^p$	$\triangle AW^p$
	1.0000	0.0769	0.1391	0.2511	0.1435	0.0139	0.0420
h	p^h	Φ^h	π_i^h	CS^h	X^h	$\triangle CW^h$	$\triangle AW^h$
0.5	0.5960	0.1873	0.1583	0.3417	0.1223	0.1256	0.1922
0.6	0.6748	0.2510	0.2128	0.3498	0.1658	0.0902	0.2658
0.7	0.7541	0.3259	0.2801	0.3582	0.2251	0.0393	0.3495
0.8	0.8343	0.4138	0.3635	0.3663	0.3049	-0.0323	0.4447
0.9	0.9161	0.5164	0.4677	0.3736	0.4113	-0.1314	0.5540

TABLE 2.3: Numerical analysis with all population ill

$z = t = \tau = 0.5$, $v = k = 1$ and $s = 1$

	p^p	Φ^p	π_i^p	CS^p	X^p	$\triangle CW^p$	$\triangle AW^p$
	1.0000	0.1111	0.2176	0.3970	0.2269	0.0295	0.0897
h	p^h	Φ^h	π_i^h	CS^h	X^h	$\triangle CW^h$	$\triangle AW^h$
0.5	0.7033	0.2626	0.1819	0.5225	0.2057	0.1762	0.1650
0.6	0.7588	0.3284	0.2133	0.5369	0.2479	0.1485	0.2001
0.7	0.8156	0.4021	0.2470	0.5507	0.2991	0.1110	0.2300
0.8	0.8742	0.4845	0.2830	0.5631	0.3611	0.0614	0.2524
0.9	0.9355	0.5767	0.3212	0.5737	0.436	-0.0029	0.2646

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However, by substantially increasing the number of prescriptions, DTCA raises the public expenditure on pharmaceuticals significantly. In particular, when harassment costs h are relatively high, DTCA leads to excessive consumption of drugs. This is illustrated in the tables by the results for consumer welfare CW^h. Let us compare the two scenarios. On the one hand, when physicians are perfect agents who take their prescription decisions just to maximise the utility of the patient, DTCA can only have an informative effect. This contributes to a better public health, with more patients correctly treated, and tends to have a positive impact on consumer welfare[1]. On the other hand, when physicians are imperfect agents, DTCA may lead them to prescribe suboptimal treatments to ill people and unnecessary treatments to healthy individuals. The higher are the harassment costs h, the higher is the potential distortion caused by DTCA on prescription choices. Suboptimal treatments impact negatively on the consumer surplus (through a lower public health), while unnecessary treatments impact negatively both on consumer surplus and on public financial resources. This negative impact can only be compensated by a substantial positive impact of DTCA on consumer surplus through new prescriptions for ill people. This means that the higher is the fraction s of ill people, the better are the welfare properties of DTCA under imperfect agency. In fact, in the tables we can see that as s increases, the range of values for which DTCA is detrimental to consumer welfare gets smaller.

Finally, the impact of DTCA on aggregate welfare seems to be positive both when physicians are perfect agents and when they are imperfect agents. This is so because the excessive consumption of drugs, which has a negative impact on consumer welfare, makes in contrast a positive contribution to firm's profits. Therefore, while a 'consumer-oriented' regulator should be cautious when deciding whether to allow or not firms to advertise directly to consumers, an 'industry-oriented' regulator could have stronger reasons to decide to allow them to do it.

2.3 Conclusions

The debate about the convenience of allowing DTCA focuses on the distortions that its persuasive effect could impose on prescription decisions, eventually leading to sub-optimal prescriptions and to excessive consumption. In this chapter, we have shown that the persuasive effect of DTCA may indeed have these consequences, if physicians are sensitive to the preferences of their patients. We have shown that if physicians are

[1] Unless the copayment is too low, in which case demand becomes inelastic and firms tend to increase price without limit, with a negative impact on consumer welfare. In fact, some modifications should be introduced in the model to make it suitable to study this situation. It is, however, out of the scope of our work.

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able to act as efficient gatekeepers, prescribing the best treatments and prescribing only when necessary, then DTCA could be a reasonable way of increasing patients' information. On the contrary, if reimbursement schemes, patients' freedom to change physician or simply patients' ability to harass physicians give an incentive to avoid contradicting patients' preferences, then the persuasive potential of DTCA should be carefully taken into account.

In this paper we have proposed a model to formalise the discussion about the welfare properties of DTCA and showed how these properties depend crucially on the nature of the relationship between physician and patient. There are some extensions that will deserve some further attention. In the model presented above, there are two competing firms that produce horizontally differentiated drugs. One possible extension would consist on defining a sequential game to understand if an incumbent firm could use DTCA as a barrier to entry. That advertising costs can be conceived as endogenous sunk costs fostering market concentration has already been theorised by Sutton [16]. In our case in particular, it would be interesting to understand if DTCA before patent expiration can be used by the holder of a patent to increase its first-entrant advantage with respect to potential generic competitors. The European Commission has indeed expressed some concern about the strategic behaviours engaged by pharmaceutical firms holding patents close to the expiration date, presuming that these are essentially oriented to limiting the effects of competition from generics after patent expiration [see 5]. As far as DTCA is concerned, we must bear in mind that advertising is a way of building reputation and brand loyalty, which is stressed by Grabowski and Vernon [6] as an essential element to be taken into account in any attempt to understand competition between branded and generic drugs.

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Part II

Off-patent pharmaceuticals and generic entry: patterns and effects in European markets

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Chapter 3

A theoretical framework for the analysis of branded-generic competition in off-patent pharmaceutical markets

Abstract

In this chapter we study the impact of generic competition in off-patent pharmaceutical markets when patients perceive the branded product as being of higher quality than the generics and are allowed to pay a co-payment to consume the branded product. We show that, while generic competition always drives prices down, under certain circumstances branded and generic firms are able to coordinate around high-price equilibria with a detrimental impact on welfare. This is the case when the branded firm can commit to a certain preferred price before generics choose the quantities they produce. We argue that price regulation may facilitate this type of coordination. We also show that policy interventions that seek to increase generic market share by distorting patients' choices may have the unintended effect of softening generic competition and lead to higher generic prices.

Key words: Pharmaceuticals, Generic competition, Regulation
JEL Classifications: I11; I18; K21; L41; L65

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3.1 Introduction

This chapter provides a theoretical framework for the analysis of generic competition in off-patent pharmaceutical markets. In particular, we look at the interaction between branded original drugs and generic drugs within a regulatory environment that closely resembles that of many European pharmaceutical markets. We build our analysis around patients' perception branded products as being of higher quality than the generics and account for they willingness to pay for quality.

An interesting feature of off-patent pharmaceutical markets is the observed persistence in the demand of branded products even after generic entry and despite the price differential that often exists between branded and generic products. Although in many countries generics often account for most of the consumption in off-patent markets, the branded is only rarely driven out from the market and its share of the market tends to be higher in terms of value than of volume. We show this in chapters 4 and 5, where we present an empirical analysis of generic competition in European pharmaceutical markets. This suggests that certain physicians or patients may perceive branded original products as distinct from their generic competitors and prefer to pay a price differential for the branded product and avoid switching to the generic version.

The analysis in this chapter provides theoretical foundations to interpret the results from the econometric analysis in chapters 4 and 5. We use a model of vertical differentiation, building on the framework proposed by Brekke et al. [1]. We depart from their analysis of a branded-generic duopoly to consider the market equilibrium when the branded product faces competition from a fringe of generic entrants. We incorporate price regulation to the model and investigate whether it may lead to higher equilibrium prices and lower consumer welfare. We look at the relations between the number of generic competitors, prices and market shares, and assess the welfare properties of the set of market equilibria obtained.

In our model, branded prices are higher than generic prices in equilibrium, with both branded and generic prices decreasing with the number of generics active in the market. A higher number of generics makes the generic segment of the market more competitive, driving down both generic and branded prices. This is consistent with previous empirical literature on generic competition.

A number of empirical papers have shown a relationship between the speed and extent of generic entry and the expected profitability of the market. Main references include Hurwitz and Caves [9], Grabowski and Vernon [6] and Scott-Morton [16]. The paper by Caves et al. [2] remains as a fundamental reference to understand the transformation in the competitive dynamics in off-patent pharmaceutical markets since the introduction

of generics in the US market in the eighties. The ability of generics to deliver more competitive markets with lower prices has been shown in a number of papers, including Grabowski and Vernon [5], Grabowski and Vernon [6], Frank and S. [4], Wiggins and Maness [19], Reiffen and D. [13], Saha et al. [15] and Regan [12] among others. Attention has been devoted in these papers to the reaction of branded incumbents to generic entry. Some studies show that the branded incumbent tends to increase price after generic entry, segmenting the markets between a high-price branded segment and a low-price generic segment. Most papers, however, do not observe this behaviour, but rather show the branded incumbents lower their price in response to generic competition. Evidence suggests however that branded incumbents are able to sustain prices above their generic competitors, giving support to the segmentation hypothesis. Most of the research has been conducted for the US and relatively fewer research has been published regarding European markets. Danzon and Li-Wei [3], Kanavos et al. [10] and Puig-Junoy and Moreno-Torres [11] are some exceptions, although not the only. They tend to focus their attention on the impact of market regulation on the competitive dynamics observed in European markets.

In chapters 4 and 5 we present our empirical analysis, which is also consistent with the main features of our theoretical framework. Branded prices are indeed shown to be higher than generic prices and average market prices are negatively correlated with the number of generics active in the market. The empirical analysis also shows that the number of generics is positively correlated with the value of the market. This is compatible with the structure of the market in our model in the presence of fixed costs, that constrains the number of generics sustainable with positive profits in the market.

We also use our theoretical framework to evaluate the likely impact of a number of regulatory interventions. We show that policy interventions seeking to increase generic market share by distorting patients' choices may have the unintended effect of softening generic competition and lead to higher generic prices. We also show that, while tougher generic competition always drives prices down, under certain circumstances branded and generic firms are able to coordinate around high-price equilibria with a detrimental impact on welfare. This is the case when the branded firm can commit to a certain preferred price before generics choose the quantities they produce. We argue that price regulation and especially authorised generics may facilitate this type of coordination. This hypothesis is compatible with the results of our empirical analysis, which indicate that price regulation is correlated with smaller reductions in price upon generic entry. Our empirical analysis does not look at the effect of authorised generics.

An important lesson from our analysis is that, as long as patients perceive branded drugs as being distinguishable from generic competitors, there may be a trade-off between

minimising public pharmaceutical expenditure and maximising consumer welfare, even if this tension does not have an impact on clinical outcomes. Branded and generic products are clinically equivalent, but there are non-clinical differences between drugs produced by different manufacturers. Patients may be aware of the clinical equivalence of branded and generic products, but still they may attach different subjective valuations to non-clinical characteristics of the products, which are instead irrelevant for a government that only values clinical outcomes.

The role of brands in pharmaceutical markets has attracted specific attention in the empirical literature. Grabowski and Vernon [5] and Scott-Morton [17], for instance, looked at the effect of brands as a barrier to generic entry without identifying a significant effect of brand recognition on the extent of generic entry. Richard and Van Horn [14] concludes that the effect of brand loyalty takes the form of habit, in the sense of persistence in prescription patterns and usage over time. Granlund and N. [7] provide insight by looking at consumer loyalty towards branded drugs in the Swedish market. They observe that patients are willing to pay a premium in order to receive the branded pharmaceutical instead of a cheaper non-branded generic version. There is discussion on whether branded products provide additional value to patients with respect to non-branded products. While the higher willingness to pay indicates that the subjective value of branded drugs is higher at least for a fraction of patients, it is less clear whether there is also some intrinsic clinical value to branded products. Van Wijk et al. [18] and Heaney and Sander [8], for instance, look at this question and conclude that there is no evidence that brands provide any additional relative clinical effectiveness, even though patients may often attribute a higher value to branded products. Our theoretical framework, where patients are willing to pay a premium for clinically equivalent branded products, is consistent with these findings

This chapter contributes to the existing literature by providing a formalisation of the impact of regulation on the competition between branded incumbents and generic entrants in off-patent pharmaceutical markets. It also contributes by providing analysis of the effects that a number of specific types of regulatory interventions have on market outcomes and consumer welfare.

The chapter is structured as follows. In section 3.2 we propose a model of vertical differentiation for the analysis of competition between branded and generic drugs in off-patent pharmaceutical markets. We show that, while generic competition always drives prices down, under certain circumstances branded and generic firms are able to coordinate around high-price equilibria with a detrimental impact on welfare. In section 3.3 we first study the effects of two types of policy interventions: the introduction of price ceilings and the encouragement of generic prescription and dispensation. Secondly, we

briefly discuss the relevance of brand recognition and patients' perceptions in our model. Finally, in section 3.4 we confront the implications of our theoretical framework with the results from the empirical analysis in chapters 4 and 5.

3.2 The model

3.2.1 Basic setup

We use a model of vertical differentiation to describe the different perceptions that patients have of branded and generic drugs. Consider a pharmaceutical market with a continuum of individuals uniformly distributed on the line segment $[\underline{\nu}, \overline{\nu}]$ with mass 1, where $\underline{\nu} < 1$. The location of an arbitrary individual, $\nu \in [\underline{\nu}, \overline{\nu}]$, represents the gross utility he is able to derive from receiving pharmaceutical treatment and depends on his health status.

There are two types of pharmaceutical firms in this market, an originator firm b producing a branded drug and generic firms g producing non-branded versions of the same drug. The branded drug enjoyed market exclusivity for a number of years, until patent expiry allowed generic producers to launch their non-branded versions onto the market. Years of market exclusivity allowed the originator product to accrue brand value in terms of patients' perception. Generic products are perceived as less valuable by patients, which is accounted for by a parameter $\theta \in (0, 1)$. Patients must pay a co-payment to receive the drug. More formally:

$$U(\nu, c_i) = \begin{cases} \nu - c_i & \text{if } i = b \\ \theta\nu - c_i & \text{if } i = g \end{cases} \tag{3.1}$$

where c_i is the co-payment that patients must pay to obtain drug i. We assume that patients are universally covered by a health insurance that reimburses pharmaceutical consumption up to the price of the cheapest version of a drug available in the market and that the health insurer imposes a dispensing fee to all patients. This type of reimbursement mechanism, so-called generic reference pricing, is prevalent in most European markets with some variations.[1] They share the feature that the co-payment made by the patient is the price differential between the reference price and the actual price of

[1] Puig-Junoy [11] provides a review of reimbursement mechanisms in European off-patent pharmaceutical markets.

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the drug, often plus a fixed fee, while the reference price is covered by the insurer. co-payments are therefore defined as a fixed payable fee plus the difference between the price of any dispensed drug and the price of the cheapest drug in the market:

$$c_i = f + p_i - p_r \tag{3.2}$$

where f is the fixed fee that patients pay to the health insurer and p_r is the price of the cheapest available version of the drug, which is used as a reference price for reimbursement purposes.[2] Hence, firms earn the full price p_i of their products for each unit sold and the health insurer pays the reference price p_r and earns the fixed fee f for each unit consumed by patients.

A patient will only be willing to get pharmacological treatment if he obtains a positive net utility from consumption. We assume that co-payments are designed to guarantee universal access to medical treatment which implies that $f < \underline{\nu}$. The higher the gross utility ν obtained by a patient, the more he will be willing to pay a higher co-payment in order to obtain the branded drug. Let $\hat{\nu}$ denote the patient who is indifferent between consuming a branded or a generic drug:

$$\hat{\nu} - c_b = \theta\hat{\nu} - c_g \tag{3.3}$$

Substituting for the co-payments:

$$\hat{\nu}(\mathbf{p}) = \frac{p_b - p_r - (p_g - p_r)}{1\theta} = \frac{p_b - p_g}{1 - \theta} \tag{3.4}$$

Patients with a gross utility above $\hat{\nu}$ will prefer to buy the branded version of the drug, while the remaining patients will buy the generic drug. Demands for each type of drug are defined by the following functions:[3]

$$\begin{aligned} D_b &= \overline{\nu} - \frac{p_b - p_g}{1 - \theta} \\ D_g &= \frac{p_b - p_g}{1 - \theta} - \underline{\nu} \end{aligned} \tag{3.5}$$

[2] This structure of co-payments has the propriety of not distorting the allocation of consumers amongst branded and generic products.

[3] Note that these demands are the same if patients pay the entire prices of the products instead of paying only the co-payments, as long as the price of the cheapest product is low enough for the consumer with the lowest valuation of the product not to be excluded.

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Demand for the branded drug is served by a unique firm b, while demand for the generic versions of the drug is served by a finite number n of generic firms g_i, where $i = 1, ..., n$. We initially assume n to be exogenously determined, in the sense that there is a finite number of generic producers with the technological capability to produce the drug.

In section 3.2.4 we relax this assumption and treat n as endogenous. However, it is reasonable to think that market conditions are likely to have an impact on entry decisions by potential generic competitors, thus recommending that n be treated as endogenous. We assume the marginal cost of producing the drugs is the same for all firms and equal to ω, irrespectively of whether they produce a branded or a generic drug. All generic firms incur in an entry cost $F > 0$, which the branded incumbent already paid in the past to start selling the drug while patent protected.

3.2.2 A branded product facing generic competition in a simultaneous game with vertical differentiation

In this section we assume that branded and generic firms meet in the market place and simultaneously choose their optimal strategies. In section 3.2.3 we look at the sequential case in which the branded incumbent is able to commit to a price first.

For each of these cases, we analyse first market outcomes when just one generic competitor enters the market and both the branded incumbent and the generic entrant compete by setting prices. We then look at the more general situation with multiple generic competitors entering the markets. The branded incumbent maximises profits by setting its price, each producer in the fringe of homogeneous generic competitors chooses the quantity produced and the equilibrium generic price is determined indirectly by the symmetric decisions of generic producers on the quantities produced.

Admittedly, this approach is unusual as it implies that the incumbent decides on price while generics compete in quantities. It provides, however, a simple way of introducing market segmentation into the model, with homogeneous generic products competing in quantities within the low-quality segment. Price competition amongst homogeneous generic competitors would lead to a Bertrand-like market outcome, with generics priced at marginal cost. We show that the market equilibrium in the duopoly with a branded incumbent and a generic entrant competing in prices is a particular case of our model with multiple generic entrants.

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3.2.2.1 Market equilibrium in the simultaneous game with multiple generic competitors

Firm b produces the branded drug and chooses price p_b to maximise its profits:

$$\pi_b = (p_b - \omega)\left(\overline{\nu} - \frac{p_b - p_g}{1-\theta}\right) \tag{3.6}$$

The first order condition for profit maximisation leads to the following reaction function of firm b:

$$p_b = \frac{1}{2}\left[p_g + \omega + (1-\theta)\,\overline{\nu}\right] \tag{3.7}$$

The n generic firms produce an homogeneous generic version of the same drug and compete à la Cournot to serve the demand for generics. Each generic firm i chooses the quantity it produces, d_{go}, to maximise its profits:

$$\pi_{gi} = d_{gi}\,(p_g - \omega) - F \tag{3.8}$$

Let's substitute for the generic price using the total generic demand:

$$\pi_{gi} = d_{gi}\left[p_b - (1-\theta)\left(\sum_i d_{gi} + \underline{\nu}\right) - \omega\right] - F \tag{3.9}$$

Imposing symmetry among generic firms the following set of reaction functions is obtained:

$$d_{gi} = \frac{1}{n+1}\left(\frac{p_b - \omega}{1-\theta}\underline{\nu}\right) \tag{3.10}$$

Substituting in the inverse total generic demand we obtain the generic price as a function of the price of the branded product:

$$p_g = \frac{1}{n+1}\left[p_b + n\omega - (1-\theta)\,\underline{\nu}\right] \tag{3.11}$$

Branded and generic products are strategic complements, as the cross derivatives of the reaction functions reveal:

$$\begin{aligned} \frac{\partial p_b}{\partial p_g} &= \frac{1}{2} > 0 \\ \frac{\partial p_g}{\partial p_b} &= \frac{1}{n+1} > 0 \end{aligned} \tag{3.12}$$

We can obtain equilibrium prices by solving the previous equations describing optimal responses:

$$\begin{aligned} p_b^* &= \omega + (1-\theta)\frac{1+n(1+\underline{\nu})}{2n+1} \\ p_g^* &= \omega + (1-\theta)\frac{1-\underline{\nu}}{2n+1} \end{aligned} \tag{3.13}$$

When evauated at $n = 1$, these equilibrium prices are equal to the equilibrium prices in the duopoly with one branded producer and one generic producer in the market. The case of the branded-generic duopoly if formally derived in the **??** to this chapter.

All patients must pay a fixed fee f, but patients consuming the branded product must additionally pay a co-payment equal to the difference between the branded and generic prices:

$$\begin{aligned} c_b^* &= (1-\theta)\frac{n+(n+1)\underline{\nu}}{2n+1} + f \\ c_g^* &= f \end{aligned} \tag{3.14}$$

Branded and generic market shares in equilibrium follow:

$$\begin{aligned} D_b^* &= \frac{1+n(1+\underline{\nu})}{2n+1} \\ D_g^* &= \frac{n(1-\underline{\nu})}{2n+1} \end{aligned} \tag{3.15}$$

3.2.2.2 Comparative-statics analysis in the simultaneous game

By inspecting these market outcomes, we see that the branded price is higher than the generic price and that patients must pay a higher co-payment if they choose to consume the branded product, as expected. The relative shares of branded and generic products

depend on the parameters of the model. We look now at how the number of generics active in the market has an impact on market outcomes.[4]

Proposition 3.1. *In the simultaneous game of branded-generic competition, prices of both branded and generic products, p_b^* and p_g^* decrease with the number n of generic competitors active in the market, as n increases from 1 to ∞. On the contrary, the co-payment c_b^* paid by patients consuming the branded product increases with n. Consequently, as n increases, the market share D_b^* of the branded product decreases, while the aggregated market share D_g^* of all generic products increases (fewer patients buy the branded product).*

Proof. The partial derivatives of equilibrium prices with respect to the number of generic firms are both negative:

$$\begin{aligned} \frac{\partial p_b^*}{\partial n} &= -\frac{(1-\theta)(1-\underline{\nu})}{(2n+1)^2} < 0 \\ \frac{\partial p_g^*}{\partial n} &= -\frac{2(1-\theta)(1-\underline{\nu})}{(2n+1)^2} < 0 \end{aligned} \tag{3.16}$$

The partial derivatives of the co-payment with respect to the number of generic firms is positive:

$$\frac{\partial c_b^*}{\partial n} = (1-\theta)\frac{1-\underline{\nu}}{(2n+1)^2} > 0 \tag{3.17}$$

Analogously for the branded and generic market shares:

$$\begin{aligned} \frac{\partial D_b^*}{\partial n} &= -\frac{1-\underline{\nu}}{(2n+1)^2} < 0 \\ \frac{\partial D_b^*}{\partial n} &= \frac{1-\underline{\nu}}{(2n+1)^2} > 0 \end{aligned} \tag{3.18}$$

[4] We investigate the behaviour of the equilibrium variables as n increases from 1 to ∞. In this section we are interested in the impact of additional generics entering the market, rather than in the equilibrium before and after the entry of the first generic. It is not the purpose of this chapter to provide a welfare analysis of generic entry as such, but to characterise the properties of the market equilibrium conditional to generic entry taking place. The empirical evidence shows that the entry of the first generic triggers a process of price reductions, but the final outcome of this process differs across markets. It is important to characterise the market equilibria and to identify in what situations they can be reach. On the other hand, in most European countries, before entry of the first generic the price of the branded drug is a negotiated price between the government and the branded producer. Our formalisation would not be appropriate to characterise market equilibria before generic entry.

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□

Let us look at the two limiting cases with just one generic producer and a very large number of generics. As the number of generic firms becomes very large, $n \to \infty$, generic price collapses to the level of marginal cost, ω, and the branded producer is able to sustain a price above marginal cost to maximise profits:

$$\begin{aligned} \lim_{n\to\infty} p_b^* &= \omega + \frac{1-\theta}{2}(1+\underline{\nu}) \\ \lim_{n\to\infty} p_g^* &= \omega \end{aligned} \tag{3.19}$$

Equilibrium branded and generic market shares when $n \to \infty$ are the following:

$$\begin{aligned} \lim_{n\to\infty} D_b^* &= \frac{1}{2}(1+\underline{\nu}) \\ \lim_{n\to\infty} D_g^* &= \frac{1}{2}(1-\underline{\nu}) \end{aligned} \tag{3.20}$$

When $n = 1$ the market outcome is that of a branded generic duopoly. The following equilibrium prices for the branded and generic drugs are obtained:

$$\begin{aligned} p_b^*|_{n=1} &= \omega + \frac{1-\theta}{3}(2+\underline{\nu}) \\ p_g^*|_{n=1} &= \omega + \frac{1-\theta}{3}(1-\underline{\nu}) \end{aligned} \tag{3.21}$$

Branded and generic market shares in equilibrium are the following:

$$\begin{aligned} D_b^*|_{n=1} &= \frac{1}{3}(2+\underline{\nu}) \\ D_g^*|_{n=1} &= \frac{1}{3}(1-\underline{\nu}) \end{aligned} \tag{3.22}$$

This shows that the branded-generic duopoly with price competition is a particular case of the more general model with one branded incumbent setting prices and n generic producers competing in quantities in the low-quality segment.

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As competition amongst generics drives equilibrium prices down, the branded firm tends to compete less aggressively for marginal consumers. This can be confirmed by looking at the behaviour of branded and generic market shares. As the number of generic firms increases and competition in the low-end segment of the market becomes fiercer, the generic market share increases at the expense of the branded market share. The presence of fixed costs $F > 0$ implies that there is a finite maximum sustainable number of generics that can be active in the market while earning positive profits $\pi^*_{gi} > 0$.

The equilibrium price of the branded drug does not increase with the number of generic firms active in the market, but this cannot be directly interpreted as being incompatible with the so-called 'generic paradox', the empirical observation in some markets that the branded price after generic entry tends to increase with respect to the pre-entry branded price. We have not attempted here to formalise the equilibrium branded price before generic entry and therefore nothing can be said with respect to the relation between branded equilibrium prices before and after generic entry.

In this model, a system of partial public financing of pharmaceutical consumption is in place, designed to guarantee full coverage of patient population and preserving patients' ability to choose between branded and generic products. Consumers do not fully support the cost of their pharmaceutical consumption, but just the additional cost incurred due to consumption of branded drugs instead of cheaper generic drugs. In such a framework, there is no reason why the preferences of an expenditure-minimiser government and surplus-maximiser consumers should be aligned. The following can be shown for the simultaneous equilibrium.

Proposition 3.2. *In the simultaneous game, public pharmaceutical expenditure PX^* and consumer surplus CS^* both decrease as the number n of generic firms active in the market increases from 1 to ∞. Although both p^*_b and p^*_g decrease with n, the price differential increases and so does the patient co-payment for the branded product, c^*_b. The higher co-payment reduces the number of patients consuming the branded product and increases the payment made by those patients that keep consuming it.*

Proof. Pharmaceutical public expenditure can be obtained from the formula for patients' co-payment and equilibrium prices:

$$PX^* = \omega + \frac{(1-\theta)(1-\underline{\nu})}{2n+1} - f \tag{3.23}$$

The partial derivative of public expenditure with respect to the number n of generic competitors:

$$\frac{\partial PX^*}{\partial n} = \frac{\partial p_g^*}{\partial n} < 0 \tag{3.24}$$

Consumer surplus can be expressed as follows:

$$\begin{aligned} CS^* &= \int_{\hat{\nu}}^{\overline{\nu}} \left[\nu - f - \left(p_b^* - p_g^*\right)\right] d\nu + \int_{\underline{\nu}}^{\hat{\nu}} (\nu - f)\, d\nu \\ &= \frac{1}{2}\left(\overline{\nu}^2 - \theta\underline{\nu}^2\right) - (1-\theta)\frac{n\overline{\nu} + \underline{\nu}}{2n+1}\left[\overline{\nu} - \frac{1}{2}\frac{n\overline{\nu} + \underline{\nu}}{2n+1}\right] - f \end{aligned} \tag{3.25}$$

The partial derivative of consumer surplus with respect to the number n of generic competitors:

$$\frac{\partial CS^*}{\partial n} = -\frac{(1-\theta)(1-\underline{\nu})\left[1 + n(1+\underline{\nu})\right]}{(2n+1)^3} < 0 \tag{3.26}$$

□

This result shows the tension existing between government's and patients' interest. While governments may favour tougher generic competition as a way to reduce pharmaceutical public expenditure, patients may be better off in a less competitive market. The rationale behind this result relies on the fact that patients tend to pay for only a small fraction of drugs price. If patients do not care about the size of public pharmaceutical expenditure and care only about their out-of-pocket expenses, then they may prefer the market outcome that minimises the price differential between branded and generic drugs. This is in fact the case in the simultaneous game analysed here, where the branded producer competes less aggressively and the branded co-payment increases when more generic firms are active in the market.

3.2.3 A branded product facing generic competition in a sequential game with vertical differentiation

In section 3.2.2 we have assumed that branded and generic firms simultaneously decide on price and quantities respectively. It is interesting to look at what happens when the branded product is able to set its price first, before generic actually make their decisions on quantities. In off-patent pharmaceutical markets, the branded product is typically an incumbent that has been in the market long before generic entry takes place. In this section we assume that the branded producer is able to post its price and credibly

commit to maintain it, before generic producers choose the quantities they produce. In most countries, pervasive price regulation in pharmaceutical markets introduce rigidities in the determination of prices. In some circumstances, branded producers may authorise a first generic entrant into the market through a license before loss of exclusivity. The agreement between the branded producer and the authorised generic may facilitate price commitment. We show that when this is possible, branded and generic producers are able to reach a market equilibrium that is more profitable for all of them than the simultaneous game, but that is detrimental both to consumer surplus and public interest.

3.2.3.1 Timing

To formalize the effects of generic competition in a sequential game, consider the following timing of a game played by one incumbent firm b producing a branded drug and a number n of entrants g_i producing generic versions of the same drug.

1. Incumbent b sets the price of its branded product p_b.
2. A number n of symmetric generic firms compete à la Cournot, each of them producing a quantity d_{gi} of generic product to serve the low-quality segment of the market.

This framework assumes a sequential decision process where generic entrants compete with a branded incumbent that has previously set its pricing policy, enjoying a first-mover advantage.

3.2.3.2 Market equilibrium in the sequential game with multiple generic competitors

We solve this game by backwards induction, looking first at second-stage Cournot competition among generic producers. We solve the profit-maximisation problem as we did in the simultaneous game, obtaining the reaction functions.

$$d_{gi} = \frac{1}{n+1}\left(\frac{p_b - \omega}{1-\theta} - \underline{\nu}\right) \tag{3.27}$$

Substituting in the inverse total generic demand we obtain the generic price as a function of the price of the branded product:

$$p_g = \frac{1}{n+1}\left[p_b + n\omega - (1-\theta)\,\underline{\nu}\right] \tag{3.28}$$

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In the first stage, the branded incumbent decides its pricing policy to maximise profits, anticipating the decisions of generic producers in the second stage.

$$\pi_b = (p_b - \omega)\left(\overline{\nu} - \frac{p_b - p_g}{1-\theta}\right) \tag{3.29}$$

Substituting for the generic price and computing the with respect to the branded price we obtain the following:

$$\frac{\partial \pi_b}{\partial p_b} = \frac{2n}{(1-\theta)(n+1)}(\omega - p_b) + (1 + 2\underline{\nu}) \tag{3.30}$$

The following equilibrium prices are obtained from combining this first order condition and the expression for generic price as a function of the branded price:

$$\begin{aligned} p_b^{**} &= \omega + (1-\theta)\frac{1 + n(1+\underline{\nu})}{2n} \\ p_g^{**} &= \omega + (1-\theta)\frac{1 + n(1-\underline{\nu})}{2n(n+1)} \end{aligned} \tag{3.31}$$

All patients must pay a fixed fee f, but patients consuming the branded product must additionally pay a co-payment equal to the difference between the branded and generic prices:

$$\begin{aligned} c_b^{**} &= \frac{1-\theta}{2}\left(1 + \frac{n+2}{n+1}\underline{\nu}\right) + f \\ c_g^{**} &= f \end{aligned} \tag{3.32}$$

Branded and generic market shares in equilibrium follow:

$$\begin{aligned} D_b^{**} &= \frac{1}{2} + \frac{n\underline{\nu}}{2(n+1)} \\ D_g^{**} &= \frac{1}{2} - \frac{n\underline{\nu}}{2(n+1)} \end{aligned} \tag{3.33}$$

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3.2.3.3 Comparative-statics analysis in the sequential game

In the sequential game, as in the simultaneous game, we see that the branded price is higher than the generic price and that patients must pay a higher co-payment if they choose to consume the branded product, as expected. In contrast, now the branded product is able to retain a higher share of patients than the generics. Again, we look at how the number of generics active in the market has an impact on market outcomes.[5]

Proposition 3.3. *In the sequential game of branded-generic competition, like in the simultaneous game, prices of both branded and generic products, p_b^{**} and p_g^{**} decrease with the number n of generic competitors active in the market. The co-payment c_b^{**} paid by patients consuming the branded product decreases with n in the sequential game. Consequently, as n increases, the market share D_b^{**} of the branded product increases, while the aggregated market share D_g^{**} of all generic products decreases.*

Proof. First derivatives of equilibrium prices and the co-payment with respect to the number of generic firms are all negative:

$$\begin{aligned}
\frac{\partial p_b^{**}}{\partial n} &= -\frac{1-\theta}{2n^2} < 0 \\
\frac{\partial p_g^{**}}{\partial n} &= -\frac{1-\theta}{2n^2\left(n+2\right)^2}\left[1+n\left(2+n\left(1-\underline{\nu}\right)\right)\right] < 0 \\
\frac{\partial c_b^{**}}{\partial n} &= -\frac{\left(1-\theta\right)\underline{\nu}}{\left(n+1\right)^2} < 0
\end{aligned} \tag{3.34}$$

First derivatives of branded and generic market shares:

$$\begin{aligned}
\frac{\partial D_b^{**}}{\partial n} &= \frac{\underline{\nu}}{2\left(n+1\right)^2} > 0 \\
\frac{\partial D_g^{**}}{\partial n} &= -\frac{\underline{\nu}}{2\left(n+1\right)^2} < 0
\end{aligned} \tag{3.35}$$

□

In the sequential game, unlike what we found for the simultaneous game, as competition amongst generics drives equilibrium prices down, the branded firm tends to compete

[5] As in the simultaneous game, it can be shown that the branded-generic duopoly with price competition presented in section **??** is a particular case of the more general model with one branded incumbent setting prices and n generic producers competing in quantities in the low-quality segment.

more aggressively for marginal consumers, the branded co-payment decreases as the difference between branded and generic prices gets smaller and the branded market share increases at the expense of the generic market share. Again, the presence of fixed costs $F > 0$ implies that there is a finite maximum sustainable number of generics that can be active in the market while earning positive profits $\pi^{**} > 0$.

In contrast with the simultaneous game, in the sequential game the preferences of an expenditure-minimiser government and surplus-maximiser consumers are aligned. The following can be shown.

Proposition 3.4. *In the sequential game, public pharmaceutical expenditure PX^{**} decreases and consumer surplus CS^{**} increases as the number n of generic firms active in the market increases.*

Proof. Pharmaceutical public expenditure can be obtained from the formula for patients' co-payment and equilibrium prices:

$$PX^{**} = \omega + (1-\theta)\frac{1+n(1-\underline{\nu})}{2n(n+1)} - f \tag{3.36}$$

The partial derivative of public expenditure with respect to the number n of generic competitors:

$$\frac{\partial PX^{**}}{\partial n} = \frac{\partial p_g^{**}}{\partial n} < 0 \tag{3.37}$$

We have already shown that, as n increases, the co-payment that patients need to pay for the branded product decreases and a higher share of patients are willing to pay for it. Consumers that would have in any case bought the branded product are better off because they pay a lower co-payment, while a share of consumers that would otherwise buy the branded product are better off because they get access to the branded product. Hence, CS^* increases as n increases.

□

In contrast with the result from the simultaneous game, there is no tension between the objectives of an expenditure-minimiser government and surplus-maximiser consumers. Both governments and consumers benefit from generic competition because, as the number of active generic firms increases, the branded firm tends to reduce its price relatively more than the equilibrium generic price is reduced. Consequently, the branded co-payment is lower with more generic firms in the market and a higher share of patients enjoy consuming the branded product.

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The intuition behind these results runs as follows. In the simultaneous game, as the number of generics increases, competition in the low segment of the market drives generic prices down. The branded producer reacts by increasingly focusing on fewer patients with highest willingness to pay, instead of following generics reducing its price. By comparison with the simultaneous game, in the sequential game the branded producer chooses to target fewer patients with higher willingness to pay by setting a relatively high price even when there is only one generic in the market. The generics responds by setting a price below the branded price such that the resulting co-payment paid by the patient is higher in the sequential game than in the simultaneous game. As the number of generics increases, competition in the low segment of the market drives generic prices down. To avoid losing its few highly valuable patients, the branded producer is forced to reduce its price.

3.2.4 Entry decisions by generic competitors

The analysis so far has been done assuming the number of generic firms n to be exogenous. As we have argued in section 3.2.1, there are a number of reasons to think that the number of potential generic entrants into the market of a given drug may be exogenous to a certain degree. However, it is reasonable to think that market conditions are likely to have an impact on entry decisions by potential generic competitors, thus recommending that n be treated as endogenous. In this section we develop a simple way to endogenise n by letting potential generic competitors to simultaneously decide whether or not to enter the market in the first period, before firms actually meet in the market.

Each potential generic competitor correctly anticipates the competitive equilibrium that will be reach in the market in the later periods and decides to enter the market if and only if the expected profits of entering the market are non-negative:

$$\pi_{gi} = d_{gi}\left(p_g - \omega\right) - F \geqslant 0 \tag{3.38}$$

Substituting for equilibrium prices and quantities in the simultaneous game, we obtain that a generic firm decides to enter the market if the following condition holds:

$$(1-\theta)\left(\frac{1-\underline{\nu}}{2n+1}\right)^2 - F \geqslant 0 \tag{3.39}$$

The only sub-game perfect Nash equilibrium will be that in which every generic firm that enters the market earns non-negative profits and no additional generic firm can

enter without earning negative profits. Therefore, the number of generic firms n in equilibrium in the simultaneous game is the integer given by the following expression:

$$n^* = \lfloor n \rfloor \text{ where } n = \frac{1}{2}\left[\left(\frac{1-\theta}{F}\right)^{\frac{1}{2}}(1-\underline{\nu}) - 1\right] \tag{3.40}$$

Analogously, substituting for equilibrium prices and quantities in the sequential game, we obtain that a generic firm decides to enter the market if the following condition holds:

$$(1-\theta)\left[\frac{1+n(1-\underline{\nu})}{2n(n+1)}\right] - F \geqslant 0 \tag{3.41}$$

The only sub-game perfect Nash equilibrium will be that in which every generic firm that enters the market earns non-negative profits and no additional generic firm can enter without earning negative profits. Therefore, the number of generic firms n in equilibrium in the simultaneous game is the integer given by the following expression:

$$n^* = \lfloor n \rfloor \text{ where } n = \frac{1}{2}\left[\left(\frac{1-\theta}{F}\right)^{\frac{1}{2}}(1-\underline{\nu}) - 1\right] \tag{3.42}$$

It can be shown that the number of entrants in equilibrium is higher in the sequential game than in the simultaneous game:

$$n^* \lesssim n^{**} \tag{3.43}$$

Proof. Inequalities 3.51 and 3.53 imply that the maximum sustainable n^* and n^{**} are such that:

$$\frac{1-\underline{\nu}}{2n+1} \simeq \frac{1+n(1-\underline{\nu})}{2n(n+1)} \tag{3.44}$$

From this, it follows that $n^* \lesssim n^{**}$.

□

3.2.5 Anticompetitive effects of branded leadership and authorised generics

Beyond the properties of the simultaneous and sequential market equilibria separately, we are interested in comparing their welfare implications. In the sequential game, the

branded producer is able to commit to a higher price than the price it charges in the simultaneous game. Although this implies that the branded producer is able to attract a smaller share of patients, the higher profitability obtained from each patient more than offsets the negative impact that a lower demand has on profits. Branded and generic products behave as strategic complements, meaning that a higher branded price implies a higher generic price in equilibrium.

Proposition 3.5. *Both branded and generic equilibrium prices, as well as the branded co-payment in equilibrium, are higher or equal in the sequential game than they are in the simultaneous game, while the equilibrium market share of the branded product is lower in the sequential game than it is in the simultaneous game:*

$$\begin{aligned} p_b^* < p_b^{**} \quad &, \quad p_g^* \leqslant p_g^{**} \\ D_b^* > D_b^{**} \quad &, \quad D_g^* < D_g^{**} \\ c_b^* \quad &< \quad c_b^{**} \end{aligned} \tag{3.45}$$

Profits of branded and generic firms and public expenditure are higher in the sequential equilibrium than it is in the simultaneous equilibrium. Conversely, consumer surplus is lower in the sequential equilibrium than in the simultaneous equilibrium:

$$\begin{aligned} \pi_b^* < \pi_b^{**} \quad &, \quad \pi_g^* < \pi_g^{**} \\ PX^* \quad &\leqslant \quad PX^{**} \\ CS^* \quad &> \quad CS^{**} \end{aligned} \tag{3.46}$$

Proof. Let's start by showing these results when the number of generic entrants is exogenously determined to be the equal in the simultaneous and in the sequential games.

Assume on the contrary that $p_b^* > p_b^{**}$. This implies:

$$p_b^{**} - p_b^* = (1-\theta)\left[\frac{1+n\,(1+\underline{\nu})}{2n} - \frac{1+n\,(1+\underline{\nu})}{2n+1}\right] < 0 \tag{3.47}$$

Which is a contradiction because the denominator of the first fraction is smaller than that of the second fraction, while numerators are equal. Hence, it must be that $p_b^* < p_b^{**}$.

Similarly, assume that $p_g^* > p_g^{**}$. This implies:

$$p_g^{**} - p_g^* = (1-\theta)\left[\frac{1+n\,(1+\underline{\nu})}{2n\,(n+1)} - \frac{1-\underline{\nu}}{2n+1}\right] < 0 \tag{3.48}$$

This inequality is only true if $\underline{\nu} < -\frac{n+1}{n}$, which is contradictory with $? \in [0,1]$. Hence, it must be that $p_g^* < p_g^{**}$.

In relation to the branded co-payments, assume that $c_b^* > c_b^{**}$. This implies:

$$c_b^{**} - c_b^* = (1-\theta)\left[\frac{1+n+(n+2)\,\underline{\nu}}{2\,(n+1)} - \frac{n+(n+1)\,\underline{\nu}}{2n+1}\right] < 0 \tag{3.49}$$

For this inequality to hold it must be that $1 + n(1+\underline{\nu}) < 0$, which is not true. Hence, it must be that $c_b^* < c_b^{**}$.????

Limits of branded market shares when $n \to \infty$ are the following:

$$\lim_{n\to\infty} D_b^* = \frac{1}{2}\,(1+\underline{\nu}) > \lim_{n\to\infty} D_b^{**} = \frac{1}{2} \tag{3.50}$$

Recall that:

$$\begin{aligned} \frac{\partial D_b^*}{\partial n} &< 0 \\ \frac{\partial D_b^{**}}{\partial n} &> 0 \end{aligned} \tag{3.51}$$

Therefore, for all n, it must be that $D_g^* > D_g^{**}$. Given that $D_b^* + D_g^* = D_b^{**} + D_g^{**} = 1$, this implies that $D_g^* < D_g^{**}$.

Branded profits must be higher in the sequential equilibrium because the branded producer has chosen it in spite of the simultaneous equilibrium being an attainable strategy in the sequential game. The simultaneous equilibrium is not a profit-maximising strategy for the branded producer in the sequential game.

Generic profits must be higher in the sequential game because both the generic price and the generic demand are higher in the sequential equilibrium than they are in the simultaneous equilibrium.

Let's consider now the case in which the number of generic entrants is endogenously determined. In equilibrium the following holds:

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$$\frac{1-\underline{\nu}}{2n+1} \simeq \frac{1+n\left(1-\underline{\nu}\right)}{2n\left(n+1\right)} \tag{3.52}$$

Recall expressions 3.19 and 3.43:

$$\begin{aligned} p_g^* &= \omega + (1-\theta)\frac{1-\underline{\nu}}{2n+1} \\ p_g^{**} &= \omega + (1-\theta)\frac{1+n\left(1-\underline{\nu}\right)}{2n\left(n+1\right)} \end{aligned} \tag{3.53}$$

This implies that when the number of generic entrants is endogenously determined and the maximum number of sustainable generic competitors actually enter the market, then generic prices are the same in the simultaneous and in the sequential game, $p_g^*|_{n^*} \sim p_g^{**}|_{n^{**}}$. Consequently, $p_g^* \leq p_g^{**}$.

Moreover, we have already shown above in this proof that $D_b^* > D_b^{**}$, for all n^* and n^{**}. This implies that $c^* < c^{**}$, because otherwise more patients would be willing to pay to get the branded product in the sequential game. Given that $p_g^* \leq p_g^{**}$, it must be that $p_b^* < p_b^{**}$.

$PX^* \leq PX^{**}$ follows from $p_g^* \leq p_g^{**}$.

$CS^* > CS^{**}$ follows from $D_b^* > D_b^{**}$ and $c_b^* < c_b^{**}$.

□

If branded and generic producers are able to communicate before meeting in the competitive market place and the branded producer is able to credibly commit to a certain preferred price p_b^{**}, as it happens to be the case in the sequential game; then the market equilibrium leaves consumers and government worse off, compared to the situation where the branded and generic producers are unable to communicate before competing in the market place. Certain circumstances may facilitate this credible commitment. Price regulation through negotiation between manufacturers and governments may facilitate it, for instance, by making prices stickier. In some circumstances, branded producers may authorise a first generic entrant into the market through a license before loss of exclusivity. The agreement between the branded producer and the authorised generic may facilitate price commitment.

These results lead to the following corollary, which is valid irrespectively of whether we define government's objective as maximising consumer welfare without accounting for

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public expenditure (taxes) or as maximising consumer welfare while minimising public expenditure (taxes).

Corollary 3.6. *Branded leadership in setting prices has anticompetitive effects, leading to higher prices and profits at the expense of lower consumer surplus and higher public expenditure. Hence, a competition authority should prevent the branded producer from publicly committing to a given price before competing with generic producers in the market place.*

3.3 Policy interventions affecting branded-generic competition

A government wanting to minimise public pharmaceutical expenditure may attempt to intervene in off-patent pharmaceutical markets to foster generic competition. We analyse in this section two policy instruments that are extensively used in European off-patent pharmaceutical markets: price caps for generic products and financial incentives to modify physicians' prescription behaviour and pharmacists' dispensing practices. In the context of our simultaneous game with vertical competition, we show that these interventions may not always achieve their intended objectives.

3.3.1 Price ceilings and the risk of generic price coordination around a focal point

Governments may try to force price erosion imposing a price ceiling to generic products. Assume a price ceiling is imposed such that generic price is forced below what otherwise would be the equilibrium generic price. That is, a binding price ceiling $\overline{p}_g$ is established such that:

$$\overline{p}_g < p_g^* \tag{3.54}$$

By looking at the reaction functions of the branded price both in the simultaneous and sequential games, it can be shown that branded and generic prices behave as strategic complements, thus the lower generic price imposed by the price ceiling leads to a lower branded price in equilibrium.

$$\frac{\partial p_b}{\partial p_g} = \frac{1}{2} > 0 \tag{3.55}$$

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We have already discussed the implications for market shares, public expenditure and consumer surplus when lower prices are the result of a larger number of generic producers competing for the low-end segment of the market. A binding ceiling on generic price has analogous implications. The government achieves its objective of reducing public expenditure through the price ceiling, but the effects on consumer surplus depend on the structure of the game. In the simultaneous game, lower prices lead to a higher co-payment for the branded product, lower branded market share and lower consumer surplus. In the sequential game, lower prices lead to a lower co-payment for the branded product, higher market share and higher consumer surplus.

It is most commonly assumed that a non-binding price ceiling should not have any effect on market outcomes. It has been however suggested in the literature (Scherer and Ross, 1990) that non-binding price ceilings can weaken competition as they may serve as collusive focal points for pricing decisions (Schelling, 1960). In the context of our model, a non-binding price ceiling may serve as a focal point for generic producers when the branded producer is unable to commit ex-ante to the profit-maximising price in the sequential equilibrium. In this case, the ceiling would not be acting as a focal point for both branded and generic producers, which having different qualities are unlikely to be able to coordinate around the same price. The ceiling may hewever act as a focal point for generics and become the reference price that is reimbursed by the public health insurance, while the brande producer still prices at an even higher price. In such circumstances, generic price and public expenditure would be higher as a result of the non-binding price ceiling acting as a focal point for generics. While this hypothesis has been proposed in the literature, we do not analyse here the circumstances under which this would be a sustainable equilibrium outcome.

3.3.2 Interventions on the demand side: incentives to physicians and pharmacists

A government may try to increase the demand for generics incentivising physicians to prescribe generic products and pharmacists to substitute generic for branded products when dispensing to the patient. While we do not formalise the decision processes of prescription and dispensation, we assume that governments have the ability to move a fraction α of patients from branded to generic products. These are patients that would have chosen to buy a branded product if they had been given the chance to, but that consume generic products because they have been precluded from choosing according to their preferences. In this case, demands for branded and generic products are as follows:

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$$\begin{aligned} D'_b &= \overline{\nu} - \frac{p_b - p_g}{1-\theta} - \alpha \\ D'_g &= \frac{p_b - p_g}{1-\theta} - \underline{\nu} + \alpha \end{aligned} \tag{3.56}$$

We solve for the equilibrium prices in the simultaneous game and the following equilibrium prices are obtained:

$$\begin{aligned} p'_b &= \omega + (1-\theta)\frac{n(1+\underline{\nu}-\alpha)+1}{2n+1} \\ p'_g &= \omega + (1-\theta)\frac{1-\underline{\nu}+\alpha}{2n+1} \end{aligned} \tag{3.57}$$

Branded and generic market shares in equilibrium are the following:

$$\begin{aligned} D'_b &= \frac{1+n(1+\underline{\nu}-\alpha)}{2n+1} \\ D'_g &= \frac{n(1-\underline{\nu}+\alpha)}{2n+1} \end{aligned} \tag{3.58}$$

While the intervention on the demand side is successful at increasing the generic market share, it also has unintended effects on equilibrium prices. The branded manufacturer chooses a lower price when such a policy is in place, while generics higher demand leads to a higher equilibrium generic price. Consequently, also public expenditure is higher as a consequence of forcing patients to switch from the branded product to the generic. Patients that keep consuming the branded product are better off because they pay a lower co-payment for it, but the fraction of patients switched to the generic product are worse off because they would have preferred to pay a higher co-payment and get access to the branded product.

The results are analogous if this policy intervention takes place in the sequential game, as we show in the 3.5 to this chapter.

Proposition 3.7. *If a fraction α of patients that would prefer to consume the branded product are forced to consume a generic product, then the branded manufacturer responds by lowering its price, the equilibrium generic price increases and consequently the branded co-payment is smaller than it would be in the absence of the policy intervention. Public expenditure increases with the equilibrium generic price. More formally:*

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$$\begin{aligned} p_b' < p_b^* \quad &, \quad p_g' > p_g^* \\ D_b' < D_b^* \quad &, \quad D_g' > D_g^* \\ c_b' \quad &< \quad c_b^* \\ PX' \quad &< \quad PX^* \end{aligned} \tag{3.59}$$

3.3.3 Patients' perceptions on the quality of generics: commoditisation and the value of brands

Market segmentation is possible in this model because patients extract higher utility from consuming the branded product than they get from generic products. The parameter θ determines the relative utility from consuming a generic instead of a branded product. While both types of products are assumed to offer identical clinical efficacy, patients still have different perceptions on the value of each type of product according to non-clinical characteristics. Even when the generic segment of the market is perfectly competitive and generic price equals marginal cost, the branded product is able to retain a share of the patients at a higher price.

An obvious way to undermine firms' ability to benefit from market segmentation at the expense of public spending would be to reduce the degree of product vertical differentiation. In fact, as products are perceived as increasingly similar by patients, market outcomes approach the perfectly competitive equilibrium with prices collapsing to marginal cost:

$$\lim_{\theta \to 1} p_b^* = \lim_{\theta \to 1} p_g^* = \omega \tag{3.60}$$

In such an undifferentiated equilibrium all firms charge the marginal cost and none makes any profits. We can therefore expect generic firms to prefer relaxing price competition through product differentiation, even if this implies focusing on the low-end segment patients. We can see that by looking at the derivative of the generics' profit function with respect to the differentiation parameter θ:

$$\frac{\partial \pi_b}{\partial \theta} = -\left(\frac{1-\underline{\nu}}{2n+1}\right)^2 < 0 \tag{3.61}$$

Profits of generic firms increase with product differentiation, even though this means lowering patients' perception of the quality of their products. Any attempt by the

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government to reduce the differentiated perception of branded and generic products by patients will be undermined not only by the branded firm efforts to preserve the perception of high quality associated to its products, but also by generic firms efforts to differentiate their products as low-quality.

In the limiting case of no vertical differentiation ($\theta = 1$), no profits are made by any firm and incentives for generic entry onto the market disappear. We do not contemplate here the possibility that branded and generic firms develop strategies of horizontal differentiation to satisfy the preferences of specific groups of patients in the space of non-clinical characteristics of their products. The analysis of this question goes beyond the purpose of this work.

3.4 Discussion of the empirical evidence

Our analysis provides a theoretical framework to interpret the results of the reduced-form empirical analysis presented in chapters 4 and 5. Although our empirical analysis does not explicitly attempt to test the implications of the analysis presented here, most results in the empirical analysis are compatible with the implications of this theoretical framework.

We have proposed a model of vertical differentiation to represent competition between branded and generic drugs in off-patent pharmaceutical markets. The literature has previously looked at branded and generic drugs as vertically differentiated products and in particular we stay close to the framework developed by Brekke et al. [1]. When the manufacturer of an innovative drug loses market exclusivity upon patent expiry, it has typically been the only incumbent in the market for a number of years. The branded recognition acquired during the period of market exclusivity makes its product distinguishable to patients from generic versions of the drug that may eventually enter the market. Patients' perception of branded products as of higher quality than their generic competitors may translate into the ability of sustaining price differentials.

In our model, branded prices are higher than generic prices in equilibrium, with both branded and generic prices decreasing with the number of generics active in the market. A higher number of generics makes the generic segment of the market more competitive, driving down both generic and branded prices. Our empirical analysis supports these results. Branded prices are indeed shown to be higher than generic prices and average market prices are negatively correlated with the number of generics active in the market. The empirical analysis also shows that the number of generics is positively correlated with the value of the market. This is compatible with the structure of the market in our

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model in the presence of fixed costs, that constrains the number of generics sustainable with positive profits in the market. These results are in line with those in the empirical literature, as we discuss more thoroughly in chapters 4 and 5.

Using a sequential game, we have shown that when the branded producer is able to commit to a certain preferred price; then branded and generic producers are able to reach a market equilibrium with higher prices that leaves consumers and government worse off, compared to the situation where the branded and generic producers are unable to communicate before competing in the market place. We have argued that price regulation and authorised generics may facilitate reaching such an equilibrium. By regulating the branded price or by establishing a non-binding price ceiling, regulators may provide a focal point for generics to coordinate around. This hypothesis is compatible with the results of our empirical analysis, which indicate that price regulation is correlated with smaller reductions in price upon generic entry. Our empirical analysis does not look at the effect of authorised generics.

We have also looked at policies that forcibly switch patients from branded to generic products and argued that these interventions are successful at increasing the market share of generics, while having unintended effects on prices. In particular, we have shown that the branded producer responds to such an intervention by reducing its price, while in contrast generic price increases as a consequence of such a policy. Physicians can be given financial and non-financial incentives to prescribe generics, typically using the INN of drugs. Financial incentives take the form of variable retribution conditional to not exceeding maximum prescription budgets per patient or a certain number of branded prescriptions. Non-financial instruments for physicians range from mere recommendations to prescribe generically to compulsory INN prescription. Incentives to pharmacists typically consist of higher margins for generic products. Alternatively, in occasions compulsory substitution of generic for branded products at pharmacy level has been implemented under certain conditions.

The results of the empirical analysis confirm that obliging physicians to prescribe generics and incentivising pharmacists to dispense generics is positively correlated with higher generic market shares. These policy interventions are also correlated with lower average prices. This is not incompatible with our result that generic prices increase as a consequence of such policies, because the net effect on average market prices depends on the relative behaviour of branded and generic prices. The empirical analysis in chapter 5 does not however provide any support for the implication that follows from our model, as it does not look at the correlation with branded and generic prices separately.

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In this paper we have provided a theoretical framework for the analysis of competition between branded and generic products in off-patent pharmaceutical markets. Most features of our framework are supported by the evidence produced by the empirical analysis. Generic competition is successful at reducing prices of off-patent pharmaceuticals, thus reducing public pharmaceutical expenditure where public health insurance mechanisms partially cover the cost of drug consumption. Government intervention regulating prices may introduce rigidities that impede the full realisation of the benefits from generic competition. Imposing generic consumption on patients may have the unintended effect of softening competition between generics, resulting in higher generic prices.

Moreover, as long as patients perceive branded drugs as being distinguishable from generic competitors, there may be a trade-off between minimising public pharmaceutical expenditure and maximising consumer welfare, even if this tension does not have an impact on clinical outcomes. Branded and generic products are clinically equivalent, but there are non-clinical differences between drugs produced by different manufacturers. Patients may be aware of the clinical equivalence of branded and generic products, but still they may attach different subjective valuations to non-clinical characteristics of the products, which are instead irrelevant for a government that only values clinical outcomes.

3.5 Appendix

3.5.1 Market equilibrium in the simultaneous game with one generic competitor

Firm b produces the branded drug and chooses price p_b to maximise its profits:

$$\pi_b = (p_b - \omega)\left(\overline{\nu} - \frac{p_b - p_g}{1-\theta}\right) \tag{3.62}$$

The first order condition for profit maximisation leads to the following reaction function of firm b:

$$p_b = \frac{1}{2}\left[p_g + \omega + (1-\theta)\,\overline{\nu}\right] \tag{3.63}$$

The generic firm produces an homogeneous generic version of the same drug. It chooses the quantity it produces, d_g, to maximise its profits:

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$$\pi_g = d_g \left(p_g - \omega \right) - F \tag{3.64}$$

Maximisation of generic profits with respect to price leads to the following reaction functions:

$$p_g = \frac{1}{2} \left(p_b + \omega - 1 - \theta \underline{\nu} \right) \tag{3.65}$$

We can obtain equilibrium prices by solving the previous equations describing optimal responses:

$$\begin{aligned} p_b^* &= \omega + \frac{1-\theta}{3} \left(2 + \underline{\nu} \right) \\ p_g^* &= \omega + \frac{1-\theta}{3} \left(1 - \underline{\nu} \right) \end{aligned} \tag{3.66}$$

All patients must pay a fixed fee f, but patients consuming the branded product must additionally pay a co-payment equal to the difference between the branded and generic prices:

$$\begin{aligned} c_b^* &= (1-\theta) \frac{1 + 2\underline{\nu}}{3} + f \\ c_g^* &= f \end{aligned} \tag{3.67}$$

Branded and generic market shares in equilibrium follow:

$$\begin{aligned} D_b^* &= \frac{1}{3} \left(2 + \underline{\nu} \right) \\ D_g^* &= \frac{1}{3} \left(1 - \underline{\nu} \right) \end{aligned} \tag{3.68}$$

3.5.2 Market equilibrium in the sequential game with one generic competitor

We solve this game by backwards induction, looking first at the second-stage decision by the generic producer. We solve the profit-maximisation problem as we did in the simultaneous game, obtaining the same reaction function.

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$$p_g = \frac{1}{2}\left[p_b + \omega - (1-\theta)\,\underline{\nu}\right] \tag{3.69}$$

In the first stage, the branded incumbent decides its pricing policy to maximise profits, anticipating the decisions of the generic producer in the second stage.

$$\pi_b = (p_b - \omega)\left[\overline{\nu} - \frac{1}{2}\left(\frac{p_b - \omega}{1-\theta} - \underline{\nu}\right)\right] \tag{3.70}$$

Substituting for the generic price and computing the with respect to the branded price we obtain the following:

$$\frac{\partial \pi_b}{\partial p_b} = 1 + \frac{\underline{\nu}}{2} - \frac{p_b - \omega}{1-\theta} \tag{3.71}$$

The following equilibrium prices are obtained from combining this first order condition and the expression for generic price as a function of the branded price:

$$\begin{aligned} p_b^{**} &= \omega + (1-\theta)\,\frac{2+\underline{\nu}}{2} \\ p_g^{**} &= \omega + (1-\theta)\,\frac{2-\underline{\nu}}{4} \end{aligned} \tag{3.72}$$

All patients must pay a fixed fee f, but patients consuming the branded product must additionally pay a co-payment equal to the difference between the branded and generic prices:

$$\begin{aligned} c_b^{**} &= \frac{1-\theta}{2}\left(1 + \frac{3}{2}\underline{\nu}\right) + f \\ c_g^{**} &= f \end{aligned} \tag{3.73}$$

Branded and generic market shares in equilibrium follow:

$$\begin{aligned} D_b^{**} &= \frac{1}{2} + \frac{\underline{\nu}}{4} \\ D_g^{**} &= \frac{1}{2} - \frac{\underline{\nu}}{4} \end{aligned} \tag{3.74}$$

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3.5.3 Interventions on the demand side in the sequential game

Similar results to those in section 3.3.2 can be obtained for the sequential game. We solve for the equilibrium prices in the sequential game and the following equilibrium prices are obtained:

$$\begin{aligned} p_b'' &= \omega + (1-\theta)\frac{1+n(1+\underline{\nu}-\alpha)}{2n} \\ p_g'' &= \omega + (1-\theta)\frac{1+n(1+\underline{\nu}-\alpha)}{2n(2n+1)} \end{aligned} \tag{3.75}$$

Branded and generic market shares in equilibrium are the following:

$$\begin{aligned} D_b'' &= \frac{1}{2} + \frac{n(\underline{\nu}-\alpha)}{2(n+1)} \\ D_g'' &= \frac{1}{2} - \frac{n(\underline{\nu}-\alpha)}{2(n+1)} \end{aligned} \tag{3.76}$$

Again, while the intervention on the demand side is successful at increasing the generic market share, it also has unintended effects on equilibrium prices. The branded manufacturer chooses a lower price when such a policy is in place, while generics higher demand leads to a higher equilibrium generic price. Consequently, also public expenditure is higher as a consequence of forcing patients to switch from the branded product to the generic. Patients that keep consuming the branded product are better off because they pay a lower co-payment for it, but the fraction of patients switched to the generic product are worse off because they would have preferred to pay a higher co-payment and get access to the branded product.

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Chapter 4

Patterns of generic entry: number of entrants and time to entry

Abstract

Generic entry is the main source of competition in off-patent pharmaceutical markets. However, generic entry does not occur in every market and it often tends to occur with a significant delay from the date of loss of exclusivity by the patent holder. In this paper we look at the patterns of generic entry in a number of European countries and identify the main factors that attract early generic entry. In particular, we are interested in the impact that pervasive regulation of European pharmaceutical markets has on the occurrence and pattern of generic entry. We show that patterns of generic entry differ significantly across European countries and types of drugs, and identify some factors that explain this heterogeneity. We observe that early entry is more likely in larger markets, when price regulation is less strict and where regulatory incentives for generic prescription and dispensation are in place.

Key words: Pharmaceuticals, Generic entry, Generic competition, Regulation
JEL Classifications: I11; I18; K21; L41; L65

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4.1 Introduction

Generic entry is the main source of competition in off-patent pharmaceutical markets. However, generic entry does not occur in every off- patent market and it often tends to occur with a significant delay from the date of loss of exclusivity by the patent holder. This is specially true in European pharmaceutical markets, which are subject to a series of regulations that distinguish them from the more unregulated US pharmaceutical markets.

The literature on off-patent prescription drug markets is often concerned with identifying the factors that drive generic producers decisions to enter the market and with assessing the effects that generic entry has on drugs prices and market structure. Seminal papers in the area date from the early nineties and look at the developments in the off-patent pharmaceutical markets in the US after the approval of the Waxman-Hatch Act of 1984, which introduced the Abbreviated New Drug Application (ANDA) process. By significantly simplifying the requirements generic producers (hereafter generics) were asked to meet before being granted regulatory approval, the entry cost for generics was substantially reduced both in terms of financial investment and of administrative time length.

The determinants of generic entry in the US before the Waxman-Hatch Act were studied by Hurwitz and Caves [4], identifying pre-expiry market sales as a statistically significant determinant of the number of entrants. In the same line, Grabowski and Vernon [3] show that, as expected, pre-expiry profitability attracts generic entry. While they hypothesise that brand loyalty could be a deterrent of generic entry, they do not find any negative significant correlation between the occurrence of entry and their proxies for the degree of brand loyalty (number of years of market exclusivity enjoyed by the originator and promotion to sales ratio of the originator the year before loss of exclusivity). Scott-Morton [6] also looks at the determinants of generics decisions to enter an off-patent market in the US. She identifies larger pre-expiry revenue, share of hospital sales and the condition of chronic treatment as factors that increase incentives for generics to enter in a market. Interestingly, she also finds that generic firms tend to enter into those markets in which they already have previous expertise, thus suggesting that development and production costs may play a role in generics decisions to enter selected markets.

Bae [1] looks at generic entry as a survival problem and uses a proportional hazard method to analyse the pace of generic entry in the US market. Consistently with previous results, he finds that generic entry tends to be faster and entry rates higher for products with larger pre-expiry market revenues. He concludes that commercially successful blockbusters are more likely to face early generic entry. Also drugs for chronic

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use tend to have faster generic entry, in line with the results obtained by Scott-Morton [6].

In this paper we look at the patterns of generic entry in a number of European countries and identify the main factors that attract generic entry and facilitate early entry. In particular, we are interested in the impact that pervasive regulation of European pharmaceutical markets has on the occurrence and pattern of generic entry. We show that patterns of generic entry differ significantly across European countries and types of drugs, and identify some factors that explain this heterogeneity. Our research provides the most comprehensive and up to date look at the patterns of generic entry in Europe. It confirms that larger pre-expiry revenue attracts generic entry in terms of likelihood of entry, speed of entry and long-run number of entrants. We also provide the most exhaustive study of the impact that different types of regulation of pharmaceutical markets in Europe have had on the occurrence and speed of generic entry. We find that price-cap policies tend to discourage and delay generic entry. Incentives to physicians to prescribe generically and policies encouraging substitution at pharmacy level tend to make generic entry in a given market more attractive, thus leading to a higher probability of generic entry and to earlier entry in case of occurrence.

The paper is structured as follows. In Section 4.2 we provide some descriptive statistics of the occurrence and patterns of generic entry. In Section 4.3 we present the econometric analysis performed to identify the determinants of the occurrence and extent of generic entry. Section 4.4 shows the survival analysis performed to identify market characteristics and regulatory features that explain the delay of generic entry.

4.2 Data and descriptive analysis

The data used in this chapter 4 and in chapter 5 is described in detail in a separate Annex in chapter 6. The various econometric models used in the empirical analysis differed in terms of data requirements. The regression analyses involved the use of price data, volume data, dates (date of LoE, entry date) and qualitative information (product characteristics, characteristics of the regulatory environment).

This section provides detailed descriptive statistics about the development of prices and generic penetration after LoE in 17 European countries. The same countries are covered in the econometric analysis in following section 4.3. The analysis in section 4.4 required data for all INNs in the same therapeutic category, which forced us to limit the coverage to 9 European countries.

TABLE 4.1: Share of INNs facing entry after LoE (EU average)

	Head-count entry share	Value entry share
Entire sample, by the end of 2007	0.66	0.85
Entire sample, one year after LoE	0.47	0.70
INNs expired before 2007, one year after LoE	0.46	0.69
INNs expired before 2006, two years after LoE	0.54	0.80

4.2.1 Extent of generic entry

Table 4.1 shows, for the EU as a whole[1], the share of INNs in the sample that faced generic entry over the period 2000 2007. All shares are presented both as a head count (where within each country each INN[2] is counted as one; left-hand column) and in value terms (where within each country weights are given to the INN in relation to their sales value in the year before LoE; right-hand column).

The first row in the table gives the occurrence of entry for the entire sample of INNs irrespective of when in the period the INN lost exclusivity or generic entry took place. As can be seen, the share of INNs in the overall sample that faced generic entry at any point in time over the period 2000 - 2007 is about 66% in number terms and about 85% in value terms.

These shares may be somewhat difficult to interpret, however, in that not all INNs are in an equal position. For instance, if LoE occurred early in the period 2000 - 2007, that left a long time for entry to occur within the period under investigation. By contrast, for INNs which lost exclusivity late in the period (e.g. in autumn of 2007), little time is left for entry to occur and instances of generic entry might not be counted for these INNs. For this reason, the table also indicates the shares of INNs for which entry took place within one year, both for the entire sample (second row, mainly for comparison) and the sample which lost exclusivity up to 2006 (third row). It also indicates for this sample, the shares of INNs for which entry took place within two years (for LoE up to 2005).

[1] All EU averages in this section are calculated taking into account the relative weight of the individual country, i.e. measured by sales of the relevant INNs in the country concerned, either in the year prior to expiry (for establishing shares of generic entry, average time to entry and generic penetration) or in the year 2007 (for the indices that track the development of prices or volumes over longer periods.)

[2] INN is the International Non-proprietary Name for pharmaceutical substances. A combination product and each of the related mono-products are viewed as separate INNs.

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TABLE 4.2: Share of INNs facing entry within one year, by size class

Size class	1	2	3	4	5
Share	0.25	0.43	0.32	0.58	0.81

Unweighted averages

TABLE 4.3: Share of INNs facing entry within one year, by country

	INNs headcount	INNs weighted
Austria	0.48	0.59
Belgium	0.39	0.61
Czech Rep.	0.21	0.30
Germany	0.57	0.71
Denmark	0.52	0.83
Spain	0.32	0.52
Finland	0.52	0.79
France	0.39	0.51
Greece	0.35	0.58
Hungary	0.19	0.40
Ireland	0.38	0.75
Italy	0.37	0.70
Luxembourg	0.15	0.54
Netherlands	0.57	0.51
Portugal	0.31	0.64
Sweden	0.48	0.70
United Kingdom	0.54	0.80

The table shows that, focusing on patents which expired between 2000 and 2006 followed by entry within one year, the share of INNs that faced generic entry is about 46%. However, taking into account the importance of the INNs (in terms of sales), the entry share is higher, at 69%.

This last finding suggests that generic entry tends to concentrate especially on INNs with a high sales value. This pattern can also be seen to some extent in table 4.2, which sets out the share of generic entry for individual size classes. The set of INNs is split into five size classes, with class 1 containing the 20% of smallest INNs (in terms of their sales value in the year prior to expiry), class 2 the next smallest 20%, etc. Class 5 therefore contains the 20% of largest-selling INNs. On average, the share of generic entry appears higher for the larger size classes than for the smaller ones. This could be explained by higher incentives for the generics to enter. From the perspective of consumer welfare, generic entry without delay for this category is likely to be most valuable.

The EU averages indicated above hide considerable variation across European countries.

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TABLE 4.4: Share of INNs facing entry within one year, by country and period

	LoE between 2000 and 2003	LoE between 2004 and 2006
Austria	0.40	0.59
Belgium	0.31	0.47
Czech Rep.	0.25	0.17
Germany	0.46	0.67
Denmark	0.47	0.58
Spain	0.31	0.39
Finland	0.54	0.50
France	0.39	0.51
Greece	0.29	0.43
Hungary	0.18	0.20
Ireland	0.27	0.50
Italy	0.17	0.50
Luxembourg	0.09	0.25
Netherlands	0.42	0.64
Portugal	0.38	0.19
Sweden	0.41	0.54
United Kingdom	0.46	0.65

INNs weighted by value 6 months before LoE,

Table 4.3 provides an overview of the share of entry in a range of countries, both as a head count of INNs and with the INNs weighted by value. The figure shows that in the sample investigated, generic entry is most pervasive in Germany, Denmark, Finland, the Netherlands and the UK, with entry shares within the first year above 50% both in number and value terms.

Another interesting aspect is whether the generic entry has changed over the period in question. Table 4.4 presents the share of INNs that faced generic entry for a number of countries, drawing a distinction between INNs which experienced LoE in the period 2000 - 2003 and in the period 2004 - 2006. As can be seen in the table, the share of expiring INNs followed by generic entry within one year has in most countries increased somewhat over the period 2000 2007, although there are some exceptions.

4.2.2 Time to entry

The average time gap between LoE for an INN and the first generic entry into that INN has been computed both as an unweighted average and as an average weighted

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TABLE 4.5: Average time to entry following LoE, by size class

Size class	1	2	3	4	5
Months	18.6	18.4	18.3	7.9	4.2

Unweighted averages

by market value before LoE.[3] The unweighted average time to entry is about thirteen months, whereas it is more than seven months in weighted value terms.

It takes less time for high-value products to be faced with generic entry. As mentioned earlier, this finding is not surprising considering that top selling INNs are normally also the most attractive to enter. The conclusion is further confirmed by table 4.5 setting out the time to entry by size class. The set of INNs is split up into five size classes, where class 1 contains the 20% of smallest INNs (in terms of sales value in the year prior to expiry), class 2 the next smallest 20%, etc. By and large, the average time to entry appears to be smaller for the larger INNs (as measured by sales in the year prior to expiry). However, even for the top selling category it still took about four months on a weighted average basis before entry took place. In individual cases in this category, the time to entry ranged from 0 months (no delay) to over 50 months.

There are equally considerable differences in time to entry across European countries. Table 4.6 shows the average time to entry in a range of countries. It is relatively short in Denmark, Finland, Ireland, Sweden and the UK but exceeds half a year, on average, in Austria, Belgium, the Czech Republic, Germany, Spain, France, Greece, Hungary, Italy, Luxemburg, the Netherlands and Portugal.

Over the period, there appears to be a gradual decline in the time to entry for expiring INNs. It is, however, difficult to provide meaningful descriptive statistics in this respect, given that the choice of time horizon (the time one allows for expiry to take place) heavily influences any resulting statistic.

4.2.3 Number of generic entrants

The third aspect of the extent of entry is the number of generic companies that enter if and when entry takes place. Table 4.7 shows the trend in the number of companies active per INN over time.

[3]The period of expiries is restricted to 2000 - 2006. When calculating the average time to entry on a collection of expiring INNs, one needs to bear in mind that not all INNs are in equal position. For instance, for all INNs that expired towards the end of the period 200 - 2007 and for which entry can be observed, the time to entry is necessarily short. Taking these late observations into account would not give an unbiased estimate of the average time to entry of the sample of INNs under investigation.

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TABLE 4.6: Average time to entry following LoE, by country

	Months
Austria	9.4
Belgium	9.5
Czech Rep.	14.4
Germany	7.4
Denmark	2.8
Spain	12.7
Finland	3.9
France	10.3
Greece	14.1
Hungary	16.1
Ireland	5.8
Italy	8.7
Luxembourg	14.7
Netherlands	8.3
Portugal	11.7
Sweden	4.6
United Kingdom	3.9

INNs weighted by value 6 months before LoE,

Before entry, the average number of companies per INN per country remains stable at about 1.5, normally comprising the originator firm itself and/or the companies which have obtained a licence to produce and sell the INN concerned.[4]

One thing which is clear from the table is that the LoE leads to a considerable increase in the number of companies selling products incorporating the INN concerned. On average, after one year following the LoE, about four to five generic companies appear to be present in the market. Within three years following the LoE the ratio of generic companies to originators is about 6 to 1.

As with the share of INNs that face generic entry following LoE, the number of generic firms entering also increases as a function of the value of the market as measured by the sales of the INN in question. This is borne out by table 4.8. There is also quite some variation when it comes to the number of companies active per INN across the various countries. This is visible in table 4.9.

In the pharmaceutical markets in Germany, the Netherlands, Portugal, Spain, the UK, France and Italy a high number of generic producers are present in the market. The

[4] A small proportion of 'other' companies can also be observed prior to LoE. These may relate to INNs for which the company status had not been fully established or recorded in the IMS data set, but also to possible 'early' entries by generic firms, i.e. entries before the date of LoE.

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TABLE 4.7: Number of companies active per INN

	6 months before LoE	6 months after LoE	1 year after LoE	2 years after LoE
Originators	1.63	1.62	1.64	1.58
Generics		3.85	5.13	6.44
Total	1.63	5.47	6.77	8.02

INNs weighted by value 6 months before LoE,

TABLE 4.8: Average number of originators and generics per INN two years after LoE, by size class

Size class	1	2	3	4	5
Originators	1.2	1.2	1.1	0.9	1.0
Generics	1.5	1.7	2.6	3.9	5.1
Total	2.7	2.9	3.7	4.8	6.1

INNs weighted by value 6 months before LoE,

generic segment of the pharmaceuticals market in these countries appears therefore rather fragmented.

The above findings are also borne out by the regression analysis presented in the next section. Among other things, the value of the market per capita at the point of LoE and the size of the country's population are important drivers of the number of generic entrants, holding other factors constant.

Another interesting aspect is the number of formulations which generic companies enter with when they enter. Generic companies generally appear to enter with about 2 to 2.5 products (formulations) per INN (EU average). This is smaller than the number of products with which originator companies are typically active (about 3.5 to 4).[5] There may be two main explanations for this. First, if and when a generic company enters a certain INN, it makes sense to focus on the commercially most attractive formulations, and to leave aside formulations that sell less (e.g. niche products). Second, typically, while the INN loses exclusivity insofar as the first formulation loses exclusivity, there are still other formulations that remain exclusive and that only the originator firm or its licensees can sell.

[5] In the calculation of this number, each single formulation (for instance, a tablet of a certain strength) is counted as one, regardless of whether or not it is sold under more than one brand name.

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TABLE 4.9: Average number of originators and generics two years after, by country

	Originators	Generics	Total
Austria	1.3	3.7	45.0
Belgium	1.2	3.0	4.2
Czech Rep.	1.7	2.5	4.2
Germany	1.7	10.9	12.6
Denmark	1.2	3.7	4.9
Spain	2.1	5.6	7.7
Finland	1.3	2.8	4.1
France	1.3	5.6	6.9
Greece	1.3	3.4	4.7
Hungary	1.4	1.0	2.4
Ireland	1.0	4.3	5.3
Italy	2.2	8.2	10.4
Luxembourg	1.1	1.5	2.6
Netherlands	1.1	10.2	11.3
Portugal	1.5	6.0	7.5
Sweden	1.1	3.8	4.9
United Kingdom	1.4	7.3	8.7

INNs weighted by value 6 months before LoE,

4.3 Analysis of the occurrence of entry and the number of entrants

The econometric analysis presented in this section attempts to identify the main determinants of the pattern of generic entry observed in the data on the basis of a set of characteristics of the INN and the regulatory environment in the different countries.

The set of characteristics and potential determinants considered is presented in table 6.3, table 6.4 and table 6.5 in the annex in chapter 6. Table 6.3 sets out the list of INN characteristics used in the regression analysis. Table 6.4 sets out the list of characteristics of the regulatory environment. Table 6.5 contains other control variables used in the analysis.

The two models presented in this section analyse how this set of characteristics may affect (a) the probability of observing the entry of a generic in the market and (b) the scope of generic entry in terms of total number of generic producers entering the market. These two aspects are clearly related to each other, but nevertheless provide a different perspective on the issue of generic entry. For instance, a specific kind of price regulation in a country may make entry attractive for early generic entrants, at the disadvantage of later entrants, thereby reducing the number of entrants observed. Another example

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might be the case in which generic entry takes place under the control of the originator producer (e.g. via a distribution, license or settlement agreement). This constitutes a positive realization of generic entry, but may negatively impact upon the number of additional entrants.

For the purpose of the analysis the two dependent variables of interest, realisation of entry and number of entrants, have been recorded one year and two years after LoE. The relevant samples have been adjusted accordingly to those INNs with LoE before 2007 and before 2006, respectively. Estimation of the model for the number of entrants is also carried out with a longer term perspective using the number of entrants recorded at the end of our observation period (December 2007), taking into account the variability in the time period during which each INN is observed since the moment of LoE (the exposure time).

In order to test for the different determinants that facilitate or reduce generic entry, the entry decision by generic producers is modelled in the period around LoE, when the possibility of generic entry appears. For this purpose, a number of explanatory variables have been included as measured at the moment of expiry. For the variables available on a monthly basis, such as total revenue generated by the INN or price, the value six months before patent expiry has been used. For those variables for which information on an annual basis is collected, such as the regulation in place in the different countries, the characteristics in the year of LoE have been used.

4.3.1 Methodologic framework

We estimate a binary outcome model to analyse the determinants of the occurrence of generic entry after LoE. Binary models take into account the discreteness of the dependent variable (in our case, entry vs. no entry). Under certain distributional assumptions, this allows us to evaluate the conditional effect of each of a set of covariates or regressors (the potential determinants) on the probability of observing entry of a generic company. The most commonly used models assume either the logistic distribution or the standard normal. The first case corresponds to the logit model, the latter to the probit model. Although we estimate a probit model, both models usually lead to very similar results.

Formally, let π denote the probability of observing entry of a generic company and x the vector of regressors to be tested on their impact on this probability. The model estimates the conditional probability as

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$$\pi = Prob[y_i = 1|x_i] = F(x_i' * \beta) \tag{4.1}$$

where β is the vector of model coefficients and F is the cumulative distribution function of the logistic distribution in the logit model or of the normal distribution in the probit model.

The second model presented is a count data model of the number of generic entrants observed one and two years after LoE.[6] The Poisson distribution is the most commonly used distributional form for the count data model. In the Poisson distribution, the probability mass function of y_i, the number of generic entrants observed, conditional on x_i, the regressors, is given by $\pi = Prob[y_i = y|x_i] = [\frac{exp(-\lambda_i)\lambda_i y}{y!}]$ where $\lambda_i = exp(x_i'\beta)$. This distribution has the burdensome implication that the mean and variance of the distribution have to coincide; this property is known as equidispersion. In the present case the data do not fulfil this requirement, i.e. the sample variance of the number of generic entrants after 1-2 years is higher than its mean. In these cases the negative binomial is preferred, since it allows more flexibility in the distribution of the dependent variable.[7] The model is therefore estimated by maximum likelihood assuming a negative binomial distribution of the dependent variable and computing the marginal effect of each of the determinants on the dependent variable.

In binary models, as well as in count data models, the magnitude of the coefficients is not interpretable straightforward. The results can however be recalculated to make them interpretable also in terms of magnitude, to provide a measure of the marginal effect of each of the covariates on the outcome. The marginal effect of the change in one regressor on the probability of observing a positive outcome in the dependent variable can be obtained by differentiating the cumulative distribution function with respect to the regressor of interest: $\frac{\delta\pi}{\delta x_{ij}} = F'(x_i'\beta)?j$, where $F'(z) = \frac{\delta F(z)}{\delta z}$. The marginal effect of each of the regressors changes with the point at which this effect is measured, i.e. the value of the other regressors present in the specification.[8] The most common way is to compute the marginal effect at the sample average, which has been done in the present case.[9]

[6] One could also consider, as an intermediate solution between the two models presented, the estimation of an ordered probit model. Such a model, using a setting which is an extension of the probit model, would estimate the impact of the regressors on the entry of each additional generic producer with respect to the situation in which entry is not observed. For completeness, this model was also tested. The results are fully consistent with those presented for the count data model.

[7] For a comprehensive discussion of the different properties of these models, see Verbeek [7]

[8] See Cameron and Trivedi [2]

[9] Coefficients in the count data have not been transformed into marginal effects. In the case of a count data model, as for any model with exponential conditional mean, the coefficients would have to be converted by taking the exponential of the coefficient, in order to give a measure of the marginal effect of each of the regressors. The measure obtained in this way is called the incidence rate ratio. This modification however has not been applied and only the sign of the coefficients have been interpreted.

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To obtain robust estimates, different sets of variables have been tested as potential explanatory factors. Many of them, even if potentially interesting from an economic perspective, were dropped since they were available only for a sub-sample of INN/ countries.[10] To provide the more general results possible with respect to the molecules included in the E75 list for which statistics were provided, the choice was made to only include regressors which did not cause any further restriction in the sample.

The data set used includes the small number of INN/countries for which entry of the first generic appeared to take place before the date of LoE. For consistency, the analysis was replicated on a restricted sample excluding these problematic early entries. The results for these estimates are presented for each specification and are consistent with the ones based on the full data set.

To control for the heterogeneity of INNs and countries in the sample, heteroskedasticity robust standard errors were used in all the specifications. The constant was also always included (but not reported in the tables).

4.3.2 Regression results

Table 4.10 reports the main results for the regressions for the probability of observing entry one year and two years after LoE.[11]. In the regressions presented, attention was restricted to a subset of variables which fulfilled the statistical requirements for simultaneous inclusion in the regressions (i.e. the variables were not highly collinear).

Most standard controls (table 6.3) seem to be statistically significant and robust across specifications. The value sales of the original drug prior to LoE, included in per capita terms, seem to be a clear driver of generic entry. At the same time, also the geographical size of the market, taken into account by the population of the country, seems to attract entry of generic producers.

On average, INNs for which a high number of different formulations are present tend to attract entry more than others. The negative coefficient for the price prior to LoE, having controlled for the revenue generated by the product prior to LoE, may suggest that generic companies tend to enter in those medicines that are less innovative or sophisticated to produce, to the extent that price reflects development and production costs.

[10]The variables referring to the ATC4 category of each INN were available only for certain countries. The same applies to the variable promotional expenditure.

[11]Results are robust to the exclusion of early entries, as shown by the results in table 4.13

TABLE 4.10: Probit estimation of ocurrence of entry

	First entry within 1 year from LoE	First entry within 2 years from LoE
Price caps	-0.14***	-0.07
	(0.04)	(0.05)
Compulsory substitution	0.11*	0.13**
	(0.06)	(0.06)
Physicians incentives	0.07	0.09
	(0.05)	(0.06)
Frequent adjustment	0.05	0.03
	(0.05)	(0.05)
Differential copayment	-0.02	-0.01
	(0.07)	(0.07)
Lowest price policy	-0.06	0.01
	(0.05)	(0.05)
Log of pre-expiry value	0.11***	0.11***
	(0.02)	(0.02)
Log of population	0.05**	0.05**
	(0.02)	(0.02)
Log of pre-expiry price	-0.07***	-0.07***
	(0.02)	(0.02)
Pre-expiry formulations	0.03**	0.02
	(0.01)	(0.01)
Biosimilar	0.11***	0.22***
	(0.04)	(0.04)
Other ATC4	0.05	0.04
	(0.06)	(0.06)
Countries expired	0.02**	0.01
	(0.01)	(0.01)
Controlled entry	0.41***	0.35***
	(0.12)	(0.12)
Expiry year	0.05***	0.06***
	(0.01)	(0.02)
Pseudo-R^2	0.224	0.242
Sample Size	765	675

Robust standard errors in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively; constant included.

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TABLE 4.11: Count data estimation of number of generic entrants

	1 year after LoE	2 years after LoE	Long run
Price caps	-0.56***	-0.37***	-0.28***
	(0.13)	(0.12)	(0.09)
Compulsory substitution	0.44**	0.51***	0.45***
	(0.17)	(0.16)	(0.12)
Physicians incentives	0.45***	0.23	0.17
	(0.15)	(0.15)	(0.11)
Frequent adjustment	-0.12	-0.11	-0.18
	(0.14)	(0.13)	(0.11)
Differential copayment	0.03	0.05	0.2
	(0.20)	(0.19)	(0.16)
Lowest price policy	0.11	-0.02	-0.04
	(0.14)	(0.13)	(0.10)
Log of pre-expiry value	0.42***	0.41***	0.36***
	(0.06)	(0.05)	(0.04)
Log of population	0.33***	0.36***	0.37***
	(0.06)	(0.05)	(0.04)
Log of pre-expiry price	-0.27***	-0.23***	-0.18***
	(0.05)	(0.05)	(0.04)
Pre-expiry formulations	0.08***	0.08***	0.06***
	(0.03)	(0.03)	(0.02)
Biosimilar	0.21*	0.28**	0.56***
	(0.12)	(0.11)	(0.09)
Other ATC4	0.27	0.21	0.00
	(0.17)	(0.15)	(0.11)
Countries expired	0.01	0.02	-0.02
	(0.02)	(0.02)	(0.02)
Controlled entry	1.17***	1.20**	0.63*
	(0.44)	(0.50)	(0.33)
Expiry year	0.14***	0.16***	0.12**
	(0.04)	(0.04)	(0.03)
AIC	2445.71	2558.20	3194.80
BIC	2524.59	2634.95	3271.79
Sample Size	765	675	675

Robust standard errors in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively; constant included.

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The results also show an improvement over time in terms of generic entry to markets, both in the short term and in the longer term perspective. The probability of observing the first generic entry within the first year increases on average by 5% each year.[12]

For what concerns the regulatory variables (table 6.4) the full set of variables was tested.

Policies involving compulsory substitution of generic products by pharmacists seem to positively affect the probability of entry. The coefficient found is positive and statistically significant in all the specifications.[13]

The presence of price caps appears to negatively affect the probability of entry, at least in the short run. The other regulatory variables included do not seem to show coefficients that are statistically significant in a stable manner.

The regressions include a number of additional control variables (table 6.5). The first is a control variable for the presence of a generic entry controlled by the originator company. The variable takes the value one for the case in which an entry took place either as the result of a distribution agreement between originator and generic producer, or in the context of a settlement. The coefficient is positive and statistically significant.[14] In cases in which a controlled entry was recorded, the probability of observing generic entry increases significantly.

When deciding whether or not to enter a specific market, a generic producer may take into consideration the fact that the product in question has lost exclusivity also in other countries. In that case, entering in several countries might lead to economies of scale and enhance the attractiveness of entry in one particular country. This aspect has been taken into account with a variable that reports the number of other countries where the

[12] This figure should be interpreted with care since the relevant time window for the first generic entry (i.e. one year) overlaps to a large extent with the average time to entry calculated at a head count. Therefore a very small downward change over time in the values situated in the proximity of the central point (here one year) may have an important impact on the presented probability. The possible presence of multicollinearity between the expiry year and pre-expiry value was checked (so as to see whether INNs expiring later in the period also tend to have higher sales values and therefore attract more entry), but the correlation coefficient is lower than 0.2.

[13] A slightly modified version of this specification was also tested, including of the interaction between the presence of compulsory substitution and of incentives to physicians to substitute generics. When these two policies take place at the same time, i.e. both physicians and doctors are encouraged/obliged to dispense generic products, the probability of observing swift generic entry seems to further increase.

[14] In cases in which a controlled entry was recorded, the probability of observing independent generic entry would accordingly appear to increase. This finding may be partly explained by the fact that in a number of cases involving controlled entry, it was not possible to distinguish the date of first generic entry and first independent entry. As a result, the estimated coefficient may pick up some cases of controlled entry rather than independent entry. It is also important to bear in mind that the number of cases identified as controlled entry is rather low. See annex in chapter 6 for further details.

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INN has previously expired. The estimated coefficient has the expected positive sign, even though it is not always statistically significant.[15]

As explained above, INNs that belong to different ATC4 categories are present in the data set in the form of multiple observations. It might be reasonable to consider that for these INNs the decision to start selling products for one ATC4 class may be linked to the possibility of selling products based on the same INN in another class. At the same time, where the ATC4 classes are different there might be a selection by the generic company to enter the simpler and/or bigger ATC4 category. In the regressions presented, this is controlled for by the dummy variable that takes unit value when the INN belongs to more than one ATC4 category. This control variable, even if always presents a positive coefficient, is never statistically significant.[16]

Also the level of promotional effort undertaken by the originator producer before the LoE was considered. However, an endogeneity problem may occur when including this measure in the model specification. Being a potential tool for the originator company to maintain brand recognition even after LoE, promotional activity might be a response to the observed increased probability of having swift generic entry. In addition to this econometric problem, the data availability for promotional expenditure was limited to seven countries, significantly restricting the sample.

With respect to the determinants of the number of generic entrants, estimates of the count data model go in the same direction as the probit analysis. The value of the market before expiry is positively correlated with the number of entrants while again the pre-expiry price is negatively correlated with it, leading to the same interpretations. The number of formulations with which the originator drug was present in the market before expiry, seems to have a positive effect on the number of generic producers entering, although significant only at the 5% level in the probit regressions one year after LoE.

A positive and statistically significant effect of compulsory generic substitution on the number of entrants is confirmed by the statistical significance in all regressions. The negative effect of price caps, affecting the probability of entry only in the short run, seems to have a consistent and long lasting effect on the number of generic entrants.

[15] To check robustness, alternative approaches were considered. A simple alternative is the use of a dummy variable to account for the presence of at least one other country in which the INN in question lost exclusivity. Another alternative is to use the aggregate value sales of the INN in these countries before LoE. Results for these two alternatives are consistent with the one presented.

[16] Alternative specifications were also considered to check robustness. First, a specification using the number of ATC4 classes per INN was tested. Additionally, the probit specification was run with standard errors clustered at the INN/country level, to take into account the possible correlation between the choices of entering different ATC4 categories for the same INN. Finally, also a specification on the data set at country/INN level, i.e. ignoring therefore the possible ATC differentiation within INNs, was run. The results obtained with these three variations were consistent with the base line specification presented in table 4.10 and table 4.11

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The results for controlled entry are consistent with the probit model, as well as all other controls, that report the expected sign.

These results are also obtained when observing the total number of generic producers present at the end of the period of observation, presented in the last column in table 4.11. [17]

4.4 Analysis of the time to entry

The econometric analysis in this section aims at identifying the determinants of the delay of generic entry, i.e. the length of the time period between LoE and the first actual entry of a generic producer. Even if entry of generic producers eventually takes place, its delay vis-à-vis the date of LoE is potentially costly to patients. Without the delay (or with shorter delay), any potential benefits to consumers from competition between originator and generic producers would accrue earlier. For this reason, it is interesting to search for determinants of the delay.

4.4.1 Methodological framework

Time to entry (the time span between LoE and the entry of the first generic company) can be best analysed using methods to model time-to-event data. These methods have been developed to describe the time an individual spends in a state until the transition to another state and to study the relationship between the individual's characteristics and transition patterns.[18]

The time spent in the state, in our case the time between LoE and the first generic firm's entry, is called a spell. The random variable to be studied is the length of the spell. Let T be a continuous random variable representing the length of a spell, with a cumulative distribution function $F(t)$ and a density function $f(t)$. The survivor function is $S(t) = 1 - F(t)$, i.e. the probability of transition before t. The hazard rate is defined as $\theta(t) = \frac{f(t)}{S(t)}$, which is the 'instantaneous transition intensity' at moment t, provided that there was no transition until t.

The hazard rate is assumed to fulfil the proportional hazard assumption:

$$\theta(t, X_{ijt}) = \theta_0(t)e^{\beta' X_{ijt}} \tag{4.2}$$

[17] The sample has been restricted to those country/INNs for which observations are available for at least two years after LoE. Estimation takes into account the difference in time period during which each INN is observed since the moment of LoE (exposure time).

[18] See Jenkins [5] for a comprehensive exposition of survival analysis methods.

where $\theta_0(t)$ is called the baseline hazard function and depends only on the time since LoE, while vector X_{ijt} depends on other factors and can be time-dependent. The hazard rate for different molecules is therefore the baseline hazard multiplied by a factor related to the vector of the characteristics of the molecule.

The hazard rate can be specified in terms of discrete or continuous time. Entry of a generic firm can in principle take place at any point in time, so a continuous time approach seems appropriate. On the other hand, only monthly data are available and entries are grouped by month (so-called ties). When such cases are common, a discrete representation of a continuous time process would be preferable. Both approaches are used in the analysis.

4.4.2 Implementation

A panel dataset was used for this purpose. One observation in the data set is related to a molecule in an ATC4 category, in a country, in a month. Molecules from 17 countries were analysed and the time period covered is from January 2000 to December 2007.[19] For each molecule per country, the first observation comes from one month before LoE and the last observation is either in the month with the first generic firm entry or in December 2007 which is the last month in the data set. The dataset corresponds to right truncated spell data with varying censoring point. It means that for each country-INN-ATC4, at the end of a spell, we observe if entry of a generic firm did or did not take place and the length of the spell is different for different country-INN-ATC4 combinations.

The dependent variable d_{ijt} is a dummy variable which is equal to one if there was first generic firm entry for molecule i in country j in month t since LoE and zero otherwise. For different specifications of the hazard rate, different link functions are used.

As in the previous section, covariates from table 6.3, table 6.4 and table 6.5 are used: a set of regulatory variables, a set of INN characteristics and a country-specific variable population. In addition, to capture the time trend, bi-annual dummies were created (2000 - 2001 is the benchmark and therefore omitted) to indicate in which year the INN lost patent or data exclusivity. Discrete specifications include also the baseline hazard covariates.

The hazard proportionality assumption is checked by including into the regressions all variables interacted with functions of time since LoE. If such interacted variables are not statistically significant, this indicates that their hazard is not likely to be time-dependent.

[19] The number of molecules differs depending on the treatment of negative delays (see above). When an INN with a negative delay is included, it is assumed that a generic firm entry took place immediately after LoE.

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This is done in a Cox regression with Breslow method for ties. Time functions considered are linear, quadratic and logarithmic functions of the number of months since LoE. The only variable that appears not to satisfy the hazard proportionality assumption is the dichotomous characteristic identifying biologic INN. For this reason, it was not used in the hazard models.

For several specifications the shape of the baseline hazard function needs to be selected. In continuous-time specifications, the Weibull function is used because it is flexible and can have an increasing, decreasing, as well as constant shape. In discrete-time specifications, the quadratic function is used (selection based on descriptive statistics. In addition, specifications with non-parametric baseline hazard (Cox) are considered.

To account for unobserved heterogeneity of INNs (so-called frailty), an INN-country-specific random intercept is included. Most of the regressions make distributional assumptions about the random effect (normal or inverse normal), but non-parametric frailty coming from a discrete distribution with up to two mass points is also considered.

Specifically, the following five specifications are analysed:

- Cox semi-parametric hazard model:

  The hazard rate in this model is specified as

$$\theta(t, char_{ijt}, reg_{ijt}, pop_{ijt}|v_{ij}) = \theta_0(t)e^{(\beta_1 char_{ijt}+\beta_2 reg_{ijt}+\beta_3 pop_{ijt})} \tag{4.3}$$

  The baseline hazard function $\theta_0(t)$ remains unspecified and the partial likelihood estimation method is used. Time is assumed to be continuous. Ties are treated as if generated by discrete time. Variable *char* is the vector of INN characteristics, *reg* is the vector of regulatory variables and *pop* is the country's population.

- Weibull model:

  The hazard rate in this model is specified as

$$\theta(t, char_{ijt}, reg_{ijt}, pop_{ijt}) = \alpha t^{\alpha-1} e^{(\beta_1 char_{ijt}+\beta_2 reg_{ijt}+\beta_3 pop_{ijt})} \tag{4.4}$$

  The baseline hazard has a shape of the Weibull function: $\theta_0(t) = \alpha t^{\alpha-1}$ where $\alpha > 1$. The shape parameter α is estimated together with coefficients of regressors. When α is greater than 1, the hazard is increasing. When α is lower than 1, the hazard is decreasing. Finally, when α equals 1, the hazard is constant. Time is assumed to be continuous.

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- Weibull model with frailty (INN-country-specific random effects):

  The hazard rate in this model is specified as

$$\theta(t, char_{ijt}, reg_{ijt}, pop_{ijt}|v_{ij}) = v_{ij}\alpha t^{\alpha-1} e^{(\beta_1 char_{ijt} + \beta_2 reg_{ijt} + \beta_3 pop_{ijt})} \tag{4.5}$$

  where v_{ij} is a random variable distributed independently of t, X, Y and Z and has an inverse normal distribution.

- Discrete-time specification for an underlying continuous-time process (cloglog) with parametric frailty:

  The hazard rate in this model is specified as

$$\begin{aligned} &\theta(n, char_{ijt}, reg_{ijt}, pop_{ijt}|v_{ij}) \\ &= (1 - e^{-exp(\alpha_1 n^2 + \alpha_2 n + \beta_1 char_{ijt} + \beta_2 reg_{ijt} + \beta_3 pop_{ijt} + u_{ij})}) \end{aligned} \tag{4.6}$$

  where n is the month, $u_{ij} = ln(v_{ij})$ is a random variable with the standard normal distribution and $\alpha_1 n^2 + \alpha_2 n$ is the baseline hazard function.

- Discrete-time specification for an underlying continuous-time process (cloglog) with non-parametric frailty from a discrete distribution with the support of two mass points:

  The hazard rate in this model is specified as

$$\begin{aligned} &\theta(n, char_{ijt}, reg_{ijt}, pop_{ijt}|\mu_r) \\ &= (1 - e^{-exp(\alpha_1 n^2 + \alpha_2 n + \beta_1 char_{ijt} + \beta_2 reg_{ijt} + \beta_3 pop_{ijt} + \mu_r)}) \end{aligned} \tag{4.7}$$

For all specifications except Cox, maximum likelihood estimation is used to take care of censoring. Each observation in the data set contributes to the likelihood of the information it carries: whether there was entry in period t or whether in period t the INN was still the realm of the originator company.

4.4.3 Non-parametrical estimates of time to entry

First, the Kaplan-Meier estimator of the survivor function and the Nelson-Aalen estimator of the cumulative hazard are plotted. These two estimators do not use any parametric assumptions. Intuitively, the estimate of the survival at time t is the product

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of 'survival rates' in each point in time until t, i.e. the product of the proportions of INNs which did not face the first generic entry at this time in the total number of INNs that before time t still had no generic competitors. Similarly, the cumulated hazard estimate is the sum of 'exit ratios' for each month until t. Both are presented in figure 4.1.

The estimated survivor function has a large drop of about 19% in the first month after LoE, which means that about 19% of INN-countrypairs experienced a generic firm entry right after LoE. Note that the full data set includes molecules with negative delays which for the purpose of this estimation are converted to zero delays.

The first few months after LoE, the survival probability is dropping at a decreasing pace. Later in time, the changes in the survivor function are smaller and relatively constant, resulting in the close-to-linear shape of the survival function.

The above observations are mirrored in the shape of the estimated cumulated hazard function. It starts at the level over 19%. Then it grows at a decreasing and then relatively constant pace.

The estimates suggest that the hazard rate of the first entry of a generic firm is decreasing, first at a diminishing rate and then at a relatively constant rate.

The non-parametric estimates were also calculated for the time elapsing between the first and the second entry of a generic competitor. These are presented in figure 4.2. The survival function is convex and the cumulated hazard concave, indicating that the second generic firm entry (relative to the first entry) seems to take place more quickly than the first generic firm entry (relative to LoE). Already after three months, about 50% of INN- country pairs which have experienced the first generic firm entry face the entry of the second generic firm. Only about 10% of INN-country pairs which have experienced the first generic firm entry never note entry of the second generic firm.

4.4.4 Regression results

The results for the full data set are presented in tables 4.12 and 4.13. Reported coefficients for dummy variables can be interpreted as a percentage change in the hazard rate due to a change in the covariate, holding everything else constant.

4.4.4.1 Control Variables

In all specifications, the entry of originator-controlled generics is statistically significant and greater than one. This implies that, holding everything else constant, INNs

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FIGURE 4.1: First generic entry after LoE: Kaplan-Meier estimator of the survivor function and Nelson-Aalen estimator of the cumulative hazard for all INN-country pairs analysed

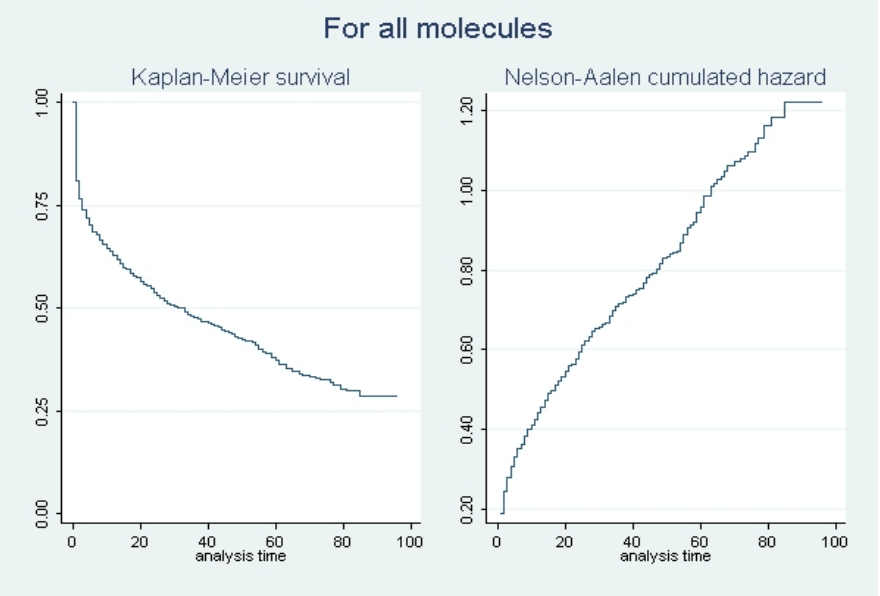

FIGURE 4.2: Second generic entry after LoE: Kaplan-Meier estimator of the survivor function and Nelson-Aalen estimator of the cumulative hazard for all INN-country pairs analysed

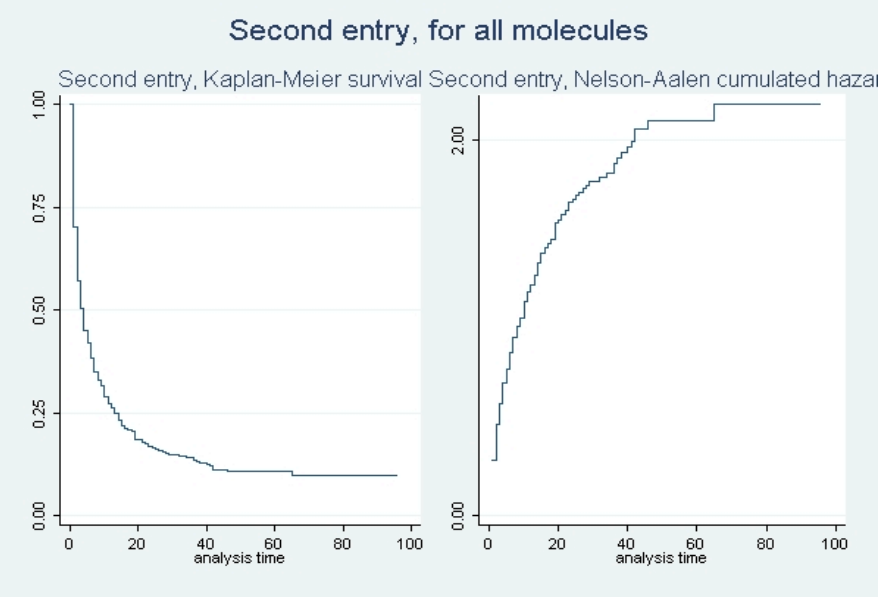

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TABLE 4.12: Estimation of time to entry

	Cox	Weibull	Weibull with inverse normal frailty
Price caps	0.752***	0.737***	0.576***
	(0.007)	(0.002)	(0.001)
Compulsory substitution	1.614***	1.603***	1.946***
	(0.001)	(0.001)	(0.002)
Physicians incentives	1.233	1.213	1.448*
	(0.104)	(0.110)	(0.050)
Frequent adjustment	1.103	1.106	1.158
	(0.367)	(0.315)	(0.368)
Differential copayment	0.766*	0.757**	0.722
	(0.064)	(0.040)	(0.128)
Lowest price policy	0.940	0.950	0.939
	(0.608)	(0.652)	(0.725)
Log of pre-expiry value	1.494***	1.488***	1.788***
	(0.000)	(0.000)	(0.000)
Population	1.000**	1.000**	1.000***
	(0.012)	(0.011)	(0.004)
Pre-expiry price	0.977***	0.975***	0.967***
	(0.000)	(0.000)	(0.000)
Pre-expiry formulations	1.035*	1.031*	1.057**
	(0.065)	(0.065)	(0.042)
Other ATC4	1.213	1.231*	1.279
	(0.138)	(0.089)	(0.204)
Countries expired	1.123	1.133	1.236
	(0.258)	(0.194)	(0.171)
Controlled entry	2.261***	1.854***	3.270***
	(0.000)	(0.002)	(0.000)
Expiry 02/03	1.668***	1.603***	1.988***
	(0.000)	(0.000)	(0.001)
Expiry 04/05	2.108***	1.983***	2.678***
	(0.000)	(0.000)	(0.000)
Expiry 06/07	2.363***	2.548***	3.596***
	(0.000)	(0.000)	(0.000)
Frailty θ=0 test, p value			0.000
Weibull parameter p		0.711	1.104
Sample Size	22326	22326	22326

p values in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively.

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TABLE 4.13: Estimation of time to entry (continuation)

	Discrete with normal frailty	Discrete with non-parametric frailty
Price caps	0.619***	0.604***
	(0.000)	(0.000)
Compulsory substitution	1.568***	1.600***
	(0.005)	(0.003)
Physicians incentives	1.450***	1.507***
	(0.010)	(0.003)
Frequent adjustment	1.055	1.131
	(0.657)	(0.304)
Differential copayment	0.951	0.894
	(0.767)	(0.498)
Lowest price policy	0.894	0.913
	(0.405)	(0.481)
Log of pre-expiry value	1.567***	1.555***
	(0.000)	(0.000)
Log of population	1.299***	1.153***
	(0.000)	(0.002)
Pre-expiry price	0.974***	0.973***
	(0.000)	(0.000)
Pre-expiry formulations	1.033	1.030
	(0.111)	(0.147)
Other ATC4	1.228	1.221
	(0.159)	(0.173)
Countries expired	1.192	1.178
	(0.132)	(0.155)
Controlled entry	2.278***	2.814***
	(0.001)	(0.000)
Expiry 02/03	1.844***	1.681***
	(0.000)	(0.001)
Expiry 04/05	2.252***	2.188***
	(0.000)	(0.000)
Expiry 06/07	2.541***	2.374***
	(0.000)	(0.000)
Survival time	0.949***	0.944***
	(0.000)	(0.000)
Survival time squared	1.001***	1.001***
	(0.000)	(0.000)
Frailty θ=0 test, p value	0.000	
Sample Size	23196	23196

p values in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively.

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with entry controlled by originator companies face significantly earlier first entry (though not necessarily independent generic entry) than other INNs. This result is not surprising since the data counts the controlled entry as the first generic firm entry. However, this result is not robust to the treatment of negative delays (see tables in section 4.6).

The variable indicating the pre-expiry number of formulations has coefficients greater than one and statistically significant in four specifications. This implies that the larger the number of formulations, the faster first generic entry tends to be.

The coefficients of the pre-expiry market value per capita are greater than one and statistically significant, implying that the larger the value of the INN/ATC4/country market, the faster first entry of a generic competitor.

The coefficients of the pre-expiry price are slightly smaller than one and always statistically significant. Therefore, it appears that faster first generic firm entry can be associated with less expensive products.

The population helps to capture the effect of the size of the market. The estimated coefficients are always statistically significant, but equal or slightly larger than one.

Two dummies are included to capture the links between the same INN across countries and different ATC4 classes within one country. The coefficient of the variable indicating the number of countries were the INN had previously already expired is always greater than one and significant in one specification. The coefficient characterising INNs that belong to more than one ATC4 category also comes out greater than one and statistically significant in the second specification, suggesting that when an INN is present in several ATC4 classes, first generic entry may be faster than otherwise.

4.4.4.2 Regulatory Variables

In all specifications the coefficient for compulsory substitution is greater than one and statistically significant. This implies that the hazard of the first generic entry for molecules in countries with compulsory generic substitution policy is higher than the hazard for molecules in countries without this policy. Therefore compulsory generic substitution policy appears to be correlated with faster generic entry. Figure 4.3 shows the predicted survivor and cumulated hazard functions estimated by the Cox regression from the first column of table 4.12.

The estimated coefficient for the dichotomous variable indicating whether physicians are encouraged to prescribe generically is always larger than one and statistically significant in more general specifications with frailty. This suggests that, holding everything else

FIGURE 4.3: Survivor and cumulated hazard functions estimated by the Cox regression, by compulsory substitution

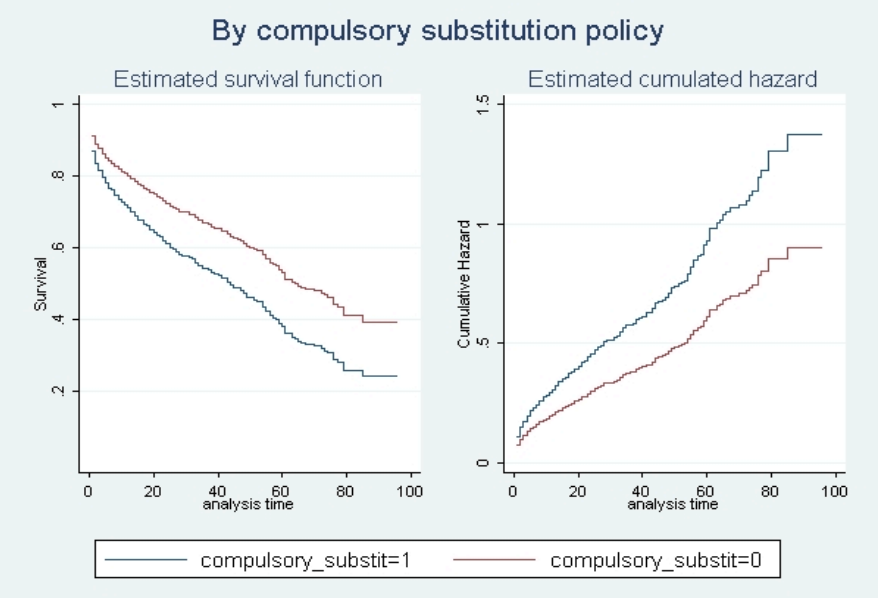
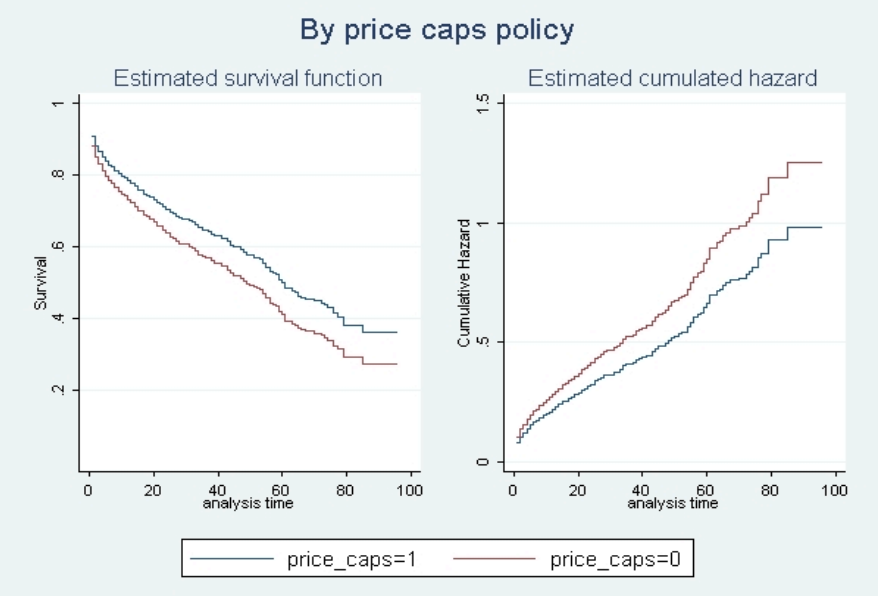


FIGURE 4.4: Survivor and cumulated hazard functions estimated by the Cox regression, by free price policy



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constant, the INNs in countries where this policy is used have a higher hazard rate of the first generic company entering than other countries.

Frequent price adjustments show in all specifications a coefficient greater than one but not statistically significant. Differential copayments show coefficient always lower than one but statistically significant only in non-frailty regressions. Statistical significance also disappears in the robustness checks (see section 4.6). Therefore, the data do not appear to identify an effect of this variable. The existence of policies obliging pharmacists to dispense the generic with the lowest price leads in all specifications statistically insignificant coefficients. The data do not appear to identify an effect of this variable.

The presence of price caps has a significant effect on time to entry, with a coefficient lower than one, meaning that the hazard of first generic firm's entry for molecules in countries with price caps is lower than the hazard for molecules in countries without price caps. It would appear therefore that a policy of mandatory discounts or price caps for generic firms is correlated with slower generic entry (see also figure 4.4 for illustration). This effect is however not very strong in that it disappears in the robustness checks.

4.4.4.3 Time Trend

Bi-annual dummy variables are statistically significant and greater than one. Furthermore, when comparing their magnitude one can observe that the magnitude is the largest for the years 2006-2007 and it gets lower the earlier LoE took place. That suggests that, holding everything else constant, the hazard rate of the first generic firm entry is larger, the later in the time period under analysis LoE occurs. (See figure 4.5 for an illustration)

4.4.4.4 Baseline Hazard

The baseline hazard function shows the shape of the hazard rate of the first generic entry over time which is shared by all INN-countrypairs. When not including frailty, this function is decreasing over time at a decreasing rate (the estimated Weibull parameter is lower than one), just as the descriptive Kaplan-Meier and Nelson-Aalen estimators suggested. When frailty is included, the hazard is almost constant over time (the estimated Weibull parameter almost equal to one). This suggests that frailty takes away the effect of very early first entries from the baseline hazard shared by all INNs.

Figure 4.6 presents the baseline cumulative hazard and the baseline survivor functions for an INN with the mean log of market value before LoE (-5.04) estimated in the Cox

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regression reported in the first column of table 4.11. Both functions have a close-to-linear shape.

4.4.5 Robustness

Tables 4.12 and 4.13 allow for several robustness checks of the results. The results of continuous- and discrete-time models are to a large extent consistent. In models with frailty, incentives to physicians to prescribe generically become statistically significant. To the contrary, differential copayments for originator and generic lose significance when frailty is included. Overall, the results are almost the same for all three frailty distributions.

Further robustness checks were done to test if the results are sensitive to the treatment of negative delays. The regressions were repeated on the data set with all negative delays dropped and on the dataset with only substantial negative delays dropped. Substantial negative delays were defined as delays exceeding 3 months. Control variables are introduced to flag INN-countrypairs with large and small negative delays. Tables 4.16, 4.17 and 4.18 present the results. Cox and cloglog with non-parametric frailty models did not converge.

The coefficient of the variable for compulsory substitution remains highly significant and greater than one in all specifications. The coefficient of the variable indicating that physicians are encouraged to prescribe generically come out greater than one and statistically significant in all specifications. The coefficients for the variables indicating the existence of differential copayments and price caps remain lower than one but never statistically significant.

4.5 Conclusions

Patterns of generic entry differ significantly across European countries and types of drugs. In this chapter we have identified some factors that explain this heterogeneity. Larger pre-expiry revenue attracts generic entry in terms of likelihood of entry, speed of entry and long-run number of entrants. Different regulation of pharmaceutical markets in Europe also have an impact on the occurrence and speed of generic entry. We have shown that price-cap policies tend to discourage and delay generic entry. Incentives to physicians to prescribe generically and policies encouraging substitution at pharmacy tend to make generic in a given market more attractive, thus leading to a higher probability of generic entry and to shorter delays wherever entry takes place.

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FIGURE 4.5: Survivor and cumulated hazard functions estimated by the Cox regression, by bi-annual dummies

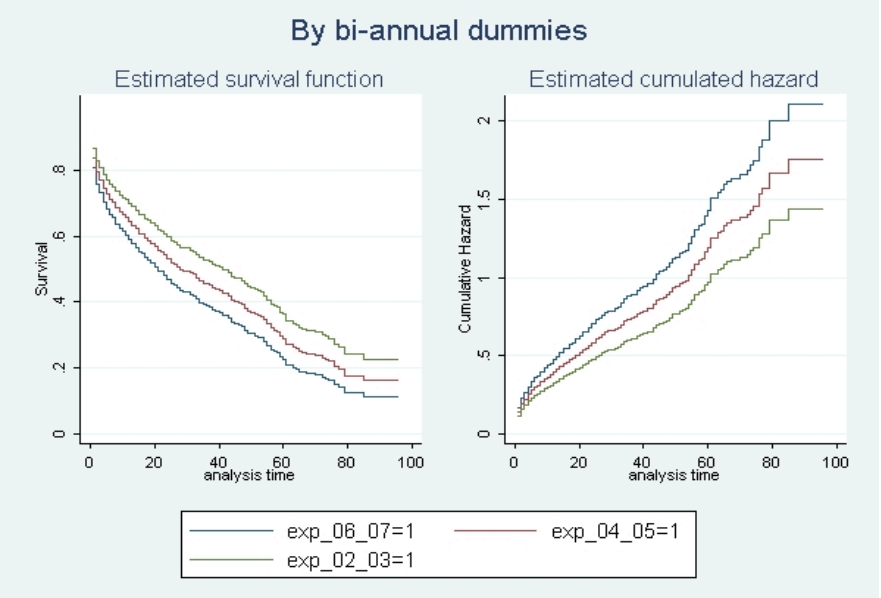
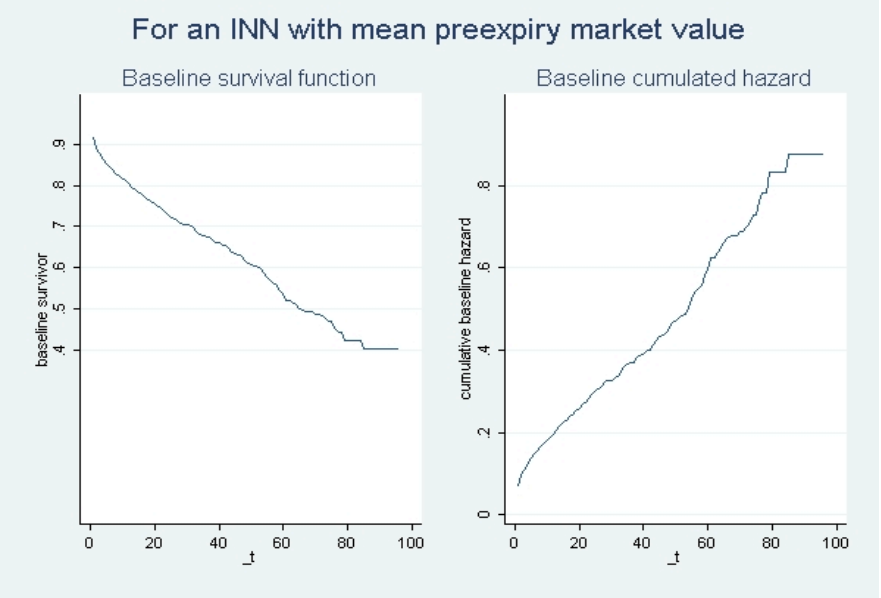


FIGURE 4.6: Baseline survivor and cumulated hazard functions estimated by the Cox regression



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4.6 Appendix

TABLE 4.14: Probit estimation of occurrence of entry

	First entry within 1 year from LoE	First entry within 2 years from LoE
Price caps	-0.10**	-0.04
	(0.04)	(0.05)
Compulsory substitution	0.14**	0.16***
	(0.06)	(0.06)
Physicians incentives	0.11**	0.13**
	(0.05)	(0.06)
Frequent adjustment	0.07	0.05
	(0.05)	(0.05)
Differential copayment	-0.02	-0.02
	(0.07)	(0.07)
Lowest price policy	-0.07	-0.01
	(0.05)	(0.06)
Log of pre-expiry value	0.10***	0.11***
	(0.02)	(0.02)
Log of population	0.04*	0.04*
	(0.02)	(0.02)
Log of pre-expiry price	-0.07***	-0.07***
	(0.01)	(0.02)
Pre-expiry formulations	0.03**	0.02
	(0.01)	(0.01)
Biosimilar	0.12***	0.24***
	(0.04)	(0.04)
Other ATC4	0.05	0.04
	(0.06)	(0.06)
Countries expired	0.01*	0.01
	(0.01)	(0.01)
Controlled entry	0.42***	0.37***
	(0.13)	(0.13)
Expiry year	0.05***	0.06***
	(0.01)	(0.02)
Pseudo-R^2	0.227	0.248
Sample Size	735	649

Robust standard errors in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively; constant included.

TABLE 4.15: Count data estimation of number of generic entrants

	1 year after LoE	2 years after LoE	Long run
Price caps	-0.43***	-0.25**	-0.23**
	(0.14)	(0.13)	(0.10)
Compulsory substitution	0.57**	0.59***	0.47***
	(0.18)	(0.17)	(0.13)
Physicians incentives	0.61***	0.34**	0.22*
	(0.16)	(0.16)	(0.12)
Frequent adjustment	-0.05	-0.06	-0.16
	(0.16)	(0.15)	(0.12)
Differential copayment	0.05	0.08	0.20
	(0.20)	(0.20)	(0.17)
Lowest price policy	0.01	-0.11	-0.07
	(0.15)	(0.14)	(0.10)
Log of pre-expiry value	0.42***	0.41***	0.35***
	(0.06)	(0.05)	(0.04)
Log of population	0.32***	0.36***	0.38***
	(0.06)	(0.06)	(0.04)
Log of pre-expiry price	-0.29***	-0.25***	-0.18***
	(0.06)	(0.05)	(0.04)
Pre-expiry formulations	0.09***	0.09***	0.06***
	(0.03)	(0.03)	(0.02)
Biosimilar	0.29**	0.36***	0.62***
	(0.12)	(0.12)	(0.09)
Other ATC4	0.29	0.22	-0.03
	(0.19)	(0.17)	(0.12)
Countries expired	0.00	0.01	-0.02
	(0.02)	(0.02)	(0.02)
Controlled entry	1.40***	1.44**	0.76**
	(0.51)	(0.57)	(0.38)
Expiry year	0.13***	0.15***	0.11***
	(0.04)	(0.04)	(0.03)
AIC	2240.00	2374.45	3017.65
BIC	2318.20	2450.53	3093.73
Sample Size	735	649	649

Robust standard errors in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively; constant included.

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TABLE 4.16: Estimation of time to entry: full dataset

	Weibull	Weibull with inverse normal frailty	Discrete with normal frailty
Price caps	0.898	0.796	0.867
	(0.286)	(0.217)	(0.155)
Compulsory substitution	1.507***	2.063***	1.455***
	(0.003)	(0.004)	(0.006)
Physicians incentives	1.218*	1.498*	1.297*
	(0.098)	(0.060)	(0.029)
Frequent adjustment	0.998	1.014	0.976
	(0.983)	(0.939)	(0.810)
Differential copayment	0.872	0.790	0.984
	(0.310)	(0.335)	(0.912)
Lowest price policy	1.110	1.197	1.057
	(0.357)	(0.379)	(0.627)
Log of pre-expiry value	1.479***	1.966***	1.456***
	(0.000)	(0.000)	(0.000)
Population	1.000	1.000	1.102**
	(0.145)	(0.114)	(0.018)
Pre-expiry price	0.980***	0.971***	0.982***
	(0.000)	(0.000)	(0.000)
Pre-expiry formulations	1.006	1.024*	1.004
	(0.167)	(0.064)	(0.121)
Other ATC4	1.258*	1.409	1.243*
	(0.057)	(0.118)	(0.072)
Countries expired	1.070	1.159	1.079
	(0.241)	(0.187)	(0.201)
Controlled entry	0.982	1.098	1.018
	(0.929)	(0.802)	(0.930)
Expiry 02/03	1.590***	2.164***	1.614***
	(0.000)	(0.001)	(0.000)
Expiry 04/05	1.939***	2.991***	1.817***
	(0.000)	(0.000)	(0.000)
Expiry 06/07	2.771***	5.266***	2.281***
	(0.000)	(0.000)	(0.000)
Large negative	12.657***	84.026***	9.235***
	(0.000)	(0.000)	(0.000)
Small negative	12.320***	78.832***	8.830***
	(0.000)	(0.000)	(0.000)
Survival time			0.951***
			(0.000)
Survival time squared			1.001***
			(0.000)
Frailty θ=0 test, p value		0.000	0.493
Weibull parameter p	0.863	1.524	
Sample Size	22326	22326	23196

p values in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively.

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TABLE 4.17: Estimation of time to entry: no large (>3 months) negative delays

	Weibull	Weibull with inverse normal frailty	Discrete with normal frailty
Price caps	0.917	0.825	0.883
	(0.414)	(0.305)	(0.235)
Compulsory substitution	1.539***	2.100***	1.491***
	(0.002)	(0.003)	(0.004)
Physicians incentives	1.287**	1.652**	1.350**
	(0.039)	(0.018)	(0.014)
Frequent adjustment	1.0044	1.110	1.009
	(0.684)	(0.579)	(0.933)
Differential copayment	0.860	0.779	0.958
	(0.273)	(0.300)	(0.769)
Lowest price policy	1.079	1.132	1.03
	(0.514)	(0.546)	(0.784)
Log of pre-expiry value	1.497***	1.952***	1.481***
	(0.000)	(0.000)	(0.000)
Population	1.000	1.000*	1.103**
	(0.119)	(0.094)	(0.018)
Pre-expiry price	0.978***	0.967***	0.979***
	(0.000)	(0.000)	(0.000)
Pre-expiry formulations	1.010	1.034	1.008
	(0.132)	(0.145)	(0.176)
Other ATC4	1.293**	1.455*	1.283**
	(0.041)	(0.092)	(0.048)
Countries expired	1.082	1.177	1.092
	(0.122)	(0.143)	(0.135)
Controlled entry	1.045	1.260	1.091
	(0.839)	(0.557)	(0.689)
Expiry 02/03	1.551***	2.020***	1.630***
	(0.001)	(0.003)	(0.000)
Expiry 04/05	1.910***	2.763***	1.877***
	(0.000)	(0.000)	(0.000)
Expiry 06/07	2.720***	4.639***	2.382***
	(0.000)	(0.000)	(0.000)
Small negative	10.489***	49.391***	8.295***
	(0.000)	(0.000)	(0.000)
Survival time			0.951***
			(0.000)
Survival time squared			1.001***
			(0.000)
Frailty θ=0 test, p value		0.000	0.492
Weibull parameter p	0.832	1.413	
Sample Size	22292	22292	23129

p values in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively.

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TABLE 4.18: Estimation of time to entry: no negative delays

	Weibull	Weibull with inverse normal frailty	Discrete with normal frailty
Price caps	0.912	0.810	0.837
	(0.405)	(0.259)	(0.185)
Compulsory substitution	1.586***	2.238***	1.662***
	(0.003)	(0.002)	(0.005)
Physicians incentives	1.261*	1.663***	1.495**
	(0.068)	(0.016)	(0.011)
Frequent adjustment	1.120	1.224	1.118
	(0.328)	(0.301)	(0.417)
Differential copayment	0.785	0.701	0.888
	(0.101)	(0.151)	(0.521)
Lowest price policy	1.056	1.066	1.007
	(0.660)	(0.753)	(0.962)
Log of pre-expiry value	1.610***	2.094***	1.711***
	(0.000)	(0.000)	(0.000)
Population	1.000	1.000	1.126**
	(0.290)	(0.177)	(0.028)
Pre-expiry price	0.977***	0.967***	0.975***
	(0.000)	(0.000)	(0.000)
Pre-expiry formulations	1.016	1.045	1.025
	(0.143)	(0.136)	(0.152)
Other ATC4	1.356**	1.519*	1.366**
	(0.021)	(0.063)	(0.049)
Countries expired	1.113	1.248	1.176
	(0.214)	(0.187)	(0.165)
Controlled entry	1.053	1.182	1.114
	(0.866)	(0.755)	(0.784)
Expiry 02/03	1.547***	1.933***	1.806***
	(0.001)	(0.005)	(0.001)
Expiry 04/05	1.897***	2.565***	2.221***
	(0.000)	(0.000)	(0.000)
Expiry 06/07	2.669***	3.982***	2.768***
	(0.000)	(0.000)	(0.000)
Survival time			0.968***
			(0.000)
Survival time squared			1.000***
			(0.000)
Frailty θ=0 test, p value		0.000	0.008
Weibull parameter p	0.792	1.274	
Sample Size	22237	22237	23019

p values in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively.

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Chapter 5

Effects of generic entry on market structure and prices

Abstract

Generic entry is the main source of competition in off-patent pharmaceutical markets and generic competition is considered to be the main mechanism to erode the market power that patent-holders are able to enjoy during the period of market exclusivity. However, generics do not appear to be always equally effective at driving market prices down and at gaining market share. In this chapter we look at the development of prices and market structure after loss of exclusivity and in presence of generic entry in a number of European countries. In particular, we are interested in the impact that pervasive regulation of European pharmaceutical markets has on the competitive landscape of off-patent pharmaceutical markets. We show that prices and market shares behave differently across European countries and types of drugs, and identify some factors that explain this heterogeneity. Price competition and generic uptake are positively correlated with the value of the market, the number of generic entrants, the absence of price controls, and the existence of regulatory incentives for the prescription and dispensation of generics.

Key words: Pharmaceuticals, Generic competition, Regulation
JEL Classifications: I11; I18; K21; L41; L65

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5.1 Introduction

Generic entry is the main source of competition in off-patent pharmaceutical markets and generic competition is considered to be the main mechanism to erode the market power that patent-holders are able to enjoy during the period of market exclusivity. However, generics do not appear to be always equally effective at driving market prices down and at gaining market share. Empirical evidence shows that generic competition reduces average prices in off-patent pharmaceutical markets, but the magnitude of the drops in prices and their speed seems to vary substantially across countries, as well as generics' ability to gain market share. The economic literature tends to suggest that regulation may have an impact on these competitive dynamics.

The paper by Caves et al. [1] remains a fundamental reference to understand the transformation in off-patent markets dynamics post Waxman-Hatch Act. They provided a first picture of a number of elements that have been intensely discussed in the literature ever since: generic entry had an impact on the pricing behaviour of producers of original branded drugs (hereafter the originator) and on the structure of pharmaceutical markets after patent expiration. Caves et al. [1] found that originators' price declined with the number of generic entrants, although originators' price sensitivity decreased with successive entrants. Generics entered at discounted prices compared to the originator price and average generic prices fell to roughly 17% of the pre-expiry originator price in the long run. They also observed that the overall generic market share remained moderate despite the ratio between originators and generics prices being significantly high.

Some of these findings have been confirmed by more recent research, while others have proved more controversial. Further evidence from the US market confirms that generics tend to enter at a significant discount with respect to the originator price and that the number of generic entrants is negatively correlated with average generic prices. This is the case for Wiggins and Maness [12] and Saha et al. [11].

Others have also validated these results, while calling into question the price response by the originator to generic entry. Grabowski and Vernon [5], Grabowski and Vernon [6], Frank and S. [4] and Regan [9] find that the originators price tends to increase to some extent upon generic entry in the market. This result can be explained by considering the segmentation of the market caused by generic entry. Low-price generic entrants may attract the more price-sensitive part of the demand and confront the originator to a segment of the demand with lower average price elasticity, thus leading to higher originators' equilibrium price. This phenomenon, known as the generic paradox, has been observed mainly in the US market and its existence is a source of disagreement among researchers.

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Generic market penetration has steadily increased in the US market over the past two decades, since Caves et al. [1] published their findings. This has been observed by Grabowski and Vernon [6] and Reiffen and D. [10]. Most likely, moderate generic market shares shortly after the approval of the Waxman-Hatch Act responded to a progressive adjustment by entrants to the new legal framework and by healthcare professionals to the new class of generic products. More recent research has observed that price competition among generic entrants leads to a significant shift of demand away from the originator. Saha et al. [11] find that within a month after the first generic enters the market; overall generics accumulate a 14% share of the market in volume. This figure increases to an average of 43% within six months and to 55% one year after generic entry.

The literature that looks at European pharmaceutical markets is more limited and recent. This is no surprise as generic markets have effectively been developed in Europe only since the mid nineties, and at a different pace in each country. While the evidence available confirms the main findings from the US markets, there are some significant idiosyncrasies of European generic markets. In a number of European markets, the ratio between generic and originator prices tends to be below the estimates from the US and also the speed at which average prices decline after generic entry tends to be lower. The generic paradox is not generally observed in European markets, although results in Kanavos et al. [7] appear consistent with it. Generic market shares appear to vary substantially across European markets, and only in countries like Germany and the UK these shares are comparable to those observed in the US market. A fundamental factor underlying these differences between Europe and the US is the various ways in which European governments regulate prices, reimbursement and usage of drugs.

Danzon and Li-Wei [2] look precisely at how regulation affects competition in pharmaceutical markets in a cross-country setting. They find that price competition between generic competitors is significant in less regulated markets (US, UK, Canada and Germany), but that regulation undermines generic competition in strict regulatory systems (France, Italy and Japan). These results are consistent with the results in Kanavos et al. [7] and Puig-Junoy and Moreno-Torres [8], among others. A lesson that most authors draw form these findings is that certain price and reimbursement regulations common in European countries have undermined the potential for significant savings on off-patent drugs. Kanavos et al. [7] conclude that generic reference pricing may stave off price competition in generic markets. This is the same conclusion in Puig-Junoy and Moreno-Torres [8] from analysing the Spanish generic market.

In this paper we look at the development of prices and market structure after loss of

exclusivity and in presence of generic entry in a number of European countries. In particular, we are interested in the impact that pervasive regulation of European pharmaceutical markets has on the competitive landscape of off-patent pharmaceutical markets. We show that prices and market shares behave differently across European countries and types of drugs, and identify some factors that explain this heterogeneity. Our research provides the most comprehensive and up to date look at the effects of generic entry in Europe. It confirms that generics enter at a discounted price with respect to the price of the originator, average generic prices are inversely correlated with the number of entrants, and overall generic market share increases with the number of generics. These results are largely consistent with those in Kanavos et al. [7] and Wilsdon et al. [13]. We also provide the most exhaustive study of the impact that different types of regulation of pharmaceutical markets in Europe have had on the price and share effects of generic entry. We find that price-cap policies tend to limit both price reductions and generic penetration in the long run. Incentives to physicians to prescribe generically, policies encouraging substitution at pharmacy level, and differential copayments for originator and generics are some of the policy tools that tend to foster price competition among generics and to facilitate generic penetration.

The paper is structured as follows. In Section 5.2 we present some descriptive statistics of the impact of generic entry on prices and market structure. In Section 5.3 we present the econometric analysis performed to identify the factors that determine the impact of generic entry on prices and market structure. Section 5.4 shows the exploratory analysis of how prices of other therapeutically related drugs may react to generic entry in a given drug.

5.2 Data and descriptive analysis

The same data set used in chapter **??** was used for the analysis of the effects of generic entry on prices and market structure. The various types of analysis differed in terms of data requirements. The regression analyses involved the simultaneous use of price data, volume data, dates (date of LoE, entry date) and qualitative information (product characteristics, characteristics of the regulatory environment). This section provides detailed descriptive statistics for the development of prices and generic penetration after LoE in 17 European countries. The same countries are covered in the econometric analysis in section 5.3. The analysis in section 5.4 required data for all INNs in the same therapeutic category, which forced us to limit the coverage to 9 European countries. A detailed description of the the data set is provided in a separate Annex in chapter 6.

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TABLE 5.1: Development of average price index for INNs with and without generic entry

	6 months before LoE	1 month after LoE	6 months after LoE	1 year after LoE	2 years after LoE
No generic entry	1.00	0.98	0.99	0.99	0.97
Generic entry	1.00	0.97	0.88	0.83	0.74

Weighted average by value 6 months before LoE, index equal to one 6 months before LoE

Generic entry into a pharmaceutical market can have a significant impact, as it changes the market from one in which only the firm holding the patent could sell the product concerned (either itself or via licensees) into one where more sources of supply become available for the product. The most direct effect is likely to be on the average price level of the product concerned and the sales volumes of the originator. But other products can also be affected, both products under the INN that remain patent-protected and products based on other INNs but competing with the product that lost exclusivity.

This section first looks into the effects on prices for the INN concerned. It then turns to the effects on volumes, both the total volume of products sold and the volume sold by originators and generics respectively. Finally, it addresses, for a limited number of INNs, the effects of generic entry on possible substitute for the product that lost exclusivity.

5.2.1 Effects on prices

The first measure considered is the average price of the products sold under the INN. This average price is constructed as an index, which is set at one shortly (six months) prior to the end of the exclusivity period. Table 5.1 reports the development over time of the average price index separately for expiring INNs with generic entry and without generic entry.

Comparison of the two rows clearly shows that the average price index drops considerably on markets with generic entry, but not on markets without it. In markets with entry, average prices dropped by almost 20% after the first year following LoE and about 25% after two years. In rare cases, for some medicines in some European countries, the decrease in the average price index was as high as 80-90%.

Of course, it must be borne in mind that entry will not take place immediately after LoE for every INN. The gradual drop in levels observed in table 5.1 is therefore the result of the combination of average price levels coming down quickly in those markets where entry took place quickly and average price levels coming down later because entry took longer.

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TABLE 5.2: Development of average price index for INNs with generic entry

	6 months before entry	1 month after entry	6 months after entry	1 year after entry	2 years after entry
Average INN price	1.00	0.95	0.83	0.79	0.69
Average originator price	1.00	0.97	0.89	0.86	0.82
Average generic price		0.75	0.69	0.65	0.57

INNs weighted by value 6 months before entry, index equal to one 6 months before entry

A different picture emerges when not the date at which the INNs lost exclusivity, but the date of first generic entry is taken as the reference point. The resulting price development is illustrated in table 5.2.

Taking the date of entry as the reference point, the decreases in average prices emerge a little more clearly. The difference can be observed in the form of a somewhat sharper average price decrease in the month of entry, with the differences between the two graphs diminishing after one year.

It seems reasonable to expect a different pricing behaviour between originator and generic producers. One might expect average generic price to be significantly lower than the originator one. Another issue relates to the reaction of originator companies in their pricing strategy when facing generic entry. While in general originator producers might be expected to adapt their price to the generic one, they may well decide to take advantage of the brand recognition of their product and focus on a subset of loyal patients, willing to pay a higher price than the one of generics.

Table 5.2 shows that generics typically come onto the market at a price that is about 25% lower than the price of the originator products prior to LoE. In other words, the generic-originator price ratio on entry is about 0.75. After 2 years, the generic-originator price ratio drops to about 0.57.

Also the price levels of the originator products for INNs facing generic entry appear to decrease, albeit to a lesser extent. This may be related to a range of factors. For those products that lost exclusivity, there may have been a price response by originator companies in the face of increased generic competition. The presence of price regulation, which in some countries obliges originators to keep the prices of their products within a certain range from the lowest priced generic products, may also have played a role. At the same time, originator companies may have continued to enjoy a certain degree

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TABLE 5.3: Average number of originators and generics two years after, by size class

	Originators		Generics	
	1 year after entry	2 years after entry	1 year after entry	2 years after entry
Austria	0.78	0.69	0.52	0.48
Belgium	0.76	0.65	0.55	0.45
Czech Rep.	0.63	0.56	0.55	0.51
Germany	0.80	0.62	0.54	0.49
Denmark	0.90	0.87	0.30	0.23
Spain	0.97	0.90	0.69	0.64
Finland	0.92	0.69	0.63	0.45
France	0.97	0.93	0.61	0.58
Greece	1.04	1.02	0.81	0.82
Hungary	0.97	0.79	0.80	0.63
Ireland	1.00	0.98	0.78	0.78
Italy	0.70	0.66	0.57	0.57
Luxembourg	0.85	0.82	0.37	0.36
Netherlands	0.98	0.94	0.95	0.72
Portugal	0.97	0.84	0.63	0.59
Sweden	0.84	0.78	0.46	0.34
United Kingdom	0.90	0.83	0.78	0.55

INNs weighted by value 6 months before entry

of brand recognition or loyalty on the part of patients and doctors, allowing them to charge a higher price than generic companies.[1]

These EU averages reported so far hide considerable variation across European countries. Table 5.3 provides an overview of the price impact in a range of countries, measured one year and two years after entry, respectively.

The table shows that generic entry leads to the biggest generic price decreases in countries such as Sweden, Finland, Denmark, Austria, Germany, Belgium and Luxembourg. In each of these countries average generic prices after two years appear to be more than 50% below the price of the originator price prior to LoE. In Sweden, Denmark and Luxembourg price drops of this nature are typically achieved within the first year of entry already. Also within each country, there was quite some variation among the various INNs.

The indices reported so far relate to the prices of all products sold under the INN. The originator index may include products that have lost exclusivity and products that are

[1]Further, not all products belonging to a given INN of an originator company may have lost exclusivity at the same time, allowing an originator company to continue to charge mark-ups on these exclusive products. It should be noted that the price index for originator companies displayed in table 5.2 is a composite index of all products sold by the originator companies under the INNs concerned.

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TABLE 5.4: Generic penetration (EU average, all INNs with entry, weighted by market value)

	Share of volume	Share of market value
INNs expired before 2007, one year after first generic entry	0.30	0.25
INNs expired before 2006, two years after first generic entry	0.45	0.38

INNs weighted by value 6 months before entry

still protected. An alternative way to look at the impact of generic entry on prices is to consider only the prices of originator formulations which have been exposed to generic entry. The results are fully consistent and no significant difference is observed. Although this measure is more focused than the average indices described earlier, it is not necessarily more accurate or informative. It provides a different perspective. After all, as part of the life cycle strategy for INNs, originator companies may well have succeeded in shifting some of the demand towards formulations of the INN that still benefit from exclusivity (including second generation products) or even to other still protected INNs altogether.

5.2.2 Effects on volumes

The second main dimension in which generic entry may have an impact is on the volume of products sold and the market shares of the originator and generic companies.

The combined market share of the generic companies is often referred to as the "generic penetration rate. The higher the penetration rate, the greater the savings for the health system are likely to be for a given market size.

Table 5.4 presents, for the EU as a whole, the generic penetration rate for the INNs in the sample covered by our data set that faced generic entry. The penetration rate is measured one year and two years after LoE. Once again the set of INNs is limited in order to allow enough time to lapse before measuring the impact of generic entry. It is given in both volume[2] and value terms (right-hand column).

Again, there is considerable variation across European countries. Table 5.5 shows the generic penetration rate in a number of countries, again measured one year and two years after LoE, by volume and value respectively.

[2]For this volume index, IMS data on Standard Units are used in order to be able to aggregate consumption across different types of formulation (tablets, capsules, injections, etc.)

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TABLE 5.5: Generic penetration as share of volume and market value, by country

	1 year after entry		2 years after entry	
	by volume	by value	by volume	by value
Austria	0.32	0.26	0.45	0.41
Belgium	0.21	0.16	0.38	0.32
Czech Rep.	0.60	0.58	0.68	0.66
Germany	0.61	0.55	0.75	0.70
Denmark	0.61	0.36	0.67	0.46
Spain	0.14	0.10	0.21	0.16
Finland	0.25	0.18	0.31	0.24
France	0.33	0.25	0.47	0.37
Greece	0.06	0.05	0.22	0.18
Hungary	0.24	0.14	0.26	0.23
Ireland	0.11	0.09	0.17	0.14
Italy	0.26	0.25	0.33	0.31
Luxembourg	0.13	0.06	0.34	0.17
Netherlands	0.20	0.23	0.17	0.20
Portugal	0.38	0.27	0.58	0.47
Sweden	0.47	0.28	0.55	0.38
United Kingdom	0.40	0.37	0.49	0.43

INNs weighted by value 6 months before entry

Entry by generic companies appears to have had a very strong effect in Germany, the Czech Republic, Denmark and the UK. In Germany and the Czech Republic, generic companies built up shares above 50% both by value and by volume already within the first year. Measured only by volume, Denmark also shows a market share of generic companies exceeding 50% within the first year after entry.

Generic entry, especially when it is accompanied by significant price reductions, may also lead to an increase in overall consumption of the medicine. In the three years before LoE, the consumption volume index remained fairly close to the unit benchmark, but after generic entry the volumes consumed started to rise steadily. This maybe partly related to the fact that the lower prices for the INNs losing exclusivity draws demand away from substitute products based on other INNs.

5.2.3 Responses by originators

There are a number of ways in which the originator can anticipate or react to the entry of generics into the market. For instance, the originator can react through product proliferation, advertising, pricing or litigation.

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In terms of number of brands per corporation there appears to be little difference between originators facing entry and not facing entry. Nor do there appear to be major developments over time in this respect, although a very slight increase might be observed in the number of brands per company in the period leading up to LoE in those instances where entry took place. The average number of formulations per brand before LoE appears to show an increase in those instances where entry took place, whereas a relative decline in the number is visible in instances without entry. One tentative conclusion is that in the period before the INNs lose exclusivity, originator firms facing the prospect of entry have a tendency to increase the number of formulations per brand in anticipation of future generic entry.

Promotional activities (i.e. in the form of detailing activities, sales representatives informing doctors, advertisement) are another tool that may be used to influence the demand for individual products. In particular, it could make sense to divert promotional expenditure away from products that have lost exclusivity to products that are still protected. It appears that already well before the time of LoE promotional activities decrease significantly. Around the time of LoE, these activities stand at less than 10% of the level attained four years earlier. There is quite some variation across countries and INNs, however.

5.3 Price effects of generic entry and generic penetration

In order to assess the nature of the post generic entry structure of the pharmaceutical markets an econometric analysis of the post-entry change in the average price level and producers' market share was carried out.

Two main cross-sectional model designs were set up. In the first design the long-run market structure was analysed, which amounts to modelling the change in average drug prices at the end of the observed period relative to the price level prior to LoE, and the end-of-period shares of generic producers.

The second design is capturing four intermediate stages, or vintages, of the market. The first vintage model analyses price drops and generic shares one year after the first entry. Likewise, the second, third and fourth vintage models describe price drops and shares two, three and four years after the first entry, respectively.

The following variables were created to be used as dependent variables in the regression analysis:

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- Long-run price drop: the percent drop of the average price level between the last data period and the level prior to LoE for a given country/INN pair.
- Price drops after one, two, three and four years after generic entry: the percent drop of the average price level between the last quarter of the first, second, third and fourth years after first entry, compared to the level prior to entry for a given country/INN pair.
- Long-run generic shares: volume shares of generic products in a given country, in a given INN, in the last quarter of the sample. This variable is a measure of the generic products' market penetration.
- Generic shares one, two, three and four years after generic entry: volume shares of generic products in a given country, in a given INN, in the last quarter of the first, second, third and fourth year after first entry in the country/INN pair. This variable is also a measure of the generic products' market penetration.

5.3.1 Models

5.3.1.1 Price-drop regressions

The long-run price drop model attempts to shed light on the factors affecting the most complete price changes observable in the data and potentially related to the generic entry process. More formally:

$$\begin{aligned} dprice_{ic} &= \beta_0 + \beta_{ngenr} ngenr_{ic} + char'_{ic}\beta_{char} + reg'_c\beta_{reg} \\ &\quad + \beta_{pop} pop_c + ndel'_{ic}\beta_{ndek} + \epsilon_{ic} \end{aligned}$$

where *dprice* is the percent price drop, *ngenr* is the number of generic producers, *char* is the vector of INN characteristics, *reg* is the vector of regulatory variables, *pop* is the log of the country's populations, *ndel* is a dummy variable for negative delay cases and ϵ is the error term. INNs are indexed by i and countries by c.

The model's coefficients can be interpreted as effects on the longer-term state of the market after the occurrence of entry. Positive coefficients can be interpreted as factors inducing to tougher price competition, and the negative ones as those softening competition. Individual coefficients in the model represent partial effects. It means that each coefficient represents a complementary additional effect of a given explanatoryvariable holding the other variables constant.

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The estimation sample was restricted in each country to those INNs in which entry took place before 2006, for which two years of post-entry history had been observed. In the cross section, some INNs are 'older' which means that more time passed since the first entry, while others are younger (but still are at least two years old). This variation across INNs is captured by the generic age variable which counts the number of periods since the first entry on the given INN.

Additionally, four vintage price drop regressions were estimated. The corresponding one, two, three and four-year price drops were regressed against the same set of explanatory variables as in the long-run price drop regressions.

The series of vintage price drop models, relative to the long-run model, attempt to shed light both on the shorter and longer term effects after entry. Hence, the coefficients can still be interpreted as effects on the state of the market but this state is not necessarily the one where the market would eventually be stabilized, especially in the earlier vintages (the first and second years). Positive coefficients can be interpreted as factors conducive to tougher price competition, and the negative ones as those softening pricing.

5.3.1.2 Generic-share regressions

Similarly to the price drop regressions, generic share regressions attempt to shed light both on the short and long run effects of generic entry in terms of market structure, and on the determinants of these effects. Again regressions were estimated for long-run generic shares and for four vintage generic shares. All regressions were regressed against the same set of explanatory variables. More formally:

$$\begin{aligned} gen\_share_{ic} &= \beta_0 + \beta_{pg} price\_gen_{ic} + \beta_{po} price\_ori_{ic} + char'_{ic}\beta_{char} \\ &\quad + reg'_{ic}\beta_{reg} + \beta_{pop} pop_c + ndel'_c\beta_{ndek} + \epsilon_{ic} \end{aligned}$$

where *gen_share* is the volume share of generic products, *price_gen* is the average price of generic products, *price_ori* is the average price of originator products, *char* is the vector of INN characteristics, *reg* is the vector of regulatory variables, *pop* is the log of the country's populations, *ndel* is a dummy variable for negative delay cases and ϵ is the error term. INNs are indexed by i and countries by c.

Positive coefficients can be interpreted as factors conducive to higher generic penetration. Individual coefficients in the model represent partial effects.

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The estimation sample for the long-run generic share regressions was again restricted in each country to those INNs which already had at least two years of post-entry history. The technical details of the long-run share regressions are similar to those of the long-run price drop regressions.

5.3.2 Results

All models are linear regressions where the variation in the left hand side variable (explained variable) is explained by the right-hand side variables (explanatory variables).

5.3.2.1 Results from price-drop regressions

Tables 5.6 and 5.7 summarise the main results from the price drop regressions. The baseline long-run price drop model (Model VI) shows that the coefficient of the number of generic entrants is positive and statistically significant even though its value is small.

In the long-run price drop regressions, regulatory variables are statistically significant. The signs, with the notable exception of the price-cap regime indicator, are positive.

The pre-expiry value per capita, generic age and biosimilar variables have positive and statistically significant coefficients. The pre-expiry number of formulations estimate is negative and statistically significant. As it is explained in chapter **??**, this variable tends to have a positive effect on both the probability of entry and the number of entrants. The explanation of the different signs in the price drop and entry models could be that the number of formulations is a measure of product differentiation within a given INN. A market with more product differentiation attracts more entry and provides an opportunity to price relatively higher. The other variables do not seem to significantly contribute to the explanatory power of the regression.

The baseline vintage price drop models (Model I-V in table 5.7) show that the coefficient of the number of generic entrants has a small, statistically significant, positive estimate.

From the main regulatory variables, the price caps and lowest price policy variables are always statistically significant, the former having a negative, the latter a positive estimated coefficient. Variables signalling frequent adjustment of prices, incentives for physicians to prescribe generically and compulsory substitution at pharmacy level are significant and have a positive effect in most vintage regressions. Differential copayment is statistically significant only in the first two vintages with positive estimates.

The pre-expiry value of the INN per capita is also positive and statistically significant. Population has a statistically significant and negative estimate in most vintages. Possibly

TABLE 5.6: Price drops following entry

	Model I 1-year price drop	Model II 2-years price drop	Model III 3-year price drop
Price caps	-0.103***	-0.145***	-0.137***
	(0.000)	(0.000)	(0.001)
Compulsory substitution	0.078**	0.087*	0.144***
	(0.025)	(0.067)	(0.001)
Physicians incentives	0.138***	0.153***	0.170***
	(0.000)	(0.000)	(0.000)
Frequent adjustment	0.028	0.123***	0.110***
	(0.211)	(0.000)	(0.002)
Differential copayment	0.144***	0.121***	0.050
	(0.001)	(0.000)	(0.202)
Lowest price policy	0.074***	0.082***	0.104***
	(0.002)	(0.002)	(0.002)
Log of pre-expiry value	0.007	0.016*	0.032***
	(0.445)	(0.062)	(0.468)
Population	-0.028**	-0.040***	-0.049***
	(0.010)	(0.001)	(0.406)
Pre-expiry formulations	-0.011**	-0.012**	-0.007
	(0.048)	(0.027)	(0.002)
Biosimilar	0.025	0.050**	0.021
	(0.215)	(0.031)	(0.327)
Other ATC4	-0.027	0.042	0.039
	(0.515)	(0.236)	(0.862)
Already expired	0.005	-0.004	0.008
	(0.877)	(0.914)	(0.449)
Other countries expired	0.006	0.006	0.007
	(0.217)	(0.352)	(0.007)
Number generics	0.029***	0.017***	0.012***
	(0.000)	(0.000)	(0.419)
Controlled entry	-0.042	-0.076***	1.007***
	(0.013)	(0.000)	(0.001)
Negative delay	-0.001	0.051	0.036
	(0.981)	(0.222)	(0.641)
Negative delay 3	-0.098*	-0.143*	-0.128
	(0.099)	(0.053)	(0.157)
Constant	0.459**	0.761***	1.007***
	(0.013)	(0.000)	(0.001)
R squared	0.336	0.413	0.389
F-test of joint significance, p value	0.000	0.000	0.000
Ramsey's RESET test, p value	0.829	0.486	0.086
Sample Size	464	368	260

heteoscedasticity robust p values in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively.

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TABLE 5.7: Price drops following entry (continuation)

	Model IV 4-year price drop	Model V long-run price drop
Price caps	-0.166***	-0.201***
	(0.000)	(0.000)
Compulsory substitution	0.144***	0.168***
	(0.000)	(0.000)
Physicians incentives	0.176***	0.230***
	(0.001)	(0.000)
Frequent adjustment	0.122***	0.126***
	(0.002)	(0.000)
Differential copayment	0.017	0.078***
	(0.589)	(0.006)
Lowest price policy	0.159***	0.054*
	(0.000)	(0.056)
Log of pre-expiry value	0.039***	0.034***
	(0.235)	(0.016)
Log of population	-0.046**	-0.020
	(0.123)	(0.012)
Pre-expiry formulations	-0.016	-0.015**
	(0.005)	(0.000)
Biosimilar	0.043	0.062**
	(0.013)	(0.829)
Other ATC4	0.088**	0.007
	(0.573)	(0.305)
Already expired	-0.028	-0.035
	(0.032)	(0.146)
Other countries expired	0.021**	0.009
	(0.037)	(0.096)
Number generics	0.013**	0.010***
	(0.302)	(0.589)
Generic age		0.018***
		(0.000)
Generic age squared		0.000
		(0.096)
Controlled entry	0.058**	-0.022
	(0.010)	(0.589)
Negative delay	-0.007	-0.004
	(0.936)	(0.944)
Negative delay 3	-0.122	0.001
	(0.194)	(0.992)
Constant	1.030***	0.440**
	(0.004)	(0.049)
R squared	0.498	0.380
F-test of joint significance, p value	0.000	0.000
Ramsey's RESET test, p value	0.268	0.302
Sample Size	181	394

p values in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively.

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it picks up some of the country effects. The other variables do not seem to significantly contribute to the explanatory power of most of the regressions.

5.3.2.2 Results from generic-share regressions

Tables 5.8 and 5.9 summarise the main results from the generic share regressions. The baseline long-run generic share model (Model VI) shows that both generic and originator prices have a statistically significant estimate with the expected signs (negative and positive, respectively).[3]

Among the regulatory variables price caps, frequent price adjustments, incentives for physicians to prescribe generically, and compulsory substitution at pharmacy level are statistically significant. The signs, with the exception of price caps, are positive.

Pre-expiry value per capita, generic age, biosimilarity and population have positive and statistically significant coefficients. The controlled entry estimate appears negative and significant. The other variables do not seem to significantly contribute in a stable way to the explanatory power of the regression.

The baseline vintage generic share models (Model I-V in table 5.9) show that both generic and originator prices have a statistically significant estimate with the expected signs (negative and positive, respectively).

From the main regulatory variables, price caps and compulsory substitution are always statistically significant, the former having a negative, the latter a positive estimated coefficient. Frequent price adjustments, lowest price policy and incentives for physicians to prescribe generically are only significant with positive coefficients in the second and third vintages, respectively. The differential copayment is not significant statistically in any of the main generic share regressions.

The controlled entry variable has a statistically significant negative effect in two vintages. The biosimilar indicator appears statistically significant with a positive coefficient in three vintages. The other variables do not seem to significantly contribute in a stable way to the explanatory power of the regression.

[3] It should be noted that the price variables used in the generic share regressions are the current prices as opposed to the pre-expiry price variable in the entry models in chapter 4. The coefficients on the price variables in the share regressions measure own and cross-price effects (with respect to originator products of the same INN) on the generic shares.

TABLE 5.8: Market share following entry

	Model I 1-year share	Model II 2-year share	Model III 3-year share
Price caps	-0.156***	-0.151***	-0.150***
	(0.000)	(0.000)	(0.000)
Compulsory substitution	0.124***	0.151***	0.192***
	(0.000)	(0.001)	(0.106)
Physicians incentives	0.080***	0.065*	0.076
	(0.009)	(0.096)	(0.104)
Frequent adjustment	0.078***	0.091***	0.058***
	(0.002)	(0.002)	(0.000)
Differential copayment	-0.026	-0.010	-0.018
	(0.423)	(0.781)	(0.674)
Lowest price policy	0.092***	0.081**	0.054
	(0.001)	(0.014)	(0.186)
Log of pre-expiry value	-0.003	0.000	0.002
	(0.775)	(0.969)	(0.400)
Population	0.010	0.023*	0.014
	(0.318)	(0.067)	(0.622)
Pre-expiry formulations	-0.002	-0.009	-0.005
	(0.624)	(0.147)	(0.889)
Biosimilar	0.039*	0.069**	0.070
	(0.082)	(0.011)	(0.582)
Other ATC4	0.011	0.015	0.026
	(0.696)	(0.690)	(0.427)
Already expired	-0.058*	-0.031	0.034
	(0.052)	(0.384)	(0.163)
Other countries expired	0.010*	0.010	0.011
	(0.092)	(0.138)	(0.382)
Generic price	-0.002**	-0.005***	-0.005
	(0.048)	(0.000)	(0.033)
Originator price	0.001**	0.004**	0.008
	(0.017)	(0.018)	(0.337)
Controlled entry	-0.052	-0.101**	-0.129**
	(0.191)	(0.051)	(0.033)
Negative delay	0.194***	0.159***	0.130*
	(0.000)	(0.004)	(0.051)
Negative delay 3	-0.275***	-0.178**	-0.164*
	(0.000)	(0.018)	(0.064)
Constant	0.063	-0.048	0.187
	(0.725)	(0.824)	(0.515)
R squared	0.322	0.295	0.278
F-test of joint significance, p value	0.000	0.000	0.000
Ramsey's RESET test, p value	0.009	0.182	0.971
Sample Size	463	387	272

heteoscedasticity robust p values in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively.

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TABLE 5.9: Market share following entry (continuation)

	Model IV 4-year share	Model V long-run share
Price caps	-0.150***	-0.138***
	(0.001)	(0.000)
Compulsory substitution	0.044	0.074**
	(0.283)	(0.013)
Physicians incentives	0.120**	0.102**
	(0.047)	(0.024)
Frequent adjustment	0.264***	0.205***
	(0.000)	(0.000)
Differential copayment	-0.043	0.005
	(0.392)	(0.894)
Lowest price policy	0.033	0.038
	(0.484)	(0.280)
Log of pre-expiry value	0.043	0.087***
	(0.280)	(0.003)
Log of population	-0.006	-0.006
	(0.549)	(0.320)
Pre-expiry formulations	0.021	0.017
	(0.104)	(0.094)
Biosimilar	0.079	-0.001
	(0.109)	(0.989)
Other ATC4	0.013	0.004
	(0.780)	(0.921)
Already expired	0.001	0.000
	(0.945)	(0.972)
Other countries expired	0.019	0.049***
	(0.357)	(0.000)
Generic price	-0.056	-0.107**
	(0.375)	(0.026)
Originator price	-0.029***	-0.006***
	(0.005)	(0.002)
Generic age		0.004*
		(0.081)
Generic age squared		0.037***
		(0.000)
Controlled entry	-0.136***	-0.001**
	(0.001)	(0.026)
Negative delay	0.053	0.086*
	(0.485)	(0.099)
Negative delay 3	-0.068	-0.054
	(0.478)	(0.466)
Constant	0.197	-0.783***
	(0.581)	(0.000)
R squared	0.332	0.367
F-test of joint significance, p value	0.000	0.000
Ramsey's RESET test, p value	0.013	0.672
Sample Size	192	385

p values in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively.

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5.3.3 Robustness checks

In order to assess the stability of the results, various robustness checks were implemented.

First, the models were re-estimated by (i) dropping observations related to negative time to entry larger than 3 months, and (ii) dropping all negative time to entry related observations. Results are generally robust to these sample changes.

Second, the models has also been estimated using (i) robust regressions, controlling for potential outliers, and (ii) instrumental variables estimations controlling for potential endogeneity of the number of generic producers, the price of originator and price of generic products variables. Endogeneity of these variables might arise as prices, quantities and the number of firms is determined simultaneously in an industry equilibrium. The implemented two-step efficient GMM estimation used Hausman-Taylor-type instruments: the average number of generic producers, average prices of originator and generic products in other countries. These instruments can be motivated using the assumption that different countries represent separate markets with country specific demand shocks.[4]

The main results and qualitative conclusions from robust regressions and instrumental variables estimation, as shown in tables 5.12, 5.13, 5.14 and 5.15 in 5.5, are unchanged.

5.3.4 Conclusions on the effects of generic entry

The main patterns emerging from the regression analysis of price drops and generic shares can be summarised as follows:

- The price-cap policies seem to have a negative effect both on the extent of price competition and on the penetration of generic drugs. A possible explanation could be that in the longer run the price cap becomes a focal point for the generic companies, i.e. the producers align their pricing to this focal point and even though they could potentially undercut this price they stick to it instead. This might result in higher average prices than without a price cap.
- The frequent adjustment, physicians encourage and compulsory substitution, lowest reimbursed price and, in a somewhat less pronounced way, the differential copayment policies tend to have a positive effect on the extent of price competition.

[4] On instrumental variables estimation see Chapter 5 in Wooldridge [14]

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- The magnitudes of the coefficients on the regulatory variables (with the exception of differential copayment) in the price drop regressions tend to increase from the earlier vintages to the older ones. This pattern implies that the full effect of the different regulatory regimes on the extent of price competition is built up gradually after the first entry.
- Compulsory substitution and, in a somewhat less pronounced way, frequent price adjustments, incentives for physicians to prescribe generically and lowest reimbursed price policies tend to have a positive effect on generic drug penetration.
- The results also provide some evidence that, in the case of INNs in which controlled entry was observed, overall generic market share penetration (controlled and independent) tends to be lower.
- Consistent with standard demand theory, the average price of generic products has a negative, while the average price of originator products a positive effect on the shares of generic drugs.
- The number of generic producers of the same INN tends to positively affect price competition.

5.4 Potential effects of generic entry on other INNs in the ATC4 class

When a generic company enters with a generic version of a given INN, in the sense that it starts selling (some of the) formulations of the INN that have lost their exclusivity, this may have an impact not only on sales of the INN concerned (in particular, the total level of sales and the sales of the originator company), but also on the sales of other products based on different INNs.

In particular, generic entry in a given INN that lost its exclusivity and the subsequent reduction in the average price of this INN may attract consumption away from other INNs. ATC 4 classes contain INNs that share, to a greater or lesser extent, some therapeutic characteristics. Therefore, they constitute a reasonable starting point for the group of INNs within which to analyse patterns of potential substitution across INNs.

To identify such potential switching effects, the analysis looks at the evolution of volumes of other INNs that were active in the same ATC4 class when the LoE took place. Most of the analysis focuses on the extent of correlation between, on the one hand, the volume of INNs sold in the same ATC4 class after LoE and, on the other hand, the prices of the INN

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of reference losing exclusivity. It should be emphasized, however, that this subsection does not necessarily pretend to reflect causal relations, but rather correlations. The coefficients studied in this section are merely an indicator of potential effects of generic entry on other INNs. Further, no position is taken on the economic significance of the estimated coefficients, e.g. whether they are large or small in the context of the ATC class. With respect to the previous subsections, the analysis presented below is characterised by having mainly an exploratory purpose.

The principal dataset was combined with monthly data on sales, volumes and prices obtained from IMS for all the INNs in any ATC4 class to which at least one INN in our sample belongs. The analysis was based on 9 Member States (Denmark, France, Germany, Greece, Hungary, Italy, Netherlands, Spain and UK).[5]

Consumption volumes of the various formulations relating to given INNs were converted into daily defined doses in order to compare volume measures across different INNs within the same ATC4 class. The conversion was made using a data set obtained from the World Health Organisation. For those formulations for which this information was not available, the whole ATC4 class to which they belong was excluded from the analysis.

In a number of ATC4 classes, more than one INN lost exclusivity during the period 2000-2007. LoE by multiple INNs within the same ATC4 class in a short time span substantially complicates the identification of potential effects of generic entry on other INNs in the ATC4 class. In the analysis, attention was therefore focused on those ATC4 classes where only one LoE occurred during the period of interest. Additionally, the sample is restricted to those ATC4 classes in which the INN losing exclusivity faces generic entry, as only in these instances potential effects of generic entry on other INNs could be expected.

Volumes of other INNs were analysed over a period covering 24 months before and 24 months after the date of generic entry. Given that a key factor in the analysis is the variation of volumes over time, only INNs with observations over at least two years, containing the month of LoE, were considered.

The final sample used in the analysis included 190 INNs belonging to 29 different ATC4 classes in nine different countries. The set of INNs (and of ATC4 classes) observed is different from one country to another. In total, 57 country-ATC4 pairs were studied.

Descriptive statistics provide some indication of potential volume effects of generic entry on other INNs following LoE. On average, volumes consumed of an INN increased steadily after its LoE. This may be partly related to the fact that the lower prices for

[5] See chapter 6

the INNs losing exclusivity may stimulate demand for the product as such (e.g. lower copayments) but it might also draw demand away from other products based on other INNs.

Regression analysis was used to study patterns of potential switching at the more disaggregated level of individual INNs. The rationale for such switching is that generic entry in a given INN after LoE may drive its prices down and attract consumption away from other INNs in the same ATC4 class. Therefore, one might expect to observe a positive correlation between the average price of the INN loosing exclusivity and the volumes consumed of other INNs in the same ATC4 class.

For each INN in the sample that did not lose exclusivity during the period 2000-2007, volumes consumed every month could be regressed against a set of explanatory variables; i.e. the average price of the INN itself (the own price), the average price of the INN that has lost exclusivity in the same ATC4 class (the cross price) and a linear time trend.[6] The results of this type of analysis should however be taken with caution. In this type of model, prices would be potentially endogenous as they are an outcome of a market process where prices and quantities are simultaneously determined. The ordinary least squares estimator would produce biased estimates of the parameters in the model if the regressors are endogenous. In order to correct to some extent the potential endogeneity, panel data analysis on the pooled data for all INNs was performed.

We used the pooled data for all the INNs in the sample to make more efficient use of all the information contained in the full dataset and to filter to some degree the potential endogeneity of prices. In previous subsections, pooled-data analysis made use of a larger set of regressors than are used in this subsection. Here the analysis exploits the time dimension of the panel data, while most regressors used in previous subsections do not provide enough time variability to allow their use here. Hence, volumes consumed every month were regressed against the following set of explanatory variables:

- the average price of the INN itself (the own price);
- the average price ofthe INN that has lost exclusivity in the same ATC4 class (the cross price);

[6] A similar approach to the one proposed by Engstrom et al. [3] was followed to estimate this correlation using regression analysis. They estimate a single coefficient for the difference between the own price and the cross price. This is equivalent to imposing a restriction on the coefficients of these two variables. The null hypothesis that this restriction holds was tested and rejected for a substantial number of INNs in the sample analysed. Therefore, the less restrictive specification was chosen and both coefficients were estimated separately for each INN. They also include lags of the dependent variable in the specification to control for autocorrelation. After performing the Durbin Watson alternative test, the null hypothesis of no serial correlation was not rejected in most of the cases for the specification without the lagged dependent variable. Therefore, the specification without lags was chosen. It should be noted that the sample used in the study by Engstrom et al. [3] was related to the Swedish market only and therefore differs from the sample analysed here.

- a time trend.

More formally, the following set of specifications were estimated:

$$\begin{aligned} volume\_sales_{it} &= \beta_0 + \beta_{own} price_{it} + \beta_{cross} price\_ref_{it} + \beta_{time} time\_excit \\ &\quad + fix_i' \beta_{fix} + \epsilon_{it} \end{aligned}$$

Where *volume_sales* are the sales of the INN in number of ddd, *price* is the average price of the INN, $price\_ref$ is the average price of the INN losing exclusivity within the ATC4 and country, *time_exc* is the control for time since LoE (missing in some specifications, an either as a linear trend or time dummies in the others), fix is the vector of fixed effects (INN and country effects separately in some specifications, INN/ATC4/country effects in the others) and ϵ is the error term.

Given that the data was pooled for all the markets in the sample, fixed effects were introduced in the regression to control for specificities in each market that may explain differences in levels of consumption across markets. Fixed effects partially solve the problem of endogeneity by filtering any time-invariant endogeneity of prices. The potential time-variant endogeneity left may advise to interpret results as conservative estimates of the actual price effects. All regressions include a dummy for each INN in each ATC4 and country. With respect to the intercept, the same INN in different countries or ATC4 is treated independently. Only the coefficients for the prices are shown. In all regressions, the coefficient for the own price is negative and significant.

Regression 1 in table 5.10 reports the results when no control for time is included in the specification. In this case, the coefficient for the cross price is positive but non significant. Regression 2 includes a linear time trend while regression 3 includes dummies for the time passed since the date of LoE. One reason to think that time may matter is that a series of events happen after the LoE that may affect the environment in the market. Including a control for time passed since LoE may to some extent account for this fact, which otherwise may induce a biased estimation of the correlation between volume and cross-price. The linear time trend implies a linear relation between consumption and time, which may not be appropriate. The time dummies allow for a more flexible relationship between consumption and time. The coefficient for the cross price is positive and significant in regressions 2 and 3. Positive correlations can be interpreted as an indication of positive volume effects of generic entry in other INNs in the same ATC4. As expected, in all regressions own-price coefficients are higher in absolute value terms than cross-price coefficients.

TABLE 5.10: Shares of cross-price coefficients from one-by-one regressions at INN / ATC4 / country level

	No time control	Linear trend	Time dummies
Log own price	-0.34***	-0.33***	-0.33***
	(0.03)	(0.03)	(0.03)
Log cross price	0.03	0.14***	0.17***
	(0.02)	(0.02)	(0.03)
R squared	0.98	0.98	0.98
Sample size	14478	14478	14478

standard errors in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively.

TABLE 5.11: Shares of cross-price coefficients from pooled-data regressions

	No time control			Linear time trend			Time dummies		
	Sig.	Non-sig.	All	Sig.	Non-sig.	All	Sig.	Non-sig.	All
Positive	0.20	0.33	0.53	0.25	0.39	0.64	0.27	0.38	0.65
Negative	0.15	0.32	0.47	0.11	0.25	0.36	0.10	0.25	0.35

Partially based on IMS data

Results in table 5.10 provide additional indication about the existence, on average, of correlation between the price of the INN losing exclusivity and the level of consumption in other INNs in the same ATC4 class.

To allow for different cross-price coefficients across settings, a similar model was estimated where dummies for each INN in each ATC4 and countrywere interacted with the cross-price. This exercise, by allowing coefficients for the cross-price to differ across markets, gets closer to a disaggregated analysis. Table 5.11 reports the share of positive and negative estimated cross-price effects from the model in differences. Again positive correlations can be interpreted as an indication of potential volume effects of generic entry between these two INNs. Negative coefficients indicate a negative correlation between volumes consumed and cross prices. They might be potentially related to idiosyncratic characteristics of some markets. For instance, they may denote some degree of complementarity between INNs, which would be compatible with therapies that combine more than a single INN (e.g. cocktails of medicines). This presumption has not been further explored as it is out of the scope of this analysis.

As previously, three specifications were estimated, without time control, with a linear time trend and with time dummies. The latter provides a higher share of positive cross-price effects, which may be due to better controlling for changes in the market after LoE.

5.4.1 Conclusions on effects of generic entry on other INNs

Overall, the analysis shows that in a significant number of cases, generic entry after LoE appears to have had an impact not only on the sales of the INN concerned, but also on the sales of a number of other products based on different INN. At the same time, there is considerable heterogeneity across INNs with respect to the estimated cross-price effects seem to vary considerably from one INN to another.

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5.5 Appendix

TABLE 5.12: GMM estimate, endogenous variable: number of generics

	Model I 2-year price drop	Model II long-run price drop
Price caps	-0.134***	-0.205***
	(0.000)	(0.000)
Compulsory substitution	0.035	0.158***
	(0.523)	(0.002)
Physicians incentives	0.194***	0.294***
	(0.000)	(0.000)
Frequent adjustment	0.164***	0.170***
	(0.000)	(0.000)
Differential copayment	0.138***	0.068**
	(0.000)	(0.042)
Lowest price policy	0.077**	0.044
	(0.018)	(0.162)
Log of pre-expiry value	-0.019	0.011
	(0.261)	(0.421)
Population	-0.090***	-0.060***
	(0.001)	(0.003)
Pre-expiry formulations	-0.014**	-0.018***
	(0.023)	(0.004)
Biosimilar	0.003	0.023
	(0.917)	(0.431)
Other ATC4	0.071*	0.038
	(0.065)	(0.244)
Already expired	0.059	0.010
	(0.218)	(0.796)
Other countries expired	0.001	0.008
	(0.934)	(0.218)
Number generics	0.055***	0.031***
	(0.000)	(0.000)
Generic age		0.007***
		(0.003)
Generic age squared		0.000
		(0.970)
Controlled entry	-0.024	-0.001
	(0.633)	(0.970)
Negative delay	-0.046	-0.070
	(0.420)	(0.279)
Negative delay 3	-0.027	0.076
	(0.767)	(0.308)
Constant	1.190***	0.927***
	(0.000)	(0.001)
R squared	0.194	0.267
F-test of joint significance, p value	0.000	0.000
Ramsey's RESET test, p value	0.018	0.004
Hansen test, p value	0.967	0.155
rank test, p value	0.000	0.000
Endogeneity test, p value	0.002	0.002
Sample Size	368	394

p values in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively. [a] H0: overidentification restrictions hold [b] H0: rank condition does not hold [c] H0: exogeneity of endogenous variable

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TABLE 5.13: Robust estimates of price drops

	Model III 2-year price drop	Model IV long-run price drop
Price caps	-0.140***	-0.198***
	(0.000)	(0.000)
Compulsory substitution	0.129***	0.176***
	(0.000)	(0.000)
Physicians incentives	0.183***	0.215***
	(0.000)	(0.000)
Frequent adjustment	0.114***	0.145***
	(0.000)	(0.000)
Differential copayment	0.113***	0.064*
	(0.001)	(0.067)
Lowest price policy	0.085***	0.054*
	(0.003)	(0.050)
Log of pre-expiry value	0.015*	0.039***
	(0.082)	(0.000)
Log of population	-0.042***	-0.010
	(0.001)	(0.399)
Pre-expiry formulations	-0.013**	-0.011**
	(0.030)	(0.044)
Biosimilar	0.048*	0.043*
	(0.050)	(0.079)
Other ATC4	0.029	0.027
	(0.347)	(0.370)
Already expired	-0.019	-0.030
	(0.560)	(0.337)
Other countries expired	0.005	0.009*
	(0.376)	(0.072)
Number generics	0.016***	0.008***
	(0.000)	(0.001)
Generic age		0.016
		(0.399)
Generic age squared		0.000
		(0.463)
Controlled entry	-0.050	-0.027
	(0.191)	(0.463)
Negative delay	0.040	0.033***
	(0.322)	(0.393)
Negative delay 3	-0.084	-0.087
	(0.122)	(0.108)
Constant	0.782***	0.328
	(0.000)	(0.142)
R squared	0.412	0.422
F-test of joint significance, p value	0.000	0.000
Ramsey's RESET test, p value	0.012	0.367
Sample Size	368	394

p values in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively.

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TABLE 5.14: GMM estimates, endogenous variables: prices

	Model I 2-year share	Model II long-run share
Price caps	-0.169***	-0.155***
	(0.000)	(0.000)
Compulsory substitution	0.141***	0.206***
	(0.004)	(0.000)
Physicians incentives	0.076*	0.112**
	(0.064)	(0.011)
Frequent adjustment	0.121***	0.087***
	(0.000)	(0.003)
Differential copayment	0.006	0.020
	(0.878)	(0.603)
Lowest price policy	0.086***	0.024
	(0.008)	(0.493)
Log of pre-expiry value	-0.004	0.019*
	(0.704)	(0.066)
Log of population	0.023*	0.049***
	(0.082)	(0.000)
Pre-expiry formulations	-0.011*	-0.010
	(0.085)	(0.113)
Biosimilar	0.044	0.081***
	(0.112)	(0.005)
Other ATC4	0.025	0.005
	(0.538)	(0.892)
Already expired	-0.003	0.009
	(0.944)	(0.801)
Other countries expired	0.005	0.000
	(0.474)	(0.945)
Generic price	-0.004***	-0.005***
	(0.000)	(0.000)
Originator price	0.002**	0.003***
	(0.036)	(0.006)
Generic age		0.036***
		(0.000)
Generic age squared		-0.001**
		(0.011)
Controlled entry	-0.144***	-0.116**
	(0.009)	(0.011)
Negative delay	0.179***	0.070
	(0.001)	(0.162)
Negative delay 3	-0.198**	-0.005
	(0.013)	(0.936)
Constant	-0.057	-0.765***
	(0.798)	(0.000)
R squared	0.336	0.377
F-test of joint significance, p value	0.000	0.000
Ramsey's RESET test, p value	0.631	0.815
Hansen test, p value	0.679	0.524
rank test, p value	0.075	0.000
Endogeneity test, p value	0.103	0.135
Sample Size	326	377

p values in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively. [a] H0: overidentification restrictions hold [b] H0: rank condition does not hold [c] H0: exogeneity of endogenous variable

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TABLE 5.15: Robust estimates of market shares

	Model III 2-year share	Model IV long-run share
Price caps	-0.166***	-0.173***
	(0.000)	(0.000)
Compulsory substitution	0.169***	0.239***
	(0.000)	(0.000)
Physicians incentives	0.081**	0.120***
	(0.039)	(0.005)
Frequent adjustment	0.097***	0.102***
	(0.002)	(0.001)
Differential copayment	-0.012	-0.023
	(0.772)	(0.595)
Lowest price policy	0.080**	0.027
	(0.020)	(0.414)
Log of pre-expiry value	0.003***	0.025***
	(0.782)	(0.007)
Log of population	0.027*	0.053***
	(0.061)	(0.000)
Pre-expiry formulations	-0.011	-0.012*
	(0.121)	(0.080)
Biosimilar	0.080***	0.093***
	(0.006)	(0.002)
Other ATC4	0.017	0.000
	(0.657)	(0.991)
Already expired	-0.034	0.009
	(0.384)	(0.809)
Other countries expired	0.012*	0.002
	(0.064)	(0.724)
Generic price	-0.005**	-0.005**
	(0.046)	(0.022)
Originator price	0.004	0.004
	(0.148)	(0.113)
Generic age		0.039***
		(0.000)
Generic age squared		-0.001*
		(0.061)
Controlled entry	-0.105**	-0.085*
	(0.024)	(0.061)
Negative delay	0.174***	0.105**
	(0.000)	(0.026)
Negative delay 3	-0.179***	-0.055
	(0.008)	(0.409)
Constant	-0.119	-0.850***
	(0.636)	(0.002)
R squared	0.306	0.411
F-test of joint significance, p value	0.000	0.000
Ramsey's RESET test, p value	0.056	0.175
Sample Size	387	385

p values in parentheses; stars indicate significance at 10 (*), 5 (**), and 1 (***) percent levels, respectively. [a] H0: overidentification restrictions hold [b] H0: rank condition does not hold [c] H0: exogeneity of endogenous variable

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Chapter 6

Annex on data sources and management

6.1 Data

This section describes the data sources used for the analysis conducted in chapters 4 and 5 as well as the methodology applied to prepare the datasets.

6.1.1 Data Sources

The analysis is based on two main sources of data. First, the analysis used data collected from pharmaceutical companies in the context of the sector inquiry conducted by the Commission. All data from the companies were gathered for each of the 27 EU Member States, except for price data, where the set of countries in which the companies were requested to provide data was limited to ten: Denmark, France, Germany, Greece, Hungary, Italy, the Netherlands, Poland, Spain and the United Kingdom.

Second, the analysis has used data requested from IMS Health, a provider of pharmaceutical data services. IMS data were obtained for all 27 Member States. The data obtained from IMS included, for the period 2000 - 2007 and for each company active in the INN concerned, monthly data on sales (local currency), volumes, prices and discounts (local currency) at the pack level, as well as dates concerning loss of exclusivity, launch dates. For some Member States, IMS data were also available as regards the level of promotional activity (on a quarterly basis) at the brand level. Most emphasis has been given at sales and prices at the ex-manufacturer level. Finally, for the ten countries mentioned in the previous paragraph, IMS data were also obtained for all INNs belonging to ATC4 classes, within which LoE took place at some point in the period 2000 - 2007.

The IMS dataset and the datasets from the companies were integrated into one dataset. The IMS dataset served as the "central" dataset into which the corresponding data items

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of the companies were combined (except where company data were not available or in individual cases where these data appeared inaccurate or incomplete).

The two datasets must be seen as complementary. The combined use of the IMS dataset and the company datasets made it possible to use company data to the largest extent possible, while being able to fill in gaps in one dataset with information available in the other dataset.

For instance, in order to keep the informational burden on companies limited, information on prices was asked for 10 Member States only (see above). All analyses of price developments in the other 17 Member States (Austria, Belgium, Bulgaria, the Czech Republic, Cyprus, Estonia, Finland, Ireland, Lithuania, Latvia, Luxemburg, Malta, Portugal, Romania, Slovakia, Slovenia, Sweden) therefore rely on IMS data. Likewise, the calculation of EU averages involved the use of IMS data for the price component relating to the 17 countries mentioned. Furthermore, the sample of firms to which questionnaires were sent did not comprise the entire universe of firms active in the production and supply of medicines for human use. The sample contained 43 originator companies and 27 generic companies. The IMS dataset aims at tracking the sales of all actors in the field. For that reason, for those companies not part of the inquiry the analysis relied on information provided by the IMS dataset.

On the other hand, some types of data were only available from the companies themselves, not from IMS. For instance, the IMS dataset only contained expiry dates for Austria, Belgium, the Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, the Netherlands, Portugal, Spain, Sweden and the United Kingdom: in other words, for most of the EU 15 Member States plus the Czech Republic. In addition, IMS expiry dates were sometimes only available for some of the relevant products within the countries, not for all products.

Similarly, information on actual average transaction prices and discounts granted by the companies was not available in the IMS dataset, as this is information to which IMS has no access. IMS bases itself mainly on public sources, such as list prices and regulated prices. It then applies a conversion factor to take into account what it understands to be normal discount applicable to that industry level. Prices in the IMS dataset are therefore not actual average transaction prices. In the sector inquiry, by contrast, companies were specifically asked to provide actual average transaction prices.

For each INN, the date of LoE in the country concerned was defined as either the date at which the first product based on the INN lost patent protection (including SPC protection) or the date at which the INN seized to be protected by data exclusivity, whichever

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was the more recent in time.[1] This applied to all INNs for which this information was provided by the companies. IMS only reported a single date (month and year) for the date of LoE, but its definition of LoE is based on the same principles.[2] Finally, in a number of cases, a given INN is used for distinct medical indications and is part of several distinct ATC classes. These cases have been treated separately as the LoE and/or entry date for a given INN may differ across ATC.

The date of first generic entry was established on the basis of the first occurrence of sales by generic companies as recorded in the IMS sales dataset, combined with information provided by the companies. During the analysis, the Commission services received data corrections from a number of companies as well as additional information on the presence of SPCs and data protection. Further, in a number of cases, the Commission corrected entry dates, where they did not appear to reflect entry by independent generic companies, but rather the launch of a company's own generic product or the launch of a product by companies authorised to do so by the originator company, e.g. as part of a distribution or licence agreement.

Consumption volumes of the various formulations relating to given INNs were converted into DDD (Daily Defined Dosage) in order to compare volume measures across different formulations based on the same INN. This conversion was made using a dataset obtained from the World Health Organisation. For the small number of formulations for which this information was not available, volumes in mg were used to the extent possible for the volume analysis at INN level.

Information on the regulatory framework in the various Member States was compiled on the basis of the big report of 2006[3], the answers given by the authorities of the Member States to the Commission questionnaire of July 2008, information from the Pharma Forum, as well as other sources.[4]

[1] During the public consultation it was submitted that for the purposes of measuring delays to generic entry caused by the behaviour of originator companies, the loss of patent protection (or SPC protection) cannot be compared with the loss of data protection given that generic companies were, during the reference period 2000 - 2007, only able to submit abridged applications for marketing authorisation to the competent authorities after the moment of loss of data protection. However, the concept of time to entry is not confined to delays to generic entry caused by the behaviour of originator companies, but also comprises other factors such as the time that generic companies need for standard regulatory procedures in the country concerned (including requests relating to the pricing and reimbursement status). In any event, the number of instances (INNs and countries) in which loss of data protection came after patent expiry (including SPC protection) was 52, out of a total of 713 for which it was possible to make the comparison. It appears, therefore, that the impact of these cases is rather limited on the descriptive statistics.

[2] For a description of the determination of the LoE date by IMS, see CRA International, Factors Affecting Generic Entry in Europe, June 2008.

[3] OBIG [1]

[4] Information was coded for each year between 2000 and 2007, taking into account possible evolutions in the different regulatory systems. Nevertheless, a large majority of the variables listed is time invariant.

6.1.2 Selection of INNs

The first list of INNs selected were the 75 top-selling INNs that faced the LoE in the period 2000 - 2007 in France, Germany and the UK. In each of the three countries, this list represented well over 90% of value sales of all INNs that faced LoE in the period 2000 - 2007. The combination of the top 75 molecules in each of these countries provided a final list of 128 INNs. In this paper, this list is referred to as "E75".

The second group of INNs was chosen from the list of the 50 top-selling INNs (whether protected or not) for each of the three countries mentioned above. In total, this led to the identification of 90 INNs (of which 61 INNs were not part of the E75 list). It is referred to as "T50".

The third group of INNs was selected by choosing the 50 top-selling INNs having faced first generic entry in each of the selected countries. This led to the identification of 95 INNs (30 new INNs in comparison with the E75 and T50 lists mentioned above). Finally, the list contained a number of INNs that might be of interest in the light of other market information available to the Commission.

The combination of these three lists, with a view to obtaining a sample of INNs likely to be representative for the EU as a whole, makes up the final list of 219 INNs presented in 6.6.

The main part of the analysis was performed on the basis of the "E75" list of INNs for which the Commission requested information from the companies.

For each of the Member States, the relevant sample was defined as the national subset of the E75 list, i.e. those INNs that (i) were effectively sold in that Member State and (ii) that faced LoE in the period 2000 - 2007 in that Member State.

As the result, based on the IMS dataset, the national subsets of INNs in the various Member States contained the numbers of INNs reported in table 6.1.[5]

As is clear from the above table, there are major disparities between the subsets of molecules that were subject to analysis. This is a natural consequence of significant disparities between the national markets for pharmaceutical products in the EU.[6] [7] The differences are explained in part by the fact that the set of INNs sold in each country

[5] The dashes (-) in the table relate to the fact that the IMS dataset did not contain expiry dates for these countries.

[6] For similar observations, see Wilsdon et al. [2]. They observe that out of the 271 molecules that lost protection in the period 2000 - 2007 in one of the five largest national markets for pharmaceutical consumption in the EU (namely France, Germany, Italy, Spain, and United Kingdom), only 30 of them lost protection (in the same time frame, 2000 - 2007) in all five countries.

[7] A factor that may also have contributed to the disparities may be that IMS expiry dates were sometimes only available for some of the relevant products within the countries, not for all products.

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TABLE 6.1: Number of INNs on the E75 list relevant to each Member State

Austria	68	Germany	82	Netherlands	25*
Belgium	75	Greece	38	Poland	-
Bulgaria	-	Hungary	-	Portugal	35
Czech Republic	15	Ireland	55	Romania	-
Cyprus	-	Italy	71	Slovakia	-
Denmark	63	Latvia	-	Slovenia	-
Estonia	-	Lithuania	-	Spain	51
Finland	56	Luxembourg	-	Sweden	71
France	93	Malta	-	United Kingdom	84

* The fact that the number of expiring INNs for the Netherlands is somewhat low is related to the fact that data for the Netherlands are available only as of April 2002.

differs. Further, the differences relate to the period considered and the fact that INNs may have different LoE dates in different Member States. For a given Member State, if an INN lost exclusivity before the year 2000 or after 2007, it was excluded from the sample. Consequently, the requirements (i) and (ii) mentioned in the previous paragraph resulted in subsets of molecules that were different (in size and composition) among the various Member States.[8]

After merging company information with IMS dataset, the number of INNs that could be used for the analysis in a number of countries changed to a mild extent.[9] The merged dataset led to national subsets of INNs in the various Member States with the numbers of INNs reported in table 6.2.

Only a few INNs were available for study in Slovakia, Slovenia, Poland, Latvia, Lithuania, Estonia, Cyprus and Malta. A contributing factor to the relatively low number of observations may be that few INNs may have effectively faced LoE in the relevant period 2000 - 2007 in the countries concerned. However, a substantial number of companies appeared unable to provide comprehensive information on the patent expiry date in these countries (many entries contained "N/A"). Further, the process of merging the company data with the IMS data turned out, from a technical perspective, less successful than for the other Member States. For this reason, chapters **??** and **??** do not contain descriptive statistics for these countries.

[8]Focusing on products with the majority of their sales in the retail segment, CRA (2008) reports that the total number of products losing exclusivity in the period 2000 - 2007 was 105 in the UK, 143 in France, 114 in Germany, 106 in Spain and 141 in Italy. In each of these countries, the top 50 of the products losing exclusivity in the period 2000 - 2007 (in terms of value) accounted for over 85-90% of sales of all products losing exclusivity. CRA International, Factors Affecting Generic Entry in Europe, June 2008 (p. 23-24).

[9]In the public consultations, it was noted that the number of INNs went slightly down in some countries. It is primarily because by applying company information the LoE date was revised to a date falling outside the reference period 2000 - 2007. Further additional data cleaning led some INNs to be removed from the lists in some countries.

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TABLE 6.2: Number of INNs on the E75 list relevant to each Member State

Austria	61	Germany	75	Netherlands	25
Belgium	73	Greece	38	Poland	5
Bulgaria	14	Hungary	17	Portugal	35
Czech Republic	15	Ireland	59	Romania	11
Cyprus	-	Italy	73	Slovakia	5
Denmark	63	Latvia	3	Slovenia	6
Estonia	1	Lithuania	4	Spain	56
Finland	48	Luxembourg	41	Sweden	76
France	91	Malta	-	United Kingdom	83

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The number of available observations (INNs) for Romania and Bulgaria, who became Member States in 2007, is also small. Further, there were data issues in the information provided for these countries. For this reason, chapters **??** and **??** do not contain descriptive statistics for these two countries.

Correspondingly, the analysis was based on 17 countries, i.e. all EU Member States with the exception of Slovakia, Slovenia, Poland, Latvia, Lithuania, Estonia, Cyprus, Malta, Romania and Bulgaria.

The various types of analysis further differed in terms of data requirements. The regression analyses involved the simultaneous use of price data, volume data (in DDD), dates (date of LoE, entry date) and qualitative information (product characteristics, characteristics of the regulatory environment). For six INNs, such comprehensive information was not available and therefore they were not used for the regression analysis.

Ultimately, the principal dataset used for the regression analyses was based on 1085 observations in total (cross-sectional, by country-INN-ATC4), relating to 17 countries, 122 INNs and 924 country-INN pairs.

The analysis of substitution within ATC4 classes presented in chapter **??** was performed on the data available in 9 countries (Denmark, France, Germany, Greece, Hungary, Italy, the Netherlands, Spain and the United Kingdom), i.e. all countries for which information on ATC4 classes was obtained from IMS with the exception of Poland.

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6.2 Methodology for data management

6.2.1 Measures Analysed

All EU descriptive statistics (entry rates, market shares, price indices, etc.) presented are calculated taking into account the relative importance of the individual Member States as measured by the sales of the relevant INNs in the Member State concerned, either in the year prior to expiry (for establishing shares of generic entry, average time to entry and generic penetration) or in the year 2007 (for the indices that track the development of prices or volumes over longer time periods).

The rate used for the conversion of exchange rates is the average exchange rate in the year 2007.[10]

Descriptive statistics on the impact of generic entry are mostly presented both as a "head count" measure (where within each country each INN is counted as equal) and as a weighted measure (where within each country each INN receives a weight to account for its relative importance).[11] Two types of weights are used for the latter purpose, depending on the context. For the purposes of establishing shares of generic entry, average time to entry and generic penetration, the weight is the sales value of an INN in the year before the LoE. This weight is constant over time. By contrast, for the indices that track the development of prices over longer time periods, the weight used is the contemporary value sales of each INN sold in the month concerned. The use of contemporary weights (as opposed to constant weights, e.g. related to a fixed year) avoids problems one might encounter in relation to months where a given product is in fact non-available. The same approach is used for tracking volume indices over time.

When descriptive statistics were given by size class, the following approach was used. First, the 128 INNs on the E75 list were divided into five classes, with class one referring to the 20% of lowest-selling INNs in terms of EU sales value in 2007, class two to the next lowest 20%, etc. Class five thus refers to the 20% of highest-selling INNs onthe E75 list. Then, for each INN, the relevant statistic in each country was obtained and weighted using country weights. Finally, within each size class, the weighted average was taken over all INNs in that class.

[10] For consistency, prices and values in the dataset were expressed in Euro terms for all countries. In order to properly identify developments in local currency prices and values in a given country over time, it was decided to apply a fixed conversion rate (relating to 2007), not contemporaneous, fluctuating rates.

[11] As mentioned above, in a number of cases, INNs are used for distinct medical indications and are part of several distinct ATC classes. These cases have been treated separately as the LoE and/or entrydate for a given INN may differ across ATC, except in the case of headcount measures (as the importance of individual INNs would be inflated when it is part of multiple ATC classes).

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For the average price indices, the index level is set to 1 (i.e. unity) six months prior to the end of the exclusivity period. The benchmark was taken 6 months prior to the end of the exclusivity period instead of at the very moment exclusivity ended in order not to let incidental price cuts or small errors in the date of expiry influence the benchmark price level.

The same approach is used for the volume indices.

6.2.2 Treatment of Early Entries

The measurement of time to entry was complicated by the fact that in the IMS dataset there was a number of instances, where generic products appeared to have entered before the LoE of the INN in the country concerned. For those INNs, for which the entry date appeared to be just preceding the LoE, the small time gap can be interpreted as a measurement error. The INNs with a longer time gap are more difficult to interpret. These instances may relate to cases where the companies made a mistake when providing the date of LoE, where the IMS dataset records the date incorrectly or where there was an "early" entry by a generic firm, i.e. entry before the reported date of LoE.

The accuracy of the entry dates was improved using information on independent generic entry from the companies. Whenever the originator company indicated a later date for the first independent entry than the presumed entry date on the basis of IMS data, this later date was used as the date of the first independent generic entry.

Where the dates continued to point to early entry, the observations were further compared witha dataset prepared by CRA and IMS in the course of the sector inquiry.[12] Where this dataset gave a more plausible date of LoE and/or entrydate, this date was used. Where the INN was not considered as expiring in the country concerned in the period 2000- 2007, the country-INN pair was dropped from the analysis. For the still remaining cases with negative time to entry, the following procedure was used.

Where the negative time to entry was less than or equal to three months ("small negatives"), the time to entry was taken to be zero, on the basis that these cases may represent a small measurement error. This related to 55 cases (country-INN pairs).

Where the negative time to entry was more than three months ("substantial negative"), the time to entry was also put to zero. This related to 39 cases (country-INN pairs). In view of the limited number of cases, such treatment of these observations is not per se problematic for the analysis, but its correctness depends on certain assumptions. For

[12] Dataset used in Wilsdon et al. [3]

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the so-called controlled entries (e.g. companies entering via distribution agreement or license), it would have to be assumed that these entrants turn effectively independent at the LoE (because they are no longer restricted by patents), which is not necessarily the case. In cases of "early entry" due to an incorrectly specified LoE date, it is not clear whether entry really took place early (i.e. before the date of LoE), took place at the first moment the opportunity arose (i.e. at LoE), or took place later (i.e. after the real moment of LoE). For the purpose of obtaining conservative estimates and not overstating the time to entry for generic companies, it was preferred to interpret that entry took place at the first moment the opportunity arose (i.e. at the LoE).

In the regression analysis, the cases involving "substantial negative" time to entry were flagged (using dummies) and analysed further. Further robustness checks suggest that the results are insensitive to the method used.

Information on company agreements further shed light on some of the remaining substantial negatives. A number of supply/distribution and settlement agreements whereby originator companies allowed early entry to a generic company were used to interpret significant negative delays. These cases, 20 in total, were interpreted as a form of controlled entry. In the subsequent regression analyses, they have been specifically flagged with a dummy variable. The above procedures for treating early entries were tested for robustness (both as regards the descriptive statistics and the regression results). Checking the robustness of the results vis-à- vis the above handling of early entries was done by

- running the regression analysis both with and without the observations with the negative time to entry;
- changing the number of months above which an entry is regarded as substantial negative time to entry (e.g. taking 6 months as a threshold) and running the analysis without country-INN pairs exhibiting a relatively substantial negative time to entry;
- using a dummy variable to indicate whether or not the country-INN pair is a substantial negative time to entry.

These tests confirmed the robustness of the results towards the applied procedures.

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6.3 Variables used in the regression analysis

TABLE 6.3: INN characteristics used in the regression analysis (control variables)

preexp_value per capita	Value sales per capita (EUR) of the INN six months before patent expiry (per country)
lnpreexp_value	(idem natural log)
preexp_price	Average price (EUR) per DDD of the INN six months before patent expiry (per country)
expiry_year	Year of loss of exclusivity (per country)
exp_02_03	Loss of exclusivityin 2002 or 2003 (dummy variable, per country)
exp_04_05	Loss of exclusivity in 2004 or 2005 (dummy variable, per country)
exp_06_07	Loss of exclusivity in 2006 or 2007 (dummy variable, per country)
pre_exp_numform	Number of formulations available at the moment of patent expiry in the country
main_chron	Indicates whether INN is used mainly for chronic indications (dummy variable)
biosimilar	Indicates if INN is a biosimilar (dummy variable)
ngenr	Number of generic companies
ngenr2	(idem -squared)
gen_age	Number of months that generic companies were present in the INN (up to 12.2007)
gen_age2	(idem -squared)

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TABLE 6.4: Regulatory Variables Used in the Regression Analysis

price_caps	Indicates existence of a price cap or mandatory discounts for generic products (dummy variable, by year). The variable equals 1 if generic companies, when they enter, have to respect a maximum price level or have to price a certain percentage or amount lower than e.g. the price charged by the originator at the time of entry.
freq_adjust	Indicates whether there is frequent adjustment (e.g. once every 6 months) of maximum reimbursement prices.
physicians_encourage_gen	Indicates whether physicians are required or encouraged to prescribe an INN, rather than a specific brand (by budget restrictions or budget incentives).
compulsory_substit	Indicates whether pharmacies are obliged to dispense generic products when these are available and less expensive (compulsory substitution).
diff_copay	Indicates whether patients need to pay the difference between the price of the product purchased and the reference price.
lowest_price_policy	Indicates whether the reimbursement level, at whatever point it is fixed, is set at the price level of the cheapest generic available on the market.

TABLE 6.5: Other Control Variables Used in the Regression Analysis

controlled_entry	Indicates whether there has been controlled generic entry (e.g. through an early distribution agreement, license agreement or settlement agreement
neg_delay	Indicates whether the implied time to entry is negative
neg_delay3	
large_neg3	Indicates whether the implied time to entry is negative by more than 3 months
small_neg3	Indicates whether the implied time to entry is negative, but less than 3 months
population	Population of the country
n_countries_expired	Number of other countries in which the INN had already lost exclusivity at the time of LoE.

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6.4 List of INNs

Table 6.6: List of the 219 INN's included in the data set

ACARBOSE *	ADALIMUMAB	ADRAFINIL
ALENDRONIC ACID *	ALFUZOSIN *	AMISULPRIDE *
AMITRIPTYLINE	AMLODIPINE *	AMOROLFINE *
AMOXICILLIN + CLAVULANIC ACID *	AMOXICILLIN + LANSOPRAZOLE + CLARITHROMYCIN *	ANASTROZOLE
ATENOLOL	ATORVASTATIN	AZITHROMYCIN *
BALSALAZIDE *	BECLOMETASONE	BENAZEPRIL *
BISOPROLOL *	BRIMONIDINE *	BRIVUDINE *
BUDESONIDE *	BUDESONIDE + FORMOTEROL	BUFLOMEDIL
BUPRENORPHINE	BUSERELIN *	CABERGOLINE *
CALCIPOTRIOL *	CALCIPOTRIOL + BETAMETHASONE *	CANDESARTAN CILEXETIL
CANDESARTAN CILEXETIL + HYDROCHLOROTHIAZIDE	CAPSAICIN	CAPTOPRIL + HYDROCHLOROTHIAZIDE *
CARTEOLOL *	CARVEDILOL *	CEFATRIZINE *
CEFIXIME *	CEFPODOXIME PROXETIL *	CEFTIBUTEN *
CEFTRIAXONE *	CEFUROXIME AXETIL *	CELECOXIB
CELIPROLOL *	CETIRIZINE *	CICLETANINE *
CICLOSPORIN *	CIPROFIBRATE *	CIPROFLOXACIN *
CISAPRIDE *	CITALOPRAM *	CLARITHROMYCIN *
CLODRONIC ACID	CLOPIDOGREL	CROMOGLICIC ACID + REPROTEROL *
CYPROTERONE + ETHINYLESTRADIOL	DALTEPARIN SODIUM *	DARBEPOETIN ALFA
DESOGESTREL + ETHINYLESTRADIOL *	DIACEREIN *	DICLOFENAC
DIENOGEST + ETHINYLESTRADIOL *	DOMPERIDONE *	DONEPEZIL
DOXAZOSIN *	EBASTINE *	ENALAPRIL *
ENOXAPARIN SODIUM	EPOETIN ALFA *	EPOETIN BETA
ESOMEPRAZOLE	ESTRADIOL *	ESTRADIOL + NORETHISTERONE *
ETANERCEPT	ETHINYLESTRADIOL + GESTODENE *	ETIDRONIC ACID *
ETODOLAC	EZETIMIBE	FELODIPINE *
FENOFIBRATE	FENTANYL *	FEXOFENADINE *
FINASTERIDE *	FLECAINIDE	FLUCONAZOLE *
FLUOXETINE *	FLUPIRTINE *	FLUTICASONE *
FORMOTEROL	FOSFOMYCIN TROMETAMOL *	FOSINOPRIL *
GABAPENTIN *	GALANTAMINE	GLATIRAMER ACETATE
GLIMEPIRIDE *	GOSERELIN *	HYDROCHLOROTHIAZIDE + BENAZEPRIL *
HYDROCHLOROTHIAZIDE + BISOPROLOL *	HYDROCHLOROTHIAZIDE + ENALAPRIL *	HYDROCHLOROTHIAZIDE + IRBESARTAN
HYDROCHLOROTHIAZIDE + LISINOPRIL *	HYDROCHLOROTHIAZIDE + RAMIPRIL *	HYDROMORPHONE *
IBANDRONIC ACID	ILOPROST *	IMATINIB
INFLIXIMAB	INSULIN ASPART	INSULIN GLARGINE

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INSULIN HUMAN BASE	INSULIN HUMAN BASE + INSULIN HUMAN ISOPHANE	INSULIN HUMAN ISOPHANE
INTERFERON BETA-1A	INTERFERON BETA-1B	IPRATROPIUM BROMIDE + SALBUTAMOL *
IRBESARTAN	ISOTRETINOIN	ITRACONAZOLE *
LACIDIPINE *	LAMOTRIGINE *	LANSOPRAZOLE *
LETROZOLE	LEUPRORELIN *	LISINOPRIL *
LORATADINE *	LOSARTAN	LOSARTAN + HYDROCHLOROTHIAZIDE
LOVASTATIN *	MELOXICAM *	METHYLPHENIDATE
METOCLOPRAMIDE + ACETYLSALICYLIC ACID	METOPROLOL	METRONIDAZOLE *
MIRTAZAPINE *	MODAFINIL *	MOMETASONE *
MONTELUKAST	MOXIFLOXACIN	MOXONIDINE *
NADOXOLOL	NADROPARIN CALCIUM *	NEDOCROMIL *
NICARDIPINE *	NICORANDIL *	NIFEDIPINE
NIZATIDINE *	NOMEGESTROL *	NORFLOXACIN *
NORGESTIMATE + ETHINYLESTRADIOL *	OCTREOTIDE *	OFLOXACIN *
OLANZAPINE	OMEPRAZOLE *	ONDANSETRON *
OXALIPLATIN *	PACLITAXEL *	PANTOPRAZOLE
PAROXETINE *	PEGFILGRASTIM	PERGOLIDE *
PERINDOPRIL *	PERINDOPRIL + INDAPAMIDE *	PIOGLITAZONE
PIROXICAM BETADEX *	PRAMIPEXOLE	PRAVASTATIN *
PRAVASTATIN + ACETYLSALICYLIC ACID *	PREGABALIN	QUETIAPINE
QUINAPRIL *	QUINAPRIL + HYDROCHLOROTHIAZIDE *	RABEPRAZOLE
RAMIPRIL *	RANITIDINE	RIBAVIRIN
RILMENIDINE *	RISEDRONIC ACID	RISPERIDONE *
ROFECOXIB	ROSIGLITAZONE	ROSUVASTATIN
ROXITHROMYCIN *	SALBUTAMOL	SALMETEROL *
SALMETEROL + FLUTICASONE	SERTRALINE *	SILDENAFIL
SIMVASTATIN *	SIMVASTATIN + EZETIMIBE	SOMATROPIN *
SUMATRIPTAN *	TAMSULOSIN *	TELMISARTAN
TERBINAFINE *	TESTOSTERONE *	TIAGABINE
TIBOLONE *	TILIDINE + NALOXONE	TINZAPARIN *
TIOTROPIUM BROMIDE	TIZANIDINE	TORASEMIDE *
TRAMADOL	TRAMADOL + PARACETAMOL	TRAZODONE
TRIPTORELIN *	VACCINE, HEPATITIS B	VACCINE, HEPATITIS B + VACCINE, ACEL.PERT.DIP.TET. POLIO + HIB
VACCINE, HEPATITIS B + VACCINE, DIP.TET.PERT.POLIO + HIB.	VACCINE, INFLUENZA	VACCINE, PNEUMOCOCCAL
VACCINE, PNEUMOCOCCAL CONJUGATE	VACCINE, TICK BORNE ENCEPHALITIS	VALACICLOVIR
VALPROATE SEMISODIUM *	VALSARTAN	VALSARTAN + HYDROCHLOROTHIAZIDE

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VENLAFAXINE	VIGABATRIN *	ZOLPIDEM *

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