The London School of Economics and Political Science

Studies in Pricing and Competition in Regulated Pharmaceutical Markets

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A thesis submitted to the Department of Social Policy of the London School of Economics for the degree of Doctor of Philosophy, London, July 2010

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Declaration

I certify that the thesis I have presented for examination for the PhD degree of the London School of Economics and Political Science is solely my own work other than where I have clearly indicated that it is the work of others (in which case the extent of any work carried out jointly by me and any other person is clearly identified in it).

Abstract

This PhD thesis studies three aspects of competition in pharmaceutical markets using data from the EU, and recommends appropriate policies to address inefficiencies.

The first study examines the effect of patent expiry on originator drug prices in the presence of price regulation. Using econometric panel data methods, I find that neither generic entry nor generic market penetration affect the prices of originator drugs downwards. Instead, prices of originator drugs often appear to increase post-generic entry. Findings suggest that no savings to health services should be expected post-patent expiry if the originator product is dispensed, and any savings occur solely from generic uptake.

The second study examines whether generic entry leads to a switch in total consumption (both originator and generic) from an off-patent branded molecule to a different in-patent molecule of the same therapeutic class. Using panel data analysis, I find that a switch in consumption post-patent expiry took place for the first ACE inhibitor which went off-patent, and in some cases for the second and third product. Such a switch leads to increased costs because it removes any substitution power from health authorities.

The third study examines the effects of parallel trade on price competition. The topic is first approached from a game-theoretic point of view, predicting that parallel trade does not trigger price competition. Descriptive statistics demonstrate differences, if any, between prices of locally sourced and parallel traded products in the presence of different regulatory policies. Finally, the econometric analysis shows that there is upward price convergence in the presence of parallel trade. However,

some regulatory interventions may lead to a spread between prices of locally sourced products and parallel traded products. Findings suggest that parallel trade should not always be considered a cost-containment mechanism and other ways to address rising pharmaceutical expenditures should be considered.

Acknowledgements

I am grateful to my formidable supervisors, Dr Panos Kanavos and Professor Alistair McGuire for their guidance throughout the pursuit of my doctoral work. Both contributed generously, and above all conscientiously, to all aspects of my research. Their continuous support and encouragement were indispensable during the entire process.

I would also like to thank my wonderful family for their immense help and support. In particular, I am grateful to my parents Theodora and Dimitris, and my sisters Angela, Christina and Markella.

Recognition must be given to the London School of Economics and Political Science for backing me with a scholarship.

Thanks are also due to Professor Elias Mossialos, Professor Julian Le Grand, Katherine Carman, Chris Muris, Georgina Blanco-Mancilla, Pedro Raposo, Miguel Carvalho, Peter Muris, Geraldo Cerqueiro, Irene Papanicolas and Pedro Bom for useful comments and suggestions. I greatly appreciate Peter van der Windt's and Tania Teixeira's moral support during the early stages of my doctoral studies. Last but not least, I would like to thank my officemate (and good friend) Lucia Kossarova for sharing the office and the fascinating experience of pursuing a PhD.

London, July 2010

Thesis Structure

This thesis follows the 3-paper format, as approved by the Department of Social Policy for dissertations in economics-related topics. The papers have to be thematically linked and tied together with an introduction and a conclusion.

The introduction consists of chapters 1, 2 and 3. The three papers of the thesis are chapters 4, 5 and 6, while chapter 7 concludes.

The second paper (switching effects post patent expiry) is single authored. The first and the third paper (the generics paradox revisited and the impact of parallel trade on competition) are primarily authored by the author of this PhD thesis and co-authored by Panos Kanavos, who provided the datasets, approved the methodology and critically reviewed the studies. Panos Kanavos also provided background information on legal issues surrounding parallel trade.

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List of Abbreviations

AAP:	Atypical Antipsychotics
ACE I:	Angiotensin-converting enzyme inhibitors
CBO:	Congressional Budget Office
CBT:	Cross - Border Trade
CEA:	Cost Effectiveness Analysis
DDD:	Daily Defined Dosage
DoH:	Department of Health
DK:	Danish Krone
ECJ:	European Court of Justice
EFPIA:	European Federation of Pharmaceutical Industries and Associations
EGA:	European Generics Association
EMEA:	European Agency for the Evaluation of Medicinal Products
EU:	European Union
GDP:	Gross Domestic Product
HAS:	Haute Authorite de Sante
HFA:	Health For All
IPR:	Intellectual Property Rights
IMS:	Intercontinental Medical Statistics
INN:	International Nonproprietary Name
NHS:	National Health Service
NICE:	National Institute for Health and Clinical Excellence
OBIG:	Osterreichisches Bundesistitut fur Gesundheitswesen
OECD:	Organisation for Economic Co-operation and Development
OFT:	Office of Fair Trading
OTC:	Over-The-Counter
PHRMA:	Pharmaceutical Research and Manufacturers of America
PI:	Parallel Importer
PPI:	Proton Pump Inhibitors
PPRI:	Pharmaceutical Pricing and Reimbursement Information
PPRS:	Pharmaceutical Price Regulation Scheme
PT:	Parallel Trade
R&D:	Research and Development

SE:	Standard Error
SEK:	Swedish Krona
SNRI:	Serotonin Norepinephrine Reuptake Inhibitor
SSRI:	Selective Serotonin Reuptake Inhibitor
TRIPS:	Trade-Related Aspects of Intellectual Property Rights
UK:	The United Kingdom
USA:	The United States of America
USD:	United States Dollar
WHO:	World Health Organization
WTO:	World Trade Organization

1. Background and Motivation

1.1 Background

Poor health affects people's lives and decreases their utility directly, but also from a financial perspective, addressing health problems accounts for a significant proportion of GDP in OECD countries[1] (OECD Health Data 2009). In the context of their contribution to wealth and to overall health spending, pharmaceuticals play an important part in treatment of illnesses and their cost is a large part of health spending. In addition, pharmaceutical spending per capita has been constantly rising in OECD countries, making the analysis of these markets an important component in understanding efficiency and assessing what works in pharmaceutical policy and what does not.

Analyzing pharmaceutical markets is not straightforward. Pharmaceutical markets involve patients, physicians who act on patients' behalf, pharmaceutical manufacturers, regulators, payers and (wholesale and retail) distributors among others[2]. The multiplicity of agents involved in the health care decision making makes the problem of understanding the drivers of pharmaceutical spending and the pursuit of efficiency a complex one.

The extent of regulation in pharmaceutical markets is not the same across European countries. Different regulatory measures apply to different health systems, and the combination of various policies makes it difficult to isolate the separate effects of each measure. Interventions apply both on the supply side, through direct or indirect controls of prices, and on the supply side, by diverting consumption

[1] These data are discussed in section 1.2

[2] In addition, other stakeholders may be involved, e.g. ministries of trade, industry, or, even, education.

towards more cost-effective and efficient treatments. Insurers are seeking to cost contain and use resources optimally, while manufacturers are profit maximizers. Consequently, the market equilibrium depends heavily upon the nature and extent of intervention. However, assessment of the effects of various pharmaceutical policies remains scarce. Kanavos et al (2004) underline the importance of improving methodological issues before reaching definitive policy recommendations as use of inappropriate methodology may undermine the validity and reliability of any results.

1.2 Motivation

1.2.1 The special Nature of Pharmaceutical Markets

Pharmaceutical markets differ from other types of markets and indeed present a number of peculiarities making the pharmaceutical market a special market (Mossialos et al, 1994). Prescribing doctors are often unaware of or not interested in prices of prescription medicines, unless they are affected by them through explicit financial or non-financial incentives. In addition, the market position of originator manufacturers is usually monopolistic due to intellectual property rights protection and can also result in them often retaining a large share of the market, even after generic entry. Patients have less information than their agents (the physicians). Patients seek advice from their physician and usually follow the treatment that is prescribed frequently without questioning the physician's decision, due to lack of relevant medical knowledge. This often creates room for possible physician-induced demand. Given the presence of moral hazard, due to third party payment, this phenomenon can possibly become even more intense.

A very important characteristic of the pharmaceutical market, predominantly in insurance-dominated markets, is the fact that the consumer of a pharmaceutical product and the payer are different agents. This occurs because most individuals are insured and have prescription medicines reimbursed either totally or partly[3]. This has two important implications: First, in this market where consumers and payers are different agents, moral hazard issues arise. Second, the consumer has a very low elasticity of demand with respect to price, which various studies have estimated to be between 0 and -0.3 (Gemmill et al. 2007, Grootendorst et al. 1997, Leibowitz et al. 1985, Johnson et al. 1997, Gardner et al. 1997, Hughes and McGuire 1995, Lavers 1989, O'Brien 1989, Ryan and Birch 1991, Smith and Watson 1990, Contoyannis et al. 2005). This suggests that the price of prescription medicines has, at best, a small effect on consumers' purchasing decisions, particularly if large co-payments are involved. In the absence of regulation, pharmaceutical producers would be setting the monopoly price.

Prescription medicines are fully or partially covered by health insurance in most EU countries (PPRI 2007). At individual level, in the presence of health insurance and with low or no co- payments, consumers have no incentive to limit their consumption. While individual consumers care little about the prices of prescription medicines, at aggregate level the behaviour of all consumers together may cause an upward shift to premiums due to increased medical costs that insurers have to pay out of pocket. Thus, the elasticity of demand remains low, which leads to high prices in the pharmaceutical market and the insurance market.

Patents (and other intellectual property rights, such as copyrights, market exclusivity periods and patent extension terms) play an important role in this market.

[3] Health insurance is a feature in most developed countries, but is largely absent from a large number of middle- and low-income countries or/and significant sections of the population therein.

The granting of patents provides a commercial monopoly to right holders. Patent protection though does, in principle, provide right holders with the incentive to invest in research and development, as a monopolist's price and quantity, hence also profits, are higher for a monopolist than in the presence of competitors (Mas-Colell, Whinston and Green 1995).The real amount spent on R&D over the 1980-2002 period rose by an average rate of 8% per year (Aaron 2003). In 2007, $47.9 billion was spent by U.S. pharmaceutical companies on research and development of new pharmaceutical products (PhRMA 2009), while for the same year the expenditure on R&D in Europe was €26 billion (EFPIA 2010). In the absence of patent protection, little research would be done, as the innovator would be burdened by the large cost of R&D but would almost immediately face competition by generic producers who would not be subject to R&D costs.

Patent protection leaves a player in the market alone for 20 years, according to the WTO TRIPS (Trade-Related Aspects of Intellectual Property Rights) agreement (WTO-OMC TRIPS fact sheet, 2006). However, the effective patent protection period is less than 20 years. Overall, patents keep competitors out of the market and prices higher than in competitive markets during the patent protection period. On the supply-side, pharmaceutical producers are profit maximizers. Consequently, during the patent protection period and in the absence of regulation, pharmaceutical manufacturers can act as monopolists, the outcome being higher prices and lower quantities than the social optimum and therefore a decrease in social welfare (Mas-Colell, Whinston and Green 1995). In order to underwrite the latter, there is increased political pressure to exercise control on prices and, indirectly, on profits of the pharmaceutical sector.

Regulation is introduced, among other things, to control prices, which could be very high in the presence of inelastic demand and monopoly power. Markets are regulated[4] due to the absence of the normal forces of competition and because medicines are paid for in part out of public expenditure. (Mossialos et al 1994, 2004).

Regulation distorts markets though, because it moves the market equilibrium away from the level at which the market clears. As a result, the pharmaceutical market still behaves in a different way than regular free markets. All these factors (low price elasticity and monopoly power, regulation, health insurance and third party payers) move the pharmaceutical market away from what is known in economic theory as a competitive market (Mas – Colell, Whinston, Green 1995).

1.2.2 The Challenge of Increasing Health and Pharmaceutical Costs

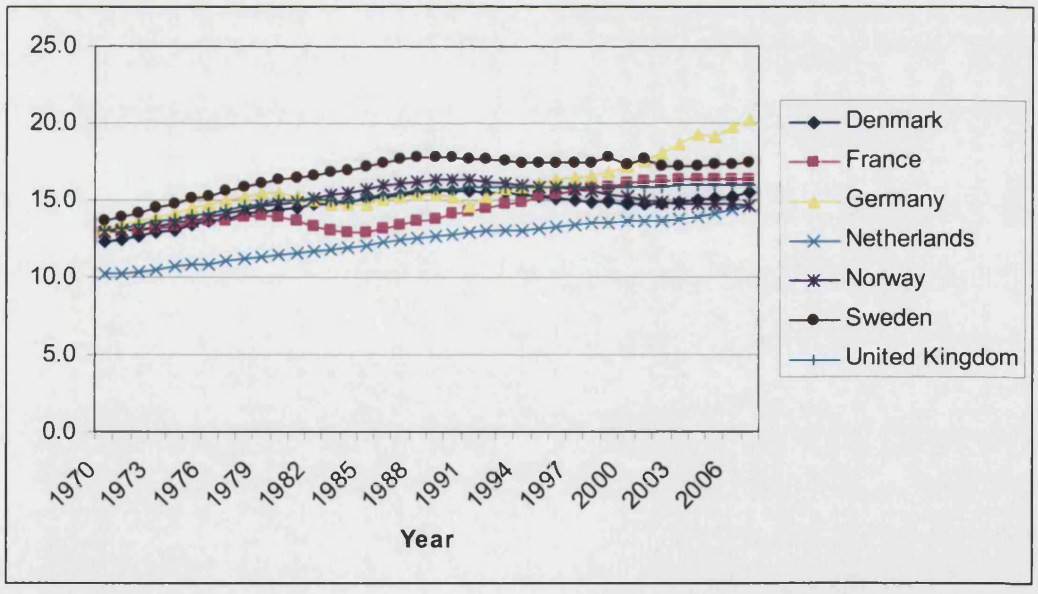
The motivation for this thesis stems from the challenging health care environment in OECD countries and the contribution of pharmaceuticals to that environment. Key trends include the increase in population over 65 years of age as a percentage of total population, an increase in health expenditure both as a percentage of GDP and as total expenditure per capita, and an increase in total pharmaceutical expenditure per capita (OECD Health Data, 2009).

Despite price and other regulation, pharmaceutical expenditure has been rising (OECD Health Data, 2009), causing many concerns about sustainability. This underlines the fact that supply - side regulation is only in part effective in addressing this problem, so demand - side measures may also be needed.

[4] Regulation in the pharmaceutical market focuses largely on prices, by intervening in the supply side. However, demand side measures (such as generic substitution and regressive pharmacy markups) also apply, in an effort to achieve more efficient spending.

Population in Europe is ageing. As shown in Figure 1.1, the percentage of people over 65 years old as a fraction of the total population has been increasing steadily across Europe since the early 1970s. In the United Kingdom, this figure increased from 13% to 16% in 37 years, from 1970 to 2007. In Germany, this increase was even steeper, from 13.2% to 20.2%. Similar increases in the over 65 ratio appear in the Netherlands (from 10.2% to 14.6%), France (from 12.9% to 16.4%), Denmark (from 12.3% to 15.5%), Sweden (from 13.7% to 17.4%) and Norway (from 12.9% to 14.6%) (OECD Health Data 2009). Ageing populations burden health budgets and lead to increasing costs due to increased demand for health care arising from chronic illnesses (Heller 2004).

Figure 1.1 Population: 65 years old and over, % of total population



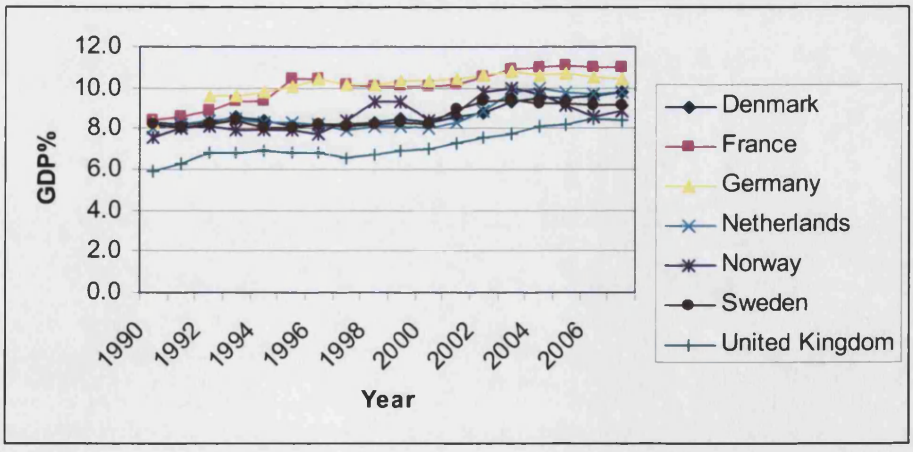
Source: *OECD Health Data 2009, November 2009*

Total expenditure on health as a percentage of GDP, which demonstrates a significant rise across Europe over the 1990 – 2007 period, is shown in Figure 1.2.

Health expenditure increased from 5.9% of GDP to 8.4% in 17 years (1990- 2007). In France expenditure increased from 8.4% to 11% and in Germany from 8.3% to 10.4%. Similar developments are observed in Denmark (from 8.3% to 9.8%), Sweden (from 8.2% to 9.1%), Norway (from 7.6% to 8.9%) and the Netherlands (from 8% to 9.8%) (OECD Health Data 2009).

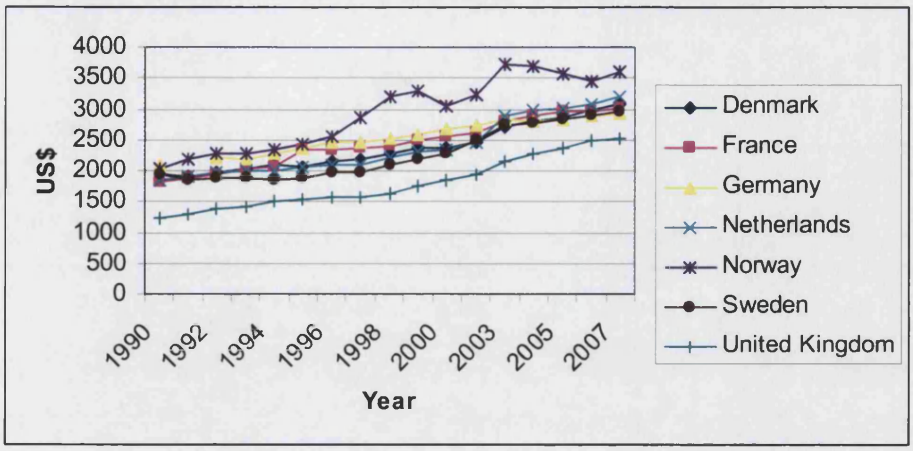
Total per capita expenditure on health has been increasing steadily in real terms in the European Union since the early 1990s (Figure 1.3). In the United Kingdom, total per capita health expenditure doubled over 17 years, as it increased from US$1,228 (PPP) in 1990 to US$2,529 (PPP) in 2008. Over the same period, expenditure increased in Germany from US$2,091 to US$2,936 (PPP). In France, expenditure rose from US$1,813 to US$3,010 per capita. Health expenditure also increased steadily in Denmark, Sweden, Norway and the Netherlands over the same period(OECD Health Data 2009).

Figure 1.2 Total expenditure on health, % gross domestic product



Source: *OECD Health Data 2009, November 2009*

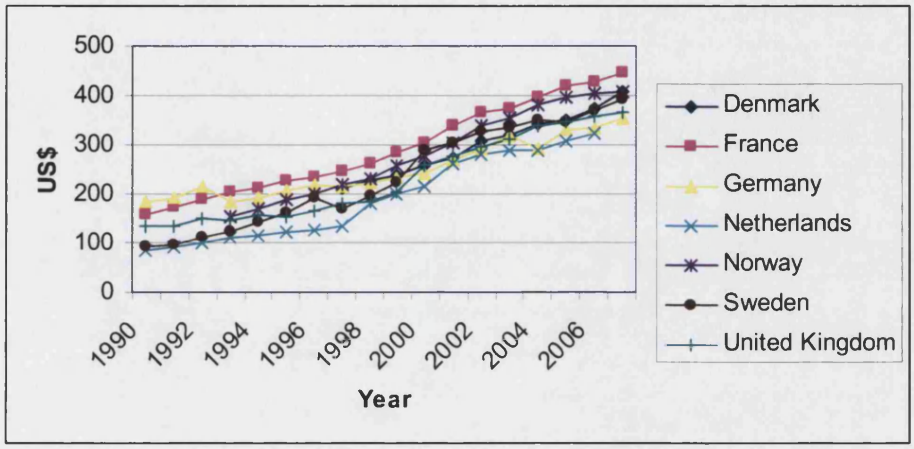
Figure 1.3 Total expenditure on health, /capita, US$ at 2000 PPP rates



Source: *OECD Health Data 2009, November 2009*

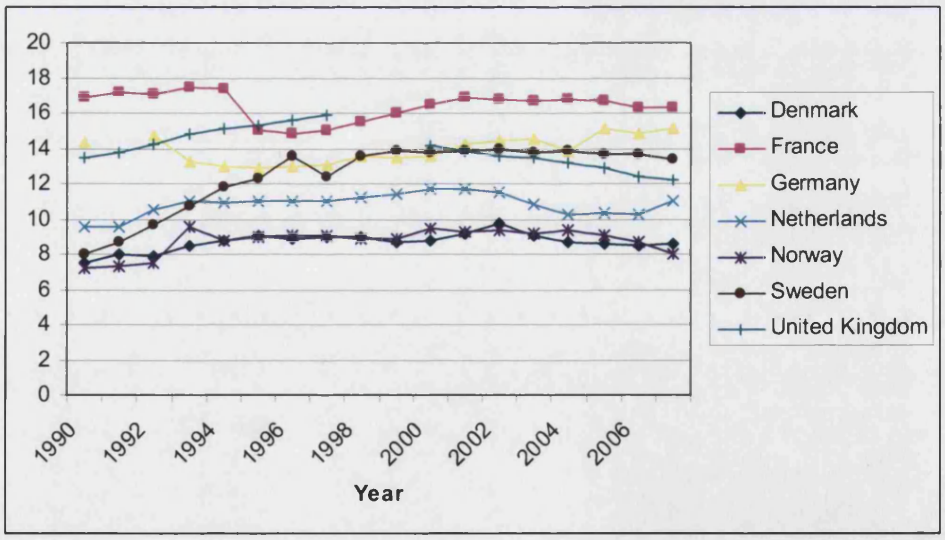
Per capita pharmaceutical expenditures have been rising steeply in Europe. In just 17 years (1990-2007) per capita pharmaceutical expenditure rose from US$134 (PPP) to US$365 (PPP) in the United Kingdom, from US$159 (PPP) to US$448 (PPP) in France, from US$184 (PPP) to US$352 (PPP) in Germany and from US$92 (PPP) to US$ 393 (PPP) in Sweden (Figure 1.4). Nevertheless, pharmaceutical expenditure as a percentage of total health expenditure has not had a particular trend in Europe and seems to be relatively stationary (Figure 1.5). This has varied between 7% and 20% of total health expenditure across all countries included in the study. France demonstrates the highest proportion, ranging from 17% in 1990 to 16% in 2007, and Norway demonstrates the lowest proportion, ranging from 7% in 1990 to 8% in 2007. Figures in all other countries are within this range (WHO HFA 2010). Faced with the challenge of increasing health costs, in some cases decentralization has been selected as a possible route towards more efficiency in the health care sector. However, the problem of coordination may still remain (Lopez-Casasnovas 2002).

Figure 1.4 Total pharmaceutical spending per capita, US$ purchasing power parity



Source: *OECD Health Data 2009, November 2009*

Figure 1.5 Total Pharmaceutical Expenditure as % of Total Health Expenditure



Source: *WHO/Europe, European HFA Database, January 2010*

1.2.3 Optimal Use of Resources

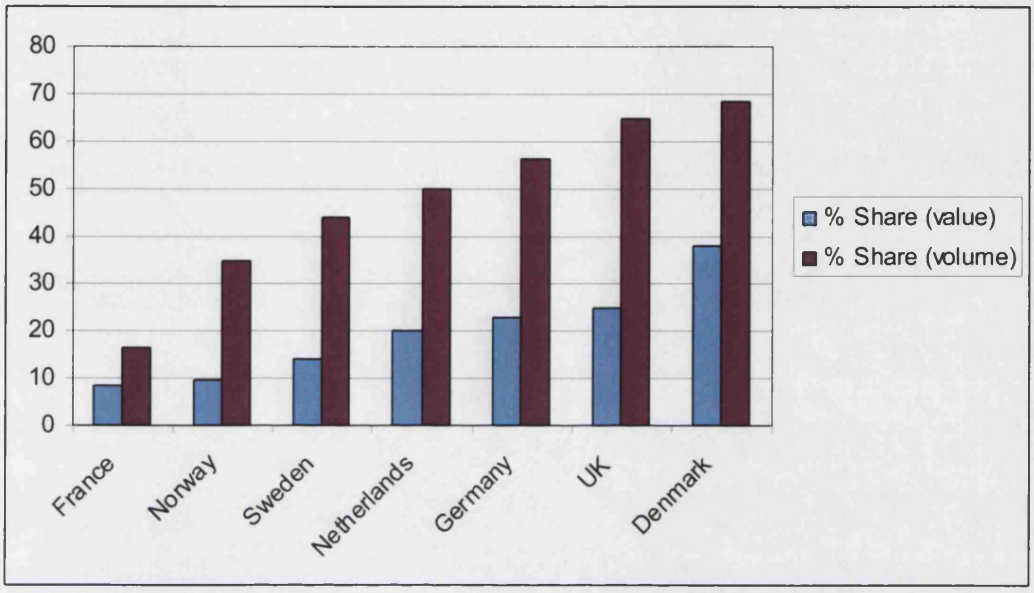
An important source of savings for health insurance is generic medicines, as they are significantly cheaper than originators. Their clinical efficacy is the same as that of originators (thus a bioequivalent), making them more cost effective. Therefore, every monetary unit spent on generics is used in a more efficient way compared to if it was spent on originators, due to the price difference. Hence the importance of generic market shares in achieving greater efficiency in the use of resources. The price difference between originators and generics – ranging from marginal to very large depending on the setting - is a result of either free market dynamics (in countries where generic prices are not regulated) or of explicit price regulation, where this is present.

Generic policies are introduced, both from the demand and the supply side, in order to encourage generic use, and through that, achieve more optimal use of pharmaceutical budgets. The pharmaceutical market in the EU in 2005 and 2006 accounted for US$138.6 billion, while the generic market in the same group of countries was US$31.1 billion (EGA 2007). Evidence from the literature suggests that the average generic penetration for a sample of 12 high selling products up to three years after first generic entry in the United Kingdom is 55%, while the potential maximum generic market share is 95%; generic uptake appears to be less swift in Germany and France, where generic penetration for the first three years is 45% and 10-20% respectively (Kanavos 2008). The average price difference between branded and generic price for the same sample of medicines was 80% in the United Kingdom, between 30 and 40% in France and between 25 and 40% in Germany.

In the United Kingdom, the market shares of generics by value rose from 8.6% in 1994 to 20.1% in 2004 (Simoens and Coster 2006). In Germany, generic volume as a fraction of the maximum potential volume of generic volume increased from 60% in 1992 to 75% in 2003 (Busse and Riesberg, 2004). This indicates that there is still space for further savings from generic prescribing and dispensing.

Total generic market shares in Europe, both in terms of value and volume, can be found in Figure 1.6. In the United Kingdom, market share in volume exceeds 60%, while in value it is just above 20%, reflecting the significant price gap between generics and originators. In the Netherlands, generics have half the market in terms of volume, and a fifth in terms of value. Generics account for almost 60% of the market volume and just over a fifth of market value. Generic penetration is low but increasing in France compared with the UK or Germany. The volume is less than a fifth of the whole market and the value does not exceed 10% (EGA 2007).

Figure 1.6 Generic Market Shares, 2006



Source: *Adapted from EGA, 2007.*

1.2.4 Regulating Pharmaceutical Markets

Regulating pharmaceutical markets presents significant challenges for policy makers. On one hand, research and development is very important in order to maintain progress in the health sector and ultimately provide better health care for people (Cutler et al 2006, Cutler et al 2007, Cutler and McClellan 2001, Kanavos 2005, Lichtenberg 1996, 2001, 2002, 2003, 2004). On the other hand, medical technology often leads to an increase in health expenditure, directly at least, as calculating indirect effects is more complicated. However, a study has shown that every dollar spent on using new pharmaceutical products (as opposed to older medicines) saves approximately $7 in other health care costs (Lichtenberg 1996). Further, the public good nature of health care (assuming health care is a public good), in combination with information asymmetries, create moral hazard issues. Patients

may not know exactly what treatment is best for them and rely on their physician and health care provider to receive the appropriate treatment. The insured though may abuse insurance and get higher levels of treatment than necessary, causing a rise in health expenses in general, and pharmaceutical expenses in particular. Tackling increasing health expenditure is a challenge for governments. Containing pharmaceutical expenditure could have an impact on technology uptake, leading to a slower rate of improvement of treatment, while increasing levels of expenditure may cause problems to the insurance funds, particularly in Europe, which has a growing elderly population (WHO HFA 2010). Faced with increasing costs in the health care sector, government policies aim to reallocate resources and increase welfare by intervening in healthcare markets.

Because pharmaceuticals are a significant component of the health care budget, payer interventions are common practice in pharmaceutical markets. Such interventions aim both at containing costs as well as ensuring access to those who need them. In order to achieve this goal, government policies are introduced.

Outside pharmaceutical markets, the main source of price reductions is the presence of competition. In in-patent pharmaceutical markets there is no direct competition from homogenous products, except for parallel trade, which is a special type of competition and is analyzed thoroughly in chapter 6 of the dissertation. To address this issue, supply-side regulation is often introduced. Naturally, savings may occur by controlling prices of products which account for pharmaceutical expenditure, medicine prices in particular.

In pharmaceutical markets, initially the product is in-patent, although facing indirect competition by other products of the same therapeutic class. Even in this situation, price competition is unlikely (Kanavos, Costa-font, McGuire 2007). At

patent expiry, there is a transition effect, as generics move into the market. At the same time though, there may be a switch within the same therapeutic class, from the off-patent molecule to an on-patent one. Parallel trade is another factor influencing market dynamics. All these dynamics are included in the dissertation, making it an in-depth analysis of competition in regulated prescription markets.

1.3 Focus of the thesis

The above sections provide the rationale for the focus of this thesis. In particular, the thesis focuses on three specific aspects of pharmaceutical market competition where there are indications that there is possible room for improvement in optimal resource allocation and efficient resource use The markets studied are subject to government intervention in the form of supply-side (and often also demand side) regulation.

There are two ways to improve efficiency in pharmaceutical markets from the supply side: Competition and regulation. Competition can reduce prices of prescription medicines. In in-patent markets, monopoly power allows a single supplier to set a higher price than in the presence of competition (Mas-Collel, Whinston and Green 1995). Apart from the supply side, measures may also focus on the demand-side by encouraging efficient prescribing and dispensing.

As already discussed earlier in this chapter, competition in pharmaceutical markets does not function in the same manner as in other markets. Third party payers, patent protection and low elasticity levels in in-patent markets may prevent competition from reducing prices as in other markets. Regulation steps in to address this problem and to make medicines affordable. In in – patent markets, negotiations between producers and health insurance, price caps and profit controls aim at

containing medicine prices below their monopoly level. Competition though exists in off-patent markets, so the originator producer has less market power, but the market is still far from perfectly competitive. Reference pricing, price caps are among the most common regulatory measures in off - patent markets. However, regulation may not always lead to the desired outcome, as this is only one of many factors which influence prices and market shares.

Studying pharmaceutical markets may reveal possible weaknesses in regulation or competition. Higher levels of efficiency can be reached by identifying areas in which there is room for improvement and suggesting interventions which can tackle any inefficiency.

Rising health care and pharmaceutical costs and the special nature of pharmaceutical markets make the study of competition in pharmaceutical markets a compelling subject. The behaviour of firms and the consumption patterns give important insights for policy makers to design appropriate policies in order to achieve the dual goal of cost containment and efficiency.

In the three studies of this PhD dissertation, I investigate (a) the effect of generic entry on prices of originators, (b) the switch in consumption from the off-patent branded product to an in-patent product with different chemical substance but of the same therapeutic category after generic entry, and (c) competition between patented products in the context of parallel trade. The subject of the research is the retail market, whereas the in-patient and OTC markets are excluded. The first study investigates post-patent competition, the second one investigates the transition at patent expiry and the third study investigates in-patent competition.

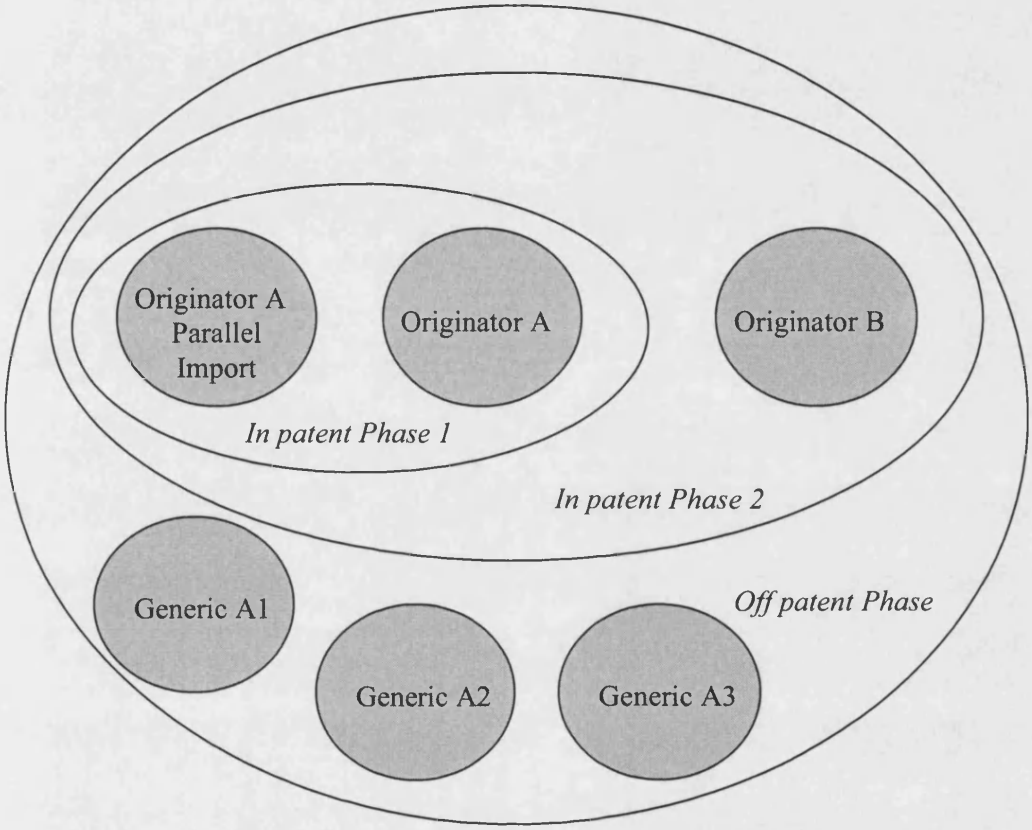
Figure 1.7 shows the three phases of pharmaceutical markets that are studied in this dissertation, considering both in- and off- patent products. These three phases

determine different levels of competition, which lead to different evolution of prices and market shares. The originator product (product A) faces competition from parallel trade[5] when in- patent. We assume no other competition exist in this phase. This is competition from an identical (perfectly homogenous) product, often down to the same formulation and dose. In phase 2, medicines of a different chemical substance, but within the same therapeutic class and with similar therapeutic effects entering the market (product B). These are known as "me – too" medicines. In this phase the manufacturer also faces within- class competition from other originator products[6]. Finally, when product A loses its patent, generic medicines enter the market (generics A1, A2, A3). These are of the same chemical substance as product A and therefore bioequivalent to it. Products A, A1, A2, A3 are homogenous. However, some consumers do not perceive them as homogenous products due to the fact that they are produced by different producers. In this phase, the manufacturer faces competition from generic alternatives, and is also faced with demand-side policies implemented by health insurance, encouraging generic prescribing and dispensing.

[5] Parallel trade occurs due to the European single market. Significant medicine price differences are present across EU countries because of differences in policies targeting medicine prices. Parallel trade involves the purchase of medicines by traders in low-price countries, which are then exported and sold in high-price countries.

[6] In this case there is some differentiation, which often concerns different side effects.

Figure 1.7 The Three Phases of Competition in Pharmaceutical Markets Studied towards Improving Efficiency



The first study (generics paradox) shows that prices of originator products across several therapeutic classes are likely to increase rather than decrease post patent expiry. This indicates that competition does not necessarily lead to lower originator prices. As a result, in order to achieve more optimal use of scarce resources, the vast majority of consumption should be diverted towards cheaper generics.

Findings from the second study (switching effects post patent expiry) suggest that within a particular therapeutic class comprising interchangeable brands, there is a switch in consumption from a brand which loses its patent towards other medicines within the same therapeutic category which are still in- patent. This happens despite supply-side and demand -side generic policies, thus revealing the weak enforcement of regulatory practices. Given that in- patent molecules have no (cheap) generic alternative, prescribing them instead of the off- patent molecule burdens the health budget with unnecessary costs which could have been avoided. Optimising consumption can lead to savings which can be used to improve health services.

Finally, as parallel trade has been perceived as a source of price cuts via enhanced price competition, the third study (on parallel trade) analyses whether parallel trade does indeed trigger competition. If not, this practice should not be perceived as a cost containment mechanism and other policies should be brought in to contain costs. Findings suggest that parallel trade does not promote price competition.

1.4 Thesis Studies

The thesis comprises 3 studies on competition and regulation in pharmaceutical markets.

- **Study 1: "The generics paradox revisited: Evidence from regulated markets"**
- **Study 2: "Switching effects post patent expiry: Empirical evidence from the European Union"**

- **Study 3: "The impact of parallel trade on pharmaceutical competition: A game theoretic approach and empirical evidence from the European Union"**

2. Literature Review and Contribution of the Thesis

2.1 Introduction

This chapter discusses previous research which is relevant to this thesis and the contribution of these three studies to the literature. Section 2.2 reviews the literature, including how the relevant literature was identified. Literature on different aspects of pharmaceutical markets, such as different types of competition and regulation, are studied separately. Section 2.3 discusses the importance of the multi-country aspect of research on pharmaceutical markets. Section 2.4 outlines the contribution of the thesis to the literature and includes all areas in which this contribution is made. Finally, section 2.5 provides a summary of the three studies.

2.2 Literature Review

This section reviews the literature relevant to the study objectives of this thesis in order to determine what has been established by previous research as well as identify the gaps in the literature of competition in regulated pharmaceutical markets. The literature is also discussed in more detail in each of the relevant studies (chapters 4, 5 and 6). In order to identify previous studies on topics analysed and discussed in this dissertation, literature searches were performed with the use of electronic resources. Searches of keywords and key phrases were conducted. The keywords and key phrases included: "pharmaceutical markets", "pharmaceutical regulation", "pharmaceutical policy", "pharmaceutical policies United Kingdom", "pharmaceutical policies Germany", "pharmaceutical policies Sweden", "pharmaceutical policies Netherlands", "pharmaceutical policies France",

"pharmaceutical policies Norway", "pharmaceutical policies Denmark", "generics", "generics paradox", "in-patent competition", "off-patent competition", "cross-border trade", "parallel trade", "parallel imports", "generic entry", "competition", "reference pricing", "advertising", "enalapril and captopril comparison", "captopril and lisinopril comparison", "lisinopril and enalapril comparison", "ACE inhibitor substitutability". Electronic resources included Econlit, PubMed, the LSE Library online catalogue and Google Scholar. Finally, standard textbooks in the field of Economics, Industrial Organization and Game Theory were used, such as Mas – Colell, Whinston and Green (1995), Tirole (1988), Tirole and Fundenberg (1991) and Gibbons (1992). In order to conduct the empirical analysis, apart from studies published in scientific journals on Econometrics, standard econometrics textbooks were also used, such as Greene (2003), Hsiao (2003) and Verbeek (2005).

Section 2.2.1 discusses how the literature shows that pharmaceutical market dynamics are different to regular markets. Section 2.2.2 presents relevant literature on generic markets and the generics paradox; section 2.2.3 outlines the literature on regulation and pricing post patent expiry; section 2.2.4 introduces advertising and section 2.2.5 provides the literature on in-patent competition. Section 2.2.6 introduces the literature on parallel trade.

2.2.1 Competition and Pharmaceutical Markets

Economic Theory suggests that the number of competitors in a market and prices are negatively correlated. The implications of that are that oligopoly prices are lower than monopoly prices and competitive prices are lower than that of any other free market (Mas – Colell, Whinston and Green, 1995, Tirole 1988). An important corollary of the above is that when a second player enters a monopoly market, prices

will drop. This is not necessarily the case in pharmaceutical markets, possibly due to the presence of brand loyalty and low price elasticity (Frank and Salkever 1993 and 1997), or because competitors compete in terms of quantities rather than prices (Kanavos et al. 2007). However, the factors that influence pricing and the prices of prescription medicines are complex and have been investigated within the context of both pre-patent and post-patent expiry (Kanavos et al. 2008, Frank and Salkever 1997, Grabowski and Vernon 1992, Kanavos et al 2007). Factors influencing the nature of competition in pharmaceutical markets include the effect of patent protection and patent expiry, advertising, purchasing by third party payers and price or volume regulation.

The existing literature clearly shows that pharmaceutical markets have their own dynamics, which differentiate them from other markets. This generates the rationale for this dissertation, as competition in ordinary non- price regulated markets has been widely covered by the literature. However, this special nature of pharmaceutical markets underlines the gap which this thesis will cover.

2.2.2 Generic Markets and the Generics Paradox

Generics are medicines of the same chemical substance as the originator product, which are bioequivalent to the originator molecule and enter the market post patent expiry. They are identical to the branded product, but are produced by other manufacturers. Usually, many generic producers gradually enter the market post patent expiry. Their price is lower than that of the originator, but generic price levels and the discounts off the medicine vary across countries. Their prices are influenced heavily by regulation. In some countries, price cap regulation is used. This type of regulation sets a price ceiling for generic products, as a proportion of

the originator price. Another common policy measure targeting generic prices is internal reference pricing or clustering, which sets a maximum ceiling on reimbursement, usually by taking into account a price basket of the cheapest products (either of the same molecule or the same price, depending on the country). Apart from generic pricing regulation, there are also policies encouraging generic market penetration, because they lead to savings for health insurance due to their relatively low price (compared to originators). Such policies include compulsory generic prescribing, generic substitution at the pharmacy level, flat pharmacy fees per script, regressive pharmacist margins, physician budgets and clawbacks.

An important potential determinant of pricing of prescription medicines relates to the study of market developments post-patent expiry. Empirical evidence from the United States suggests that generic entry leads to higher originator prices and that a necessary condition for such price increases is that entry leads to a decline in the own-price elasticity of reduced-form brand-name demand (Frank and Salkever, 1997). This is known as the "generics paradox". Further empirical evidence from the USA suggests that innovator firms do not attempt to deter generic entry through their pricing strategies and this may lead to a significant reduction in market share of the originator medicine post generic entry (CBO 1998; Grabowski and Vernon, 1992; Grabowski and Vernon, 1986). Rather, innovator firms have continued to increase their prices at the same rate as prior to entry. Rizzo and Zeckhauser (2005) found that producers of brand-name products do not decrease prices after generic entry, whereas Caves et al (1991) concluded that generic entry only leads to a slow-down in the increase of originator medicine prices. Danzon and Chao (2000a) show that generic competition lowers prices in less-regulated regimes, while Kanavos et al

(2008) suggest that regulation in pharmaceutical markets results in prices of generic medicines not declining fast enough.

The literature has provided evidence that originator prices do not decrease post patent expiry in unregulated markets. This generates the question whether the same holds in regulated markets, or does regulation lead to a decrease in originator prices. This will be answered by study 1 (the generics paradox) of the dissertation.

2.2.3 Regulatory Environment and Medicine Prices Post Patent Expiry

Supply-side regulation plays a principal role in pharmaceutical markets, at least in most EU countries. The goal of regulation is to contain costs, while safeguarding access and affordability. Pharmaceutical expenditure is rising, but there is still space for more efficient use of resources. For example, generics offer the same treatment as originators, but at a lower price, meaning that they are more cost-effective. Encouraging consumption of more cost-effective medicines is one aspect of regulation. The other aspect is controlling the prices of medicines available. Originator prices are determined after negotiating with health insurance or are subject to rate of return regulation. Generic prices are heavily regulated by price caps or reference pricing. Regulation does not only target prices, but also influences market shares. Various policies encouraging generic prescribing and dispensing are implemented across Europe, in an effort to encourage generic uptake and contain costs.

Recent studies have emphasized the importance of pharmaceutical regulation whether on the supply- or the demand-side (Caves et al 1991, Kanavos et al 2008; Kanavos et al 2005, Danzon and Chao 2000, Kyle 2007). A significant part of health expenditure continues to be allocated to pharmaceuticals while governments have

been making efforts to contain the rate of growth in pharmaceutical costs. This includes policy measures aiming to maintain medicine prices stable, decrease them, or contain their rate of increase. Further, on the demand side, interventionist policies encourage prescribing and dispensing of more cost-effective medicines.

Some studies suggest that regulation leads to lower prices of medicines, while others conclude exactly the opposite. Comparing them and the validity of their results is not an easy task due to differences in data and methodologies used. However, a brief overview of these studies is included below.

Regulation affecting the off-patent market segment may have an adverse effect on generic price reduction and generic market penetration over time. Several studies have shown different results concerning the impact of regulation on generic medicine prices. One study suggests that countries with strict price regulation have lower prices than countries with less strict regulation (Jonsson 1994). However, policy interventions do not lead to lower prices in all cases. For example, recent findings indicate that the use of price controls has a statistically and quantitatively important effect on the extent and timing of the launch of new medicines and that price regulation in one country affects entry into other countries, and may affect the strategies of domestic firms (Kyle, 2007). Imposing price ceilings in regulated markets may even lower prices in other unregulated markets (Mujumdar and Pal, 2005).

Internal reference pricing, one form of regulation that affects products or therapeutic classes characterized by patent expiries, has attracted considerable attention in the past fifteen years (Aaserud et al, 2007); in the Swedish context it has been shown to lead to a decrease in the market shares of particular originator products, suggesting higher levels of competition (Aronsson, Bergman and Rudholm

(2001)). Grootendorst and Stewart (2006) found that in the case of British Columbia, although the cost per day of therapy dispensed declined following the introduction of internal reference pricing, part of this reduction could be attributed to factors other than reference pricing. However, according to Ioannides-Demos, Ibrahim and McNeil (2002), it is difficult to reach safe conclusions about the impact of internal reference pricing on expenditure, because these effects are difficult to isolate due to the variety of potential factors influencing total pharmaceutical expenditure. Also, prices and diffusion of generics differ across countries after patent expiry (Magazzini, Pammolli, Riccaboni, 2004), making general conclusions concerning the impact of reference pricing on pharmaceutical expenditure difficult to reach.

Some studies have concluded that competition has kept prices low in markets with less regulation, particularly in markets with patent-expired molecules. At least two studies provide empirical evidence that generic competition is more effective in such countries (Kanavos et al, 2008; Danzon and Chao, 2000a). Nevertheless, Danzon and Chao (2000a) state that comparing prices of pharmaceutical products across countries gives uncertain results due to the differences in products, prices and volumes. Based on empirical evidence from Norway, the introduction of a price index that aimed in lowering entry barriers actually helped increase the market shares of generics and helped trigger price competition by reducing overall market power. (Dalen, Strom, Haabeth, 2006). This policy measure may offer consumers the alternative of cheaper medicines (generics) and therefore help reduce spending. At times, the presence of regulation, for instance in the form of a price index used in price setting, may indeed skew the market, leading to different effects than in the absence of regulation.

Overall, evidence from the literature is inconclusive on the impact of regulatory measures on medicine prices. This creates space for a study that combines the joint effect of regulation and generic entry on medicine prices.

2.2.4 The Effect of Advertising

Advertising is used by producers as a means of promoting the benefits of products, ultimately resulting in increased sales or market share. Apart from informing consumers, it also lowers price elasticity and creates product differentiations which would not have been perceived as such by consumers in its absence (Tirole 1988). Consequently, this degree of (perceived) product differentiation makes consumers more reluctant to purchasing another product.

Advertising and advertising intensity also influence the choice of pharmaceutical products in an environment of product differentiation pre-patent expiry, where products are considered to be broadly comparable or direct substitutes. Direct-to-consumer advertising is not permitted in the European Union (while it is common in the United States). Therefore advertising targets the agent (physician) rather than the patient. Empirical evidence suggests that advertising, by means of detailing, has a powerful effect and systematically lowers price sensitivity because it increases brand loyalty, in addition to the effect of increasing a product's sales (Rizzo, 1999), as well as having spillover effects, such that advertising by one firm in a therapeutic category can increase demand for other medicines in the same category (Berndt el al, 1995). Empirical evidence from detailing (sales representatives' visits to physicians) suggests that total promotion effects on medicine utilization are positive and that promotion of new medicines leads to an

increase in their market share, which is also negatively affected by promotion of old medicines (Berndt, Danzon and Kruse, 2007).

Brand loyalty is expressed in pharmaceutical markets as avoiding to switch to generic substitutes when a product loses its patent and to continue consuming the branded product, despite its higher price. Patients or physicians (who act as patients' agents) are often reluctant to switch to a generic substitute, despite the therapeutic equivalence. This, combined with regulation, triggers market dynamics which lead to surprising results in the pharmaceutical market, such as the "generics paradox", a phenomenon which suggests that generic entry (hence more competition) leads to higher originator prices. This is discussed in the first study of the dissertation, "The generics paradox revisited: Empirical evidence from regulated markets". Brand loyalty is a substantial asset for producers (Cunningham 1956). Brand loyalty varies across consumers, but is often present even if there is no difference between products apart from their brand (Tucker 1964). Higher brand trust leads to positive outcomes for producers, such as market shares (Chaudhuri and Holbrook 2001). In pharmaceutical markets, physicians may become brand loyal as a result of prescribing a particular brand only while the product is in- patent (Grabowski and Vernon 1992). The authors find that branded product producers do not try to deter generic entry through pricing strategies.

As promotional expenditure accounts for a significant part of the total pharmaceutical industry expenditure (US$12 billion were spent on promotional activities in 2006 according to the Pharmaceutical Research and Manufacturers of America based on an IMS study, while R&D spending in 2007 was US$ 58.8 billion (PhRMA 2008), it appears to be a very important contributor to market dynamics.

Nevertheless, figures on promotional expenditure by the pharmaceutical industry have been disputed by Gagnon and Lexchin (2008).

The existing literature on advertising indicates that, for the case of medicines of the same therapeutic class (which are considered to be subject to some degree of substitutability), a decrease in advertising efforts by one of the competitors will affect market shares. This is the idea upon which the second study (switching effects post patent expiry) is based.

2.2.5 Competition in In- Patent Markets

In the context of this dissertation, branded medicines are innovative medicines which are patent protected. The main cost for the producer of innovative medicines is R&D costs. The per- unit cost of production is relatively small. In order to protect the value of innovation and to encourage future research, innovative products are patent protected.

Medicines are grouped in therapeutic classes, e.g. simvastatin, atorvastatin and pravastatin all belong to the "statins" class. The first entrant in the therapeutic class establishes the class, and other manufacturers usually follow with similar but not identical molecules. Grouping is important, as it indicates medicines with some level of substitutability. Further, a practice leading to savings is reference pricing at the class level (rather than the molecule level), which forces branded off-patent products to face competition from generics of another molecule but of the same class. Therapeutic classes discussed in this thesis are statins, ACE I, ACE II inhibitors, proton pump inhibitors, antidepressants and antipsychotics.

Competition in pharmaceutical markets may involve two different branded products of the same therapeutic class, a branded product versus its generic

alternatives, or generics versus generics. In the first case, products are differentiated, while in the two latter cases the product is homogenous, as it is of the same chemical substance. However, in the branded versus generics case, the product may be perceived as differentiated by some consumers. Therefore competition is different in in-patent and off-patent markets, as in the first case the product is differentiated and both products are branded, while in the second case there is no differentiation, but not all products are branded.

Little empirical evidence exists on competition between products of the same therapeutic category. A study on competition between statins in France, UK, Germany and the Netherlands showed that price competition is present and has an impact on the first three entrants (Kanavos, Costa-Font and McGuire (2007). Danzon and Chao (2000) found no evidence of price competition within therapeutic class in the US, but small negative effect on originator prices in France, Italy, Germany and the UK. In another study, the same authors got inconclusive results about the effect of substitution across therapeutic class and the first-mover advantages on product price. In the case of cephalosporins[7], Ellison et al (1997) found significant cross-price elasticities between therapeutic substitutes. In order to study competition between different medicines of the same therapeutic class, there has to be evidence that there is a high degree of substitutability between them as, by grouping medicines in the same therapeutic class, it is recognised that there is at least some substitutability. Clinical evidence can be used for this purpose, which can compare molecules to see whether they have similar effects on patients. For example, in the case of ACE I Inhibitors, numerous studies support the view that there is very high substitutability across products in this therapeutic class (Vlasses et al. 1986,

[7] Cephalosporins are antibiotics meant for the treatment of bacteria infections.

Rumboldt et al. 1988, Foy et al. 1994, Zannad et al. 1992, Dews et al. 1989, Enstrom et al. 1992, Rumboldt et al. 1993, Morisco et al. 1997).

Research on different aspects of competition (price volume etc) between branded medicines is limited. However, there is evidence that competition is present between medicines of the same therapeutic category. Clinical evidence also provides support in favour of the view that ACE I Inhibitors demonstrate similar effectiveness in the treatment of hypertension. These findings provide the framework for the second study (switching post patent expiry), as this study analyses competition between branded products and how this evolves after one of the products faces patent expiry.

2.2.6 Parallel Trade

Significant differences occur in prices of medicines across Europe. This is mostly a result of different supply-side regulatory practices. Usually prices tend to be higher in northern European countries compared to southern European countries, although this is also dependent on other aspects such as exchange rates and demand-side regulation on addition to supply-side regulation.. Given the presence of a Single Market allowing free trading of goods, arbitrage opportunities occur. This is known as Parallel Trade (PT), Parallel Imports (PI) or as Cross- Border Trade (CBT). Parallel trade is a legal practice and the European Court of Justice has ruled on many occasions on different aspects of parallel trade over the past 20 years.

The product is perfectly homogenous, as the parallel traded product and the locally sourced product are marketed by the very same pharmaceutical firm (packaging may differ on many occasions). The parallel trader is subject to transportation costs, but realises a rent due to the difference in prices between the

acquisition and selling country. Parallel traders buy products in the low- price country and sell it in the high- priced EU country. This leads to lower profits for the manufacturer, as for him this practice is equivalent to selling the product in the highly- priced market at the price of the low- price market. Hence, parallel trade lowers the net present value of innovation, as it decreases the expected future flows of an innovative pharmaceutical product and makes investing in R&D less profitable. Policy makers in importing countries often perceive parallel trade as a means for cost containment and implement policies in order to encourage this practice because they believe that they can capitalise on the lower prices of exporting countries.

Previous studies on Parallel Trade have reached different conclusions on the impact of this practice on competition and prices. Evidence from Sweden suggests that parallel trade triggered competition, leading to lower prices (Ganslandt and Maskus 2004), but other studies associate competition with generic entry rather than parallel trade (Kanavos and Costa-Font 2005, Linnosmaa et al. 2003). A study taking into account dynamic effects does not find any evidence on downward convergence of prices of locally sourced medicines (Kanavos and Vandoros 2010).

Evidence exists that PT would lead to welfare losses in the long run, due to its effects on innovation (Bordoy and Jelovac 2003; Danzon 1998; Ganslandt and Maskus 2004; Rey 2003; Szymanksi and Valletti 2005), suggesting that parallel trade is a "threat" to innovation.

Although some studies have examined the potential savings to health systems from parallel trade (West and Mahon 2003; Kanavos and Costa-Font 2005; Enemark et al. 2006), little evidence is available on the presence or not of a price gap between originator and parallel imported prices in destination countries. Furthermore, very limited evidence exists on whether locally-sourced originator

prices decrease as a result of parallel trade and no evidence exists on the impact of policies targeting parallel trade on market dynamics.

Previous research on parallel trade has shown the effect of cross-country price difference and competition in the supply chain on parallel trade prices. Also, some limited evidence (for particular countries only) exists on whether competition is triggered in branded markets as a result of parallel trade. A holistic approach to addressing the competition effects of parallel trade on medicine prices is missing. This gap provides the ground for a game theoretic approach indicating the predictions of theory for how prices would evolve as a result of parallel trade. This theoretical approach can be supported by empirical evidence from the main parallel importing European markets, showing whether there is a price gap between locally sourced and parallel traded products, and whether prices of locally sourced products decrease as a result of parallel trade.

2.2.7 Summary of gaps in the literature

In summary, the existing literature of competition in pharmaceutical markets has a number of gaps, which this thesis addresses. It is not known how originator prices evolve post patent expiry when originator products face generic competition. This is also important from a policy perspective, as rising originator prices suggest that genericization should take place as swiftly as possible post patent expiry.

Further, a switch in consumption from a product which has lost its patent to other products of the same therapeutic class has not been explored at all. From a policy perspective, such a switch in consumption shows that generic policies are not always sufficient as there are ways for producers to increase originator market shares even post patent expiry.

Finally, there is no complete approach to the effects of parallel trade on competition and originator prices in the literature. Also, the effect of policies targeting parallel trade has not been addressed in the literature. One way forward is a game theoretic model with findings supported by empirical evidence, showing whether there is a price gap between locally sourced and parallel traded products and whether the price of the locally sourced product remains unaffected by parallel trade. The policy implications are clear, so as parallel trade does not trigger competition, it should not be viewed as a cost – containment mechanism by regulators, who should focus on other means to control costs.

2.3 The need for a multi-country analysis: Cross country comparisons

For the purpose of the PhD data from seven different European countries are used, namely Denmark, France, Germany, the Netherlands, Norway, Sweden and the United Kingdom. The reason why different countries are considered is that prices vary significantly across Europe as a result of different pricing and other regulatory policies. A comparative analysis is necessary in order to demonstrate the different dimensions of pricing and competition in pharmaceutical markets. Klein (1991) underlines the importance of a comparative cross – country analysis. Putting health care in an international context is an "antidote to the dangers of ethnocentric overexplanation" and the only way to identify what is important for a country is to compare it to other countries (Klein 1991).

Cross country variations in the prices of prescription medicines are of great importance, hence the attention this issue has attracted recently in the literature surrounding pharmaceutical markets (Danzon and Furukawa, 2003; Danzon and Towse, 2003; Danzon and Chao, 2002). Recent research has examined regulatory

practices, such as price controls and patent policy affecting launch dates of new pharmaceuticals among developed countries (Danzon et al, 2005; Kyle, 2007; Danzon and Furukawa, 2003; Desiraju et al, 2004) and developing countries (Lanjouw, 2005) and their overall effect. Kanavos and Vandoros (2010) also find significant pharmaceutical price differences across OECD countries.

This evidence on cross-country variability demonstrates the differences in pharmaceutical markets across countries. Such differences underline the importance of the consideration of various countries in the analysis, instead of limiting research to one country. Therefore, for the purpose of this PhD dissertation, a number of European countries have been included in the analysis. This becomes even more important as little evidence exists on the determinants of pharmaceutical prices across different regulatory settings. The existing literature does not fully explore the effect that factors, such as competition pre- and post-patent expiry, the type of price regulation, the age of product, and the type of cross-country price differences, put together might have on cross-country price differences in prescription medicines.

2.4 Understanding Pharmaceutical Markets

The over-arching theme of this PhD is an investigation of the determinants of prices of branded prescription medicines across different regulatory settings and health care systems, taking into account the patent status, market dynamics and the regulatory context in which they diffuse. In order to do this, price levels are analyzed for a basket of prescription medicines and their differences are investigated in a number of European countries; in addition, the impact of generic entry on public prices is studied, and the extent to which innovation, by means of introducing newer

classes of medicines, contributes to price formation across countries is explored. In pursuing this analysis, we also understand the factors that contribute to the existing differences in (retail) prices of prescription medicines across countries.

2.4.1 The three aspects of competition

Three different aspects of competition in pharmaceutical markets are analyzed in this dissertation. Forms of competition discussed originate from: first, generic entry post-patent expiry of the originator; second, medicine intra-class competition; and, third, competition from parallel imported versions of originator products.

Competition between the originator (branded) medicine and its generic substitutes post patent expiry is expected to be the main source of price reductions, according to Economic Theory. Economic Theory would suggest that generic market entry would transform a monopoly market into an oligopoly, or a type of market that could resemble perfect competition, at least with regards to the number of producers, given the homogenous nature of the product (as the originator and generics are of the same chemical substance). The important feature here is that of brand loyalty, which may lead to outcomes other than expected, i.e. an increase in originator prices when the number of competitors increases.

Findings on the impact of generic entry on the prices of originator products would indicate whether originators compete against generics in terms of price. If not, no savings should be expected by dispensing originators post patent expiry due to possible competition effects on originator prices, and the only way for health insurance to benefit from patent expiry is generic dispensing.

Another aspect of competition analyzed in this thesis is competition within a therapeutic class. Products which belong to the same therapeutic class are different molecules, but are similar, and target the same disease. Due to a certain degree of substitutability, it is reasonable to assume that there is within-class competition present. When a product goes off-patent, its producer loses a large part of the market and gains significantly lower profits. Further, any advertising efforts have a spillover effect on generic products. Thus, the producer limits his advertising and promotion efforts for this product and focuses on other products from in its portfolio, which are still patent protected. This could be observed by a switch in consumption from a product which faces generic entry towards other products of the same class which are still in- patent.

Finally, parallel trade could influence pricing dynamics in branded medicine markets. Parallel traded products may act as a competitor for the manufacturer of these products. In order for competition to be triggered, two things need to occur. The parallel trader must set the price at a lower level than that of the locally sourced product and the manufacturer must have an incentive to lower his price in response to it. Alternatively, list price is the same and the competition game is played at the discount-to-final-distributor level. It is not certain how markets with parallel trade evolve, although this is a very important aspect, given the possible savings which may occur, the impact on prices and the effects on innovation.

2.4.2 Efficiency and optimal resource allocation

Lessons learnt from research on pharmaceutical competition and regulation can lead to efficiency savings and optimal resource allocation by health insurance. The particular nature of these savings would improve social welfare, but would not

make every agent in an economy better off, while some (particularly producers) end up being worse off. For example, more competition in the generic market and a lower price of generics makes generic producers forego rents, although it leads to relatively high savings and higher levels of welfare for patients. Enhancing competition between interchangeable medicines of the same therapeutic class will lead to higher savings and a space for allocation of resources to more health inputs, but will decrease any higher rents that are captured by the industry due to the monopoly that the patent grants. Finally, reducing parallel trade may lead to the loss of some savings, but will increase the present value of resources invested in R&D and, therefore, will encourage the development of new medicines; parallel traders will be made worse off.

Implementing the policy recommendations would help distribute resources in a more equitable and efficient way and would remove some inefficiencies that monopolies, imperfect competition or information asymmetry create. Nevertheless, there are no improvements in terms of Pareto efficiency, as in order to achieve further savings, a party (a provider in particular), has to become worse off.

2.5 The Contribution of this PhD Thesis

This PhD thesis studies the determinants of prices of branded prescription medicines across different regulatory settings and health care systems, taking into account the patent status, market dynamics and the regulatory context in which they diffuse.

By studying and understanding how the pharmaceutical market works, the source of price increases or price cuts can be identified, as well as how demand is allocated to different competitors. The different regulatory measures, market

structures due to patent protection and third- party payers make the investigation of these markets more complicated than regular markets, and findings that hold for regular markets do not necessarily hold for pharmaceuticals.

Given the rise in health costs and pharmaceutical expenditure, studying the industrial organization of pharmaceutical markets is of great importance. Industrial Organization is the sub-discipline of Economics which studies the economics of markets. The core of Industrial Organization is competition, and the evolution of prices and market shares. The number of providers is crucial to the outcome of a market. Theory studies the predictions of Empirical Industrial Organization, empirically tests the predictions of theory and provides empirical evidence on how prices and market shares evolve under various competition environments. Theoretical and empirical findings are the result of the behaviour of rational agents, which include providers and consumers. Industrial Organization is of great importance for pharmaceutical markets. Findings suggest how prices and market shares evolve as a result of the degree of competition and regulation. This leads to valuable policy recommendations.

Based on the above, this thesis studies three areas of competition in pharmaceutical markets and advances the literature in a number of ways. All three studies provide answers to policy-related topics which have not been studied before in a particular context. Conclusions are met with regards to whether particular types of competition exist in pharmaceutical markets, and also how policy makers can respond to pharmaceutical market agents' behaviour, in order to contain costs and spend scarce resources more efficiently.

The contribution of the thesis is both empirical and theoretical. This contribution is discussed in the next two sections.

2.5.1 The theoretical contribution

In general, theoretical models are used to predict the outcomes of a situation in a market and empirical data are used to test the hypothesis. Further, the comparative element of research in pharmaceutical markets is also very important, as this allows to compare health systems and policies across countries and identify towards which directions various policies lead.

With regards to study 1 (the generics paradox in regulated markets), the theoretical contribution is a framework which captures the likely effects of brand loyalty on prices. The model includes two players, an originator producer and a generic manufacturer. Patients demonstrate different levels of brand loyalty (which is expressed as an aversion to generics), depending on which they are willing to pay a different price for the branded product rather than the generic. The more brand loyal a patient is, the higher the price he is willing to pay for the branded product. This leads to a price gap in the market, and the originator product is priced at a higher level than the generic. This shows how brand loyalty works and how, despite the fact that the product is homogenous, some consumers are willing to pay a higher price for a perceived product differentiation, which is nothing more than the brand name itself.

With regards to study 2 (switching post patent expiry), the theoretical contribution is a theoretical mathematical framework showing how promoting efforts drop post patent expiry, triggering this switch in consumption. The theoretical model shows the returns of advertising for an originator medicine manufacturer, before and after patent expiry. Before patent expiry the returns for each monetary unit invested in advertising are larger than post patent expiry, due to the lack of generic competitors, and any spill-over effects towards them.

Consequently, the manufacturer gains larger returns from funds invested in products which are still patent protected. Therefore he decreases efforts in the off-patent market. This gives the opportunity to other branded competitors of other products of the same therapeutic class to step in and attract part of the consumption of that particular molecule, both branded and generic. Thus the predictions of theory suggest that the switching behaviour may indeed take place as a result of less advertising.

With regards to study 3 (the effects of parallel trade on pharmaceutical competition), the theoretical contribution is the introduction of game theory in pharmaceutical market research. Although game theory is a common methodological tool in industrial organization, it had not been used to predict the outcomes of competition in the pharmaceutical market. This is a significant gap, given that game theory is a very important methodology when studying competition due to the close interdependency of all parties involved. This tool has surprisingly not been used in this field, and previous studies have used only empirical methods and conceptual frameworks, but not game theory, which is one of the main tools to pursue research on competition, known as industrial organization in the economics literature. The move of one competitor influences the behaviour of other competitors when there is at least some market power. In perfectly competitive markets this is not the case, but in pharmaceutical markets all producers usually have some degree of market power, and in in- patent markets market power is strong due to limited sources of competition. This interaction makes game theory a necessary tool in many cases. The study on parallel trade uses game theory to show that prices of locally sourced products do not respond to competition originating from parallel trade with price reductions. Prices remain constant and the parallel

traders have the incentive to price their products at the same price as the locally sourced product. The game that is included in the analysis shows that this is a Subgame Perfect Nash Equilibrium. These predictions provide the results of the theoretical analysis and set the grounds for the empirical analysis.

2.5.2 The empirical contribution

The thesis makes an important empirical contribution for each of the 3 areas of pharmaceutical competition undertaken.

With regards to study 1 (the generics paradox in regulated markets), industrial organization theory suggests that as the number of competitors increases, prices decline (Mas - Collel, Whinston and Green 1995, Tirole 1988). Frank and Salkever (1997) suggested that in the pharmaceutical market prices of originators may increase post-generic entry, rather than decrease. While this is a finding from the US market which does not regulate prices, there is no evidence as to whether this holds in markets that do regulate prices of pharmaceutical products. Study 1 studies this aspect of competition in regulated markets, by drawing on data from six European countries (Germany, Denmark, Sweden, Netherlands, Norway and the United Kingdom). Pharmaceutical market regulation gives policy makers the flexibility to intervene in order to correct any dynamics leading to an increase in costs, or withdraw any policies which contribute to increased expenditure. In this context, the first study on the generics paradox in regulated markets provides an answer to the question of whether branded product prices respond to generic entry in regulated markets. Econometrics control for important regulatory measures. Results suggest that the generics paradox is indeed present in regulated pharmaceutical markets, as originator prices increase post patent expiry. In the country specific

regressions, findings show that originator prices increase in Netherlands, Norway, Sweden and the United Kingdom. Generic entry has no effect on originator prices in Denmark, while there appears to be a decrease in prices in Germany. This is the core of the empirical contribution, as the generics paradox had not been studied in regulated markets. The findings provide valuable information to policy makers. It is shown that unless generic uptake takes place, no savings occur for health insurance post patent expiry.

With regards to study 2 (switching post patent expiry), little is known about within- therapeutic class competition between medicines. Patented markets have not attracted much attention and the literature is limited to competition among in-patent statins (Kanavos, Costa-Font McGuire 2007) and cephalosporins (Ellison et al. 1997). Furthermore, the effect of patent expiry on the market shares of the molecules of the therapeutic class was unknown. Study 2 contributes to the literature by exploring within- class competition of ACE I inhibitors, focusing on the effect of generic entry on relative volumes of the off- patent molecule and the in- patent molecules and whether there is a switch in consumption towards other products of the same therapeutic class. In addition, data were used for a long time period (1991-2006, on a quarterly basis), which allow for an in-depth exploration of the topic. Such long datasets (in terms of time) have seldom been used in research on pharmaceutical competition. Findings suggest that there is indeed a switch in consumption from a product which goes off- patent towards other products of the same therapeutic category in the case of ace inhibitors. This switch in consumption may burden health insurance with increased costs of dispensing branded products with no generic alternatives rather than off- patent molecules with generic substitutes with which, in the presence of generic prescribing and substitution

policies, lower costs would occur. As the findings show that health insurance is burdened by this switch, policy implications are included, as well as suggestions about what regulatory measures can be implemented in order to address this problem.

With regards to study 3 (the effects of parallel trade on pharmaceutical competition), the predictions of the game theoretic approach are confirmed by the combination of the descriptive statistics and econometric analysis. This study does not only look at whether there is price convergence between locally sourced and parallel traded products but also, if any, it is upward or downward. This is why this combination of methods provides a complete view of the effects of parallel trade on pharmaceutical markets. For example, in the case of the absence of policy measures promoting parallel trade, the game theoretic approach predicts that there will be upward price convergence; descriptive statistics show that in practice there is convergence and the econometric analysis confirms that the convergence is upward. Further, this study provides information on the legal aspects surrounding parallel trade and the rulings of the European Court of Justice on this important issue. Findings give rise to crucial policy implications. Parallel trade does not trigger competition in any case. Also, it should not be considered as a cost containment mechanism as in many cases prices are the same as that of the locally sourced product, which does not deviate from its initial price in the presence of parallel trade. Any savings that occur have been proved to be very small compared to the threat it poses to R&D. Consequently, parallel trade should not be considered as a means to cost containment and authorities should seek to contain costs by generic uptake, efficient prescribing and health technology assessment rather than parallel trade.

However, the great contribution of this study is that parallel trade has never been studied in a multi-dimensional way. The combination of game theory,

descriptive statistics and econometrics provide a solid insight and concrete evidence of market dynamics in the presence of parallel trade. Parallel trade is an important issue as it undermines R&D, but it has been perceived as a means for cost-containment by regulators. Previous studies on this issue were mostly empirical and no solid theoretical approach existed on the predicted evolution of prices of medicines. By using a game theoretical approach the basis for a concrete industrial organization analysis of the market is set. Insight is given into why prices evolve the way they evolve and what aspects of the market trigger competition or not. Without this game theoretical approach questions would remain with regards to why prices of locally sourced products do not respond to competition from parallel traders.

2.5.3 Summary of the contribution of this PhD dissertation

In summary, this thesis contributes to the literature: first, by studying aspects of the pharmaceutical market that had not been studied or not studied adequately before; second, by introducing a game theoretical perspective in the analysis of pharmaceutical markets (in particular for study 3); and third, by providing a multidimensional analysis of competition and regulatory issues of the pharmaceutical market, in which a combination of theoretical and empirical methods are used in order to provide a better understanding of competition and regulation. All findings are followed by implications for stakeholders and recommendations for policy makers.

The policy recommendations arising from the research conducted in this thesis relate to improvements in efficiency and resource allocation. This thesis shows that there are inefficiencies arising from poor genericisation, or from switching towards more expensive products, or from ill-targeting of competition.

Savings achieved by the dispensing of generics rather than originators or by enhancing within class competition can fund the reimbursement of in- patent medicines which are not covered due to high costs and the relative scarcity of resources.

2.6 Summary of the three studies in this PhD dissertation

2.6.1 The generics paradox revisited: empirical evidence from regulated markets

This study examines the impact of generic entry on originator prices and, in particular, aims is to investigate whether the "generics paradox" holds in regulated markets. A previous study has shown that this paradox does hold in the relatively unregulated U.S. pharmaceutical market.

Following an extensive literature review of regulation and competition in pharmaceutical markets, a conceptual framework is developed in order to demonstrate how brand loyalty may lead to higher prices even in markets subjected to some regulation. Brand loyalty and price elasticity are discussed and indicate that a paradox may indeed hold in pharmaceutical markets: Increased competition, expressed via generic entry, does not always lead to lower originator prices. As generics enter the market, most consumers switch to generics and only the most price- inelastic patients continue to consume the branded product. Given that these consumers are inelastic to changes in prices, an increase in the price on behalf of the branded producer will lead to an increase in his profits. Regulation encourages generic market penetration and may lead to even lower generic prices, hence leaving only the even more price- inelastic consumers to stick to the branded product.

Therefore it is reasonable to expect that the "generics paradox" does hold in regulated markets.

For the econometric analysis, prices, market share and regulation data are used from Denmark, Germany, the Netherlands, Norway, Sweden and the United Kingdom. The results of the instrumental variable panel data econometric analysis show that, overall, there is an increase in originator prices post generic entry, which, in principle, is counter-intuitive because of the regulation in most of these countries. At individual country level, the generics paradox appears to be present in Germany, the Netherlands, Norway, Sweden and the United Kingdom. However, in some countries it is expressed through a one-off effect, while in other countries it takes some time to materialise, and takes place gradually with generic market penetration. This finding provides valuable policy implications, as it indicates that generic entry does not trigger price competition between the originator and generics. Thus savings do not occur from the dispensing of originator products. Generic uptake must be swift in order for patent expiry to lead to savings for health insurance.

2.6.2 Switching effects post patent expiry

Little evidence exists on whether there is competition across medicines within the same therapeutic class. This study examines a possible switching in the consumption of a medicine when it loses its patent towards other medicines of the same therapeutic class.

A conceptual framework is developed, showing that the producer of a medicine which goes off- patent has the incentive to reduce his advertising and promotional efforts for the particular medicine and focus on other medicines which are still patented, leaving space for other medicines of the same class to attract part

of the total market share of the particular molecule (including both originator and generic volume).

The study draws upon the use of ACE inhibitors in six European countries, notably Denmark, France, Germany, the Netherlands, Sweden and the United Kingdom. An econometric model is set up in order to determine whether patent expiry affects the volume of the product which goes off patent, as well as the volume of the other medicines of the same class which remain in- patent. Volume of the product which goes off patent, volume of all other products of the therapeutic class which remain in- patent and the ratio of volumes are used as dependent variables in the three different models which are estimated. Explanatory variables include generic entry, regulatory variables and time dummies.

Results indicate a switch in consumption when a medicine goes off patent in Denmark, France, the Netherlands and the United Kingdom. No evidence exists that this holds in Germany or Sweden. The consumption is diverted to other medicines of the same therapeutic class, as there is sufficient substitutability. This practice increases pharmaceutical spending. Policy makers can face this by making the off-patent molecule first- line treatment or introducing reference pricing at the class level, rather than the molecule level.

2.6.3 Does parallel trade trigger competition? A game theoretic approach and empirical evidence from the European Union

This study analyses the market dynamics of parallel trade and examines whether it triggers competition in pharmaceutical markets. Parallel trade is a legal practice that takes place in the European Union due to significant differences in medicine prices across EU countries. These differences occur due to different

regulatory measures and create arbitrage opportunities. Governments in importing countries have perceived parallel trade as a cost- containment mechanism, hence providing explicit or implicit incentives for parallel trade. As parallel trade is a threat to R&D of future medicines, this study investigates whether this practice triggers competition, leading to lower prices of the locally sourced product.

The study provides insight into the behaviour of rational agents by using a game theoretic approach. The Perfect Sub Game Nash Equilibrium of the game is that the price of the locally sourced product does not respond to parallel trade. In other words, parallel trade does not trigger competition. In the absence of policies promoting parallel trade, the parallel trader will price his product at the same level as the locally sourced product. Some policy measures though may force the price of the parallel imported product to deviate downwards from the locally sourced product.

Further, empirical data are used from the main parallel importing countries (Germany, the Netherlands, Sweden and the United Kingdom) over years 2003-2006 in order to see whether there is a difference in prices of locally sourced medicines and the corresponding parallel traded products, and whether the price of the locally sourced product is pushed downwards by parallel trade competition or not.

The descriptive analysis shows that in the absence of policies promoting parallel trade (United Kingdom) there is no difference between prices of the locally sourced products and parallel traded products. The presence of policies though may cause larger (the Netherlands, Sweden) or smaller (Germany) spreads in prices. Price differences also occur when the product is off patent and parallel traders choose to compete against generics.

Finally, an instrumental variable panel data econometric model is used to estimate the effects of parallel trade on prices of locally sourced medicines. The results show that there is no downward price convergence and that prices of locally sourced medicines remain unaffected by parallel trade.

Findings show that no indirect savings occur through parallel trade due to any competition effects, as prices of locally sourced medicines do not drop. Regarding parallel imported products, in the absence of regulation targeting parallel trade (United Kingdom), there is no price difference between locally sourced and parallel traded products. When such regulation is present, parallel traded product prices may be lower than locally sourced ones, leading to direct savings for health insurance. Given the fact that parallel trade is a threat to R&D, policy makers should be careful when choosing to encourage parallel trade as a means to cost containment.

3. Data and Methodology

3.1 Data

In order to pursue the analysis data from the Intercontinental Medical Statistics (IMS) pharmaceutical sales database was used. The accuracy of the data ranges between 98 and 99% (IMS, 2002). Collected and reported data are based on actual invoiced prices and sales. Within the European context, list prices of prescription medicines are actually reimbursed by health insurance. The sample of countries and molecules are carefully selected for each study, depending on the research question, as outlined below.

The European countries included in the studies are chosen in order to reflect the different regulatory environments. Various national policies are implemented both on the supply and the demand side in order to regulate pharmaceutical expenditure, and this is partly reflected on prices, hence the cross-country price differences. The United Kingdom has a relatively free pricing type of market environment, subject to limitations, such as profit controls (PPRS) and value-based pricing for in-patent products, whilst generic pricing is free. Germany, Denmark, the Netherlands and France apply a variety of policies on in-patent products, ranging from free pricing (Germany) to value-based pricing (the Netherlands). Different variations of reference pricing for off-patent products are applied in Germany, Denmark, the Netherlands and France, while Norway and Sweden abolished reference pricing in 2001 and 2002, respectively. In France the price of a generic is by regulation at least 30-40% lower than the price of the corresponding originator. Regulation differs across countries included in the sample with regards to value-

based pricing and health technology assessment, generic substitution policies, clawback policies as well as funding of the health system, among others. In addition, there are policy changes within countries during the period studied, which would also allow to control for changes in the same market.

Data for study 1 (generics paradox in regulated markets) were obtained for the 1997-2002 period on a quarterly basis for 12 medicines from four product categories: Plain ACE inhibitors (Captopril, Enalapril, Quinapril, Ramipril); atypical anti-psychotics (Clozapine); proton pump inhibitors (PPIs) (Lansoprazole, Omeprazole, Pantoprazole); and serotonin selective reuptake inhibitors[8] (SSRIs) (Citalopram Fluoxetine, Paroxetine, Sertraline) in six European countries (Germany, United Kingdom, the Netherlands, Sweden, Norway, Denmark) for the retail (pharmacy) market in each country.

The sample of medicines studied includes leading selling prescription medicines for conditions with high prevalence which, therefore, have an impact on total pharmaceutical spending. The time period studied is a period during which certain products of every therapeutic class included in the analysis lost their patent protection and faced generic entry. In addition, some of the medicines included were patent protected throughout the period examined, allowing to control for differences between medicines which lost their patent and medicines which were patent protected for the whole period studied. Data were available for originator and generic versions of each molecule. Generics are present in the market for at least one medicine in each therapeutic category in at least one country in the sample in the time period considered for the analysis.

[8] A class of products used for the treatment of depression.

For study 2 (switching behaviour post patent expiry), data are quarterly and cover period 1991-2006 for 14 Plain ACE inhibitors (Captopril, Enalapril, Lisinopril, Quinapril, Ramipril, Trandalopril, Periodinopril, Moexipril, Fisinopril, Benazepril, Cilazapril, Zofenopril, Imidrapril, Spriapril), in six European countries (Germany, United Kingdom, the Netherlands, Sweden, France, Denmark) for the retail (pharmacy) market in each country. Both originator and generic versions of each molecule were used. Plain ACE Inhibitors were chosen because they are a common treatment for hypertension (NICE hypertension guidelines 2006, HAS hypertension clinical practice guidelines 2005), which is a highly prevalent condition in developed countries (Kearny et al 2005). Further, there is a certain degree of substitutability between different Plain ACE Inhibitors, which indicates that competition across medicines in this therapeutic class is indeed possible, as various studies suggest that ACE inhibitors have similar antihypertensive effects and mechanisms (Vlasses et al 1986, Salvetti 1990). This study could not have included medicines which are not proven to have some degree of substitutability, as competition would not be present.

The study period is long enough to capture the market dynamics from an early stage of ACE inhibitors' introduction in the market, until very recently, with 14 competitors in this therapeutic class. This would allow the entire range of market dynamics to be studied, including the evolution of volume in the presence or not of generic competitors for the three first market entrants.

The data used in study 3 (the impact of parallel trade on pharmaceutical competition) concerned the retail market in four countries (notably Germany, Sweden, the Netherlands and the United Kingdom), which faced parallel trade and whose price level for prescription pharmaceuticals was above the European average

during the study period and therefore the potential for parallel trade from lower-priced countries would in principle be significant. Observations are annual and concern the 2003-2006 period. A segment of the market, comprising six therapeutic (product) categories was selected. In total 18 molecules were considered, which were chosen because of their high volume and high price. The product categories were proton pump inhibitors (PPI) (lansoprazole, omeprazole, pantoprazole), HMG CoA reductase inhibitors (statins) (atorvastatin, pravastatin, simvastatin), Angiotensin-converting enzyme inhibitors (ACE I) (captopril, enalapril, quinapril, ramipril), Angiotensin II receptor antagonists (ACE II) (losartan, valsartan), selective serotonin reuptake inhibitors (SSRI) (citalopram, paroxetine, sertraline), and atypical antipsychotics (AAP) (clozapine, olanzapine, risperidone).

Data included prices and sales for each product in each country, and sales and prices of locally sourced and parallel traded products are clearly distinguished. Market shares were calculated based on sales for the originator and the parallel trader. Prices are presented in Euros.

3.2 Methodology

In this thesis both theoretical analyses and empirical methods are used. Theory provides a framework of how agents behave, predicts market behaviour and sets the hypotheses to be tested. Empirical methods use real data in order to define and test the causal relationship between variables and the magnitude of changes of dependent variables due to a certain change in independent variables. Theory and empirics are complementary in this respect and show a complete image of market dynamics.

3.2.1 Theoretical Modelling and Game Theory

Theory sets the foundations and discusses the core of the research question. It analyzes the dynamics and the expected behaviour of rational agents. Further, theory predicts the outcomes of a model or a game and provides a hypothesis, indicating the expected direction of changes in a variable as a result of a change in another factor. Also, theory sets the outline and determines the equations which will be tested empirically in order to see whether the hypothesis holds or not.

Game theory is a very useful tool for market analysis. Producers of goods which aim at the same group of consumers as potential buyers are de facto competitors. This means that actions of one producer (also known as "player" in game theory) influences other competitors' quantities sold and profits, making the affected competitors react by adjusting their behaviour in order to maximize their profits given the actions of other producers. There is close interaction between players and actions are not only based on observed actions of other players but also on expected actions, assuming that other players are rational agents aiming at maximizing their profits. Each competitor creates his "reaction function" (Cournot 1838), which demonstrates his strategy for each action of other competitors. This close interaction is why markets are considered as games and the theory of industrial organization is based on game theory. Game theory predicts the outcomes of markets based on the profit maximizing behaviour of firms. As this thesis studies pharmaceutical market competition and market outcomes and dynamics, game theory is a very important tool for the purpose of study 3.

3.2.1.1 Conceptual framework Study 1

In study 1, a conceptual framework is introduced to discuss and show the impact of brand loyalty on purchasing decisions of patients or physicians, the latter acting as agents for the former. The model exhibits a market with an originator and a generic product. The key role in this model is played by brand loyalty (or otherwise considered as "aversion towards generics"), which is assumed to differ across patients. There are some who insist on purchasing branded products and others who are not so loyal. Brand loyalty is included in the model because it is a core aspect on consumer choice between originators and generics. Generics are of the same chemical substance as originators, so it is actually a homogenous product. However, some consumers are reluctant to either switch from an originator to a generic or, if they are newly introduced to a molecule, to start using a generic. The reason is that generics are (falsely) perceived as a product of lower quality than the originator. This is why some people are willing to pay more out-of-pocket to purchase the originator rather than the generic. This willingness to pay and low price elasticity on behalf of certain consumers keeps the originator price from decreasing post patent expiry. In general, when demand is inelastic, providers can increase revenue by increasing their price. This leads to what is known as the "generics paradox". The model shows that the stronger brand loyalty is, the higher the price of the product.

3.2.1.2 Conceptual Framework for Study 2

Study 2 introduces a conceptual framework which shows how the manufacturer of a branded product may reduce promotion activities after his product loses its patent. This framework suggests that returns of a monetary unit invested in an off-patent medicine are lower than a monetary unit invested in a patented product.

Further, any investment on advertising for an off-patent molecule creates a positive spill-over towards generics. Therefore, advertising activities decrease and the producer invests resources in other products, of other classes which are still in – patent. This underlines the importance of advertising and sales promotion activities on the determination of market shares. As increased advertising efforts lead to higher sales, and more advertising from a competitor decreases rivals' sales (Bagwell 2005), it follows naturally that decreased advertising efforts from the manufacturer of the off- patent originator product will decrease sales volume of this particular molecule (both originator and generic) and increase competitors' sales (in – patent products of the same therapeutic category). Weaker advertising efforts allow branded competitors of the same therapeutic class to attract part of the demand which was previously attracted by the in - patent product. The expected result is that sales volume of the off –patent molecule decrease, and volume of other in – patent products of the same therapeutic class increase.

3.2.1.3 Conceptual Framework for Study 3

Study 3 uses a game theoretical approach to provide insight of how medicine prices evolve in the presence of pharmaceutical parallel trade. The manufacturers and the parallel traders act as rational profit maximizers. Based on this assumption we can foresee the moves each agent will make, based on the expectations of the move the other player will make in order to reach a strategy which will maximize his profit. In a market without parallel trade – targeted regulation the Nash Equilibrium is that the price of the parallel traded product is the same as the locally sourced product. The Folk Theorem would suggest infinite equilibria between the per-unit cost and the initial price of the locally sourced medicine. Nevertheless, each player observes that a price war will make both worse off. The manufacturer would have to

set his price at the parallel trader's break-even point. This would be the price level of the exporting country plus the per-unit cost that the parallel trader would be burdened with to import the product (transportation costs). This is significantly lower than the price of the locally sourced product, while the manufacturer would gain only the part of the market that the parallel trader had, which in most cases is up to 20%. The parallel trader knows that a price war would lead him out of the market, so he prices the product at the level of the locally sourced medicines. Another reason why he sets the price at the same level as the locally sourced product is that he manages to sell all quantities he imports (due to the limited quantities he can buy in exporting countries), so any price lower than that price would generate lower profits. In a different case, a price war could be triggered that would make him lose his market share and the profits he gains from parallel trade. Therefore, we reach the conclusion that in such an infinitely repeated game, rational agents observe market dynamics and understand that a price at the level of the monopolist price would make them both better off. This will make them adopt a price at the level of the locally sourced price before parallel trade entry. In any case, the price of the parallel imported product will equal the price of the locally sourced product. Regulation though may lead to different outcomes. There is a number of regulatory measures in the six European countries of the sample which affect the market equilibrium in the presence of parallel trade. Patient co-payments create pressure for the price of the parallel imported product to deviate downwards from the price of the locally sourced product, creating a price gap. The same happens when health insurance shares any saving occurring from dispensing parallel imported products with pharmacists. Clawbacks and quotas have the opposite effect. Thus, we have different market equilibria in the presence of different types of regulation.

3.2.2 Descriptive Statistics

Descriptive statistics help provide a general impression about trends for a variable or a series of variables. They show a general picture of a particular issue and how it evolves over time. Graphs and figures expressing these descriptive statistics may make the trends even clearer. Nevertheless, they do not control for other factors and they only allow for univariate analysis. Consequently, they do not reveal underlying issues or exhibit any causal relationships.

Descriptive statistics are used in all three studies in this dissertation. In the first study (generics paradox) they have been used to show originator price trends before and post patent expiry. Graphs are used for each off patent molecule included in the study in each of the six countries discussed. The objective is to show how originator prices evolve and whether there is some visible change in price post patent expiry. In most cases originator prices do not seem to change significantly after generic entry, while in some cases prices increase. Therefore, evidence from the descriptive analysis is inconclusive. This is why econometric analysis is employed, which clearly shows that originator prices often increase post patent expiry.

In the second study (switching behaviour post patent expiry) descriptive statistics are used to show how the ratio of volumes of off-patent products and in-patent products of the same therapeutic class evolve before and after patent expiry of one of the molecules. Graphs show a decrease in the ratio of volumes post patent expiry. This is somehow consistent to the findings of the econometric analysis, which show that there is a switch in consumption from the off patent molecule to in patent molecules.

Descriptive statistics are crucial for the analysis of the third study (the impact of parallel trade on pharmaceutical competition). The analysis and the descriptive statistics provided have four goals: First, to show whether there is an incentive for the parallel trader to set a price different from that of the locally sourced product; second, to examine if the manufacturer will change its pricing behaviour due to the presence of parallel traders; third, to show if there is a price gap between the locally sourced and the parallel traded product; and, finally, to examine whether there is upward or downward price convergence between locally-sourced and parallel traded product. The third goal is achieved using descriptive statistics. The price gap between locally-sourced and parallel traded product appeared to be positive for Germany, Sweden and the Netherlands, and mostly zero for the United Kingdom.

3.2.3 Econometric analysis

When conducting multivariate analysis, descriptive statistics may not show the whole picture, as they ignore the joint effect of factors and do not reveal causal relationships. For example, in study 1 (the generics paradox), descriptive analysis shows how originator medicine prices evolve over time, before and after generic entry, but do not control for the effect of regulation or generic market shares. In study 2 (switching behaviour post patent expiry), graphs show the evolution of the ratio of off patent ACE Inhibitors volume over in patent ACE inhibitors volume. However, the graph does not control for regulatory measures and the number of competitors. This is why our empirical analysis is based on multivariate econometric analysis. Therefore, the use of descriptive statistics in studies 1 and 2 is only indicative and is used as an introduction to the empirical analysis of the study, as the

main source for drawing conclusions are the estimation results of the econometric model.

Econometric analysis is a critical part of all three studies. Econometric methods let us examine the relationship among dependent and explanatory variables. The results of the econometric analysis show the direction of a change in a variable as a result of a change in another variable, as well as the magnitude of the change, ceteris paribus. Most importantly, econometric analysis provides greater insight than descriptive analysis because it allows for multivariate analysis. While descriptive statistics and graphical analysis show the effect of one parameter on the dependent variable, without taking into account that a change may be due to other factors, econometrics allow to control for many factors. Results show the effect of the change in one factor while all other factors remain constant.

Pharmaceutical markets are influenced by many factors. Prices and volume of pharmaceuticals depend on the structure of the market and the volume and nature of competition. But unlike other markets, regulation and policy interventions, as well as patent protection, make pharmaceutical markets even more complicated. These factors have to be taken into account in the analysis, as they jointly determine prices and volume.

Econometric analysis is used in all three studies of the dissertation, as all studies examine the impact of a number of factors on competition in pharmaceutical markets. The nature of the data provided allowed the use of panel data econometric analysis. Panel data is a combination of cross section and time series data. Indeed, it is a combination of time series over the same time span for different sections. In this dissertation, the panel identifier is each medicine in each country. Hence differences across countries and molecules are taken into account in the empirical model. The

main advantage of panel data is that it allows to analyse changes at the individual level (Verbeek 2005). In some country- specific regressions, there are not enough observations at the time level nor at the individual level to satisfy the asymptotic properties of panel data analysis. In these cases, ordinary least squares are used.

For some variables, past behaviour may influence future behaviour. This may be the case for prices, so in study 3 we also include a dynamic model, apart from the static one. The dynamic panel data method used is that of Blundell-bond (1998). This is preferred to the Arellano-bond estimator (1991), because the latter may not perform well if the autoregressive parameters are too large.

In study 1, results of the econometric analysis show that the generics paradox does indeed exist in regulated markets. In study 2, the results of the regressions show that there is a switch in consumption towards in patent molecules of the same therapeutic class when another product in the class loses its patent. Finally, in study 3, the results show that there is upward price convergence between locally sourced and parallel imported products.

Of course, appropriate control variables have been used and any endogeneity problems have been addressed with the use of instrumental variables. Finally, robust standard errors have been used to address any autocorrelation or heteroskedasticity problems.

4. The Generics Paradox Revisited: Evidence from Regulated Markets

4.1 Introduction

Patent protection grants originator medicines exclusivity in the market of the particular molecule for a nominal period of twenty years according to the WTO TRIPS (Trade-Related Aspects of Intellectual Property Rights) agreement (WTO-OMC TRIPS fact sheet, 2006), though the actual protection period is shorter. When the patent for a particular molecule expires, generic products may enter the market, turning a monopolistic market (for that molecule) into a more competitive one. The generics paradox is a phenomenon whereby, following generic entry, prices of originator products increase despite generic competition (Frank and Salkever, 1997). This finding is significant because it contradicts the prediction of economic theory, according to which prices decline when competitors for the same product enter the market (Mas – Colell, Whinston and Green, 1995, Tirole 1988). The generics paradox has been proven to be present in the US market, which is largely unregulated. In this study we test empirically whether it also holds in European Markets in the presence of intervention in pharmaceutical markets, such as reference pricing, price cuts and cost-effectiveness.

Pharmaceutical markets do not operate in the same way as regular markets and the predictions of economic theory often do not apply due to the special nature of this market. Insurance and third party payers, information asymmetry and agency relationships make this market special, and it is reasonable to expect that they lead to low levels of elasticity of demand. Numerous studies of the pharmaceutical market have shown that the price elasticity of demand is low and ranges between 0

and -0.3. (Gemmill et al. 2007, Grootendorst et al. 1997, Leibowitz et al. 1985, Johnson et al. 1997, Gardner et al. 1997, Hughes and McGuire 1995, Lavers 1989, O'Brien 1989, Ryan and Birch 1991, Smith and Watson 1990). In addition to providing prescription medicine insurance coverage, the inelastic nature of demand has led some governments to introduce regulatory measures in order to control pharmaceutical prices.

Regulatory regimes differ significantly across countries. In the United States, markets are largely unregulated and prices are determined through negotiations between manufacturers and insurers. In Europe, markets are significantly more regulated, as there is government intervention in pharmaceutical pricing and reimbursement. Some countries though do have in principal free medicine pricing. Different interventions apply to in- patent and off- patent markets. For example, in the United Kingdom, originator medicine prices are free from direct regulatory intervention, subject only to rate of return regulation, also known as profit controls (OFT 2007, DoH 2008). However, the generic market is free of price fixing, and prices are determined based on competition between generic producers. Reference pricing is the most common intervention in off- patent markets in EU countries. Countries which use reference pricing for off- patent markets include Germany, the Netherlands, France, Denmark, Spain and Italy (PPRI 2008, Kanavos and Gemmill 2005). This measure was abolished in Norway in 2001 and in Sweden in 2002. Price caps particularly for generic medicines are also present in some European countries, such as France and Italy. In this case, generic prices are set at a maximum percentage of branded prices. Finally, managed competition is used by Austria, whereby there is competition subject to a general framework in which prices can evolve, as generic and originator prices have to gradually decrease in the first years

of generic entry, according to regulation. These different regulatory environments create different market dynamics and cause price differentiation across Europe. Thus, what pricing dynamics may occur in each country, and in particular how the originator price will evolve, may heavily depend on the interventions applied.

4.2 Objectives

Whereas previous research has shown that the generics paradox exists in largely unregulated markets, such as the USA, there is no evidence of whether it would also be present in regulated or interventionist markets, and, if so, how it would manifest itself. In principal, it does seem counter-intuitive to assume that the generics paradox will be present in regulated markets because interventionist policies typically provide a tight control for price movements. However, the breadth of regulatory practices ranging from explicit price controls in in-patent and off-patent markets, to milder interventions, such as reference pricing, suggests that the generics paradox could also be present in some regulated markets. Frank and Salkever (1997) studied the generics paradox using US data. A question that remains is whether their findings would be the same in regulated markets, among them many the European ones. Thus, the objective of this study is to determine whether the generics paradox still holds in the presence of regulation and analyse the effect of price changes and overall price behaviour in the presence of different regulatory interventions. Further, this chapter will explore the impact of the findings on the ability of generic policies in different countries to deliver savings post patent expiry.

In order to achieve this we set up and test an empirical model, to test the joint effects of generic entry and regulation and other parameters on the prices of the originator products in a market. Quarterly data from 6 European Countries are used

over the period 1997-2002 in order to examine the behaviour of prices of originators (branded medicines) after generic entry.

Section 4.2 discusses the background on regulation and the generics paradox; section 4.3 provides a framework of the issues of brand loyalty and market dynamics, while section 4.4 provides a descriptive analysis. Section 4.5 introduces data and methods of the econometric analysis, whose results are in section 4.6. Section 4.7 discusses policy implications and section 4.8 concludes.

4.3 Regulation in Pharmaceutical Markets and the Generics Paradox

4.3.1 Empirical Evidence on the Generics Paradox

Several studies have empirically shown evidence of the existence of the generics paradox. The first study addressing this issue was written by Caves, Whinston and Hurwitz (1991). The authors conclude that generic entry only leads to a slow-down in the increase of originator medicine prices. Frank and Salkever (1997) suggest that the introduction of generic products on the market leads to price increases in brand name pharmaceuticals. They point out that a necessary condition for such price increases is that entry leads to a decline in the own-price elasticity of reduced-form brand-name demand. Grabowski and Vernon (1992) found empirical evidence that pioneering firms did not attempt to deter entry through their pricing strategies. Rather, in most cases, firms continued to increase their prices at the same rate as prior to entry. Rizzo and Zeckhauser (2005) also find empirical evidence that producers of brand-name products do not decrease prices after generic market entry. All four studies used US data in order to show the existence of the generics paradox.

4.3.2 Regulatory Environment and Medicine Prices Post Patent Expiry

Some studies suggest that regulation leads to lower prices, while others conclude exactly the opposite. Comparing them is not an easy task due to differences in data and methodology.

The most common measure which aims at containing costs in European countries (as well as elsewhere) is reference pricing. Reference pricing sets a maximum reimbursement price for prescription medicines. It is the average of the lowest prices of a group of products of a particular molecule, or therapeutic class.

According to Lopez-Casasnovas and Puig (2000), the goal of reference pricing is not the limitation of overall pharmaceutical expenditure, but the control of third-party expenditure on prescription medicines. They argue that "by limiting the level of public reimbursement, reference pricing aims to reduce the price of referenced products, either through (i) a relative decrease in demand for highly-priced products (a demand-sided approach) or (ii) cutting medicine prices by encouraging self restraint (supply side approach) once manufacturers face the threat of losing markets" (Lopez-Casasnovas and Puig 2000).

Nevertheless, there are concerns about how efficient this measure is: Does reference pricing relax competition between suppliers of pharmaceuticals? In some cases there is not enough competition in pharmaceutical markets, since some competitive products enter the market simultaneously at the same price. This could either be the outcome of market equilibrium or a result of some form of tacit collusion and a cooperative game between competitors.

Reference pricing systems can also be challenged in that they only address one side of the efficiency equation, the cost side, while ignoring the effectiveness side. Also, when addressing the cost issue they focus only on price instead of

including the total cost of treatment. Another challenge is that in such a reference price system the laws of a free market, where high competition leads to lower prices, may not apply. Therefore, we aim to address these concerns, namely that suppliers have no strong incentive to set a price lower than the reference price.

Empirical work by Aronsson, Bergman and Rudholm (2001), suggests that in the case of Sweden, reference pricing leads to a decrease in the market shares of particular originator products, which means higher levels of competition. Further, they suggest that reference pricing is an important determinant of price paths. Grootendorst and Stewart (2006) found that in the case of British Columbia, although the daily cost of treatment declined following the introduction of reference pricing, part of this reduction is likely due to factors other than reference pricing. Ioannides-Demos, Ibrahim and McNeil (2002) also suggest that other factors influencing total pharmaceutical expenditure have often occurred simultaneously to reference pricing and make it difficult to isolate its specific effects. They propose that further investigation is required before any valid conclusions can be drawn about the net effect of reference pricing on healthcare costs.

Another study concludes that competition has kept prices low in markets with less regulation: Danzon and Chao (2000) find empirical evidence that generic competition is more effective in such countries. Nevertheless, the authors state that comparing prices of pharmaceutical products across countries gives uncertain results due to the differences in products, prices and volumes.

It is difficult to draw general conclusions from these studies due to methodological differences in the range of products considered, the extent to which generics were included or not and other such factors (Kanavos and Mossialos 1999, Kanavos and Srivastava 2008). Furthermore, there seems to be heterogeneity across

countries concerning the prices and diffusion of generics after patent expiry (Magazzini, Pammolli, Riccaboni, 2004).

Consumers' behaviour also plays a role in pricing. Despite the low levels of price elasticity (due to insurance, as consumers pay less or nothing out of pocket) and the presence of brand-loyalty, consumers' purchasing behaviour may lead to a decrease in the originator's prices. An interesting finding by Rizzo and Zeckhauser (2005) refers to consumer choices and how they affect prices of originator medicines. They find that a 10% increase in the consumers' generic script share is associated with a 15.6% decline in the average price paid for originator medicines by consumers.

Price regulation affecting the generic market may have an adverse effect in generic price reduction over time. Various studies have shown different results concerning the impact of regulation on generic medicine prices. Some studies suggest that countries with strict price regulation have lower prices than countries with less strict regulation (Jonsson 1994).

According to evidence from Norway, the introduction of a price index that aimed in lowering entry barriers actually lead to an increase in generic market shares and helped trigger price competition by reducing overall market power. (Dalen, Strom, Haabeth, 2006). This policy measure may offer consumers the alternative of cheaper medicines (generics) and therefore help reduce spending. The last finding though, concerning price competition, is the opposite of what the generics paradox suggests. The presence of regulation, such as the price index may indeed distort the market, leading to different effects than what would happen in the absence of regulation.

On the other hand, Razzolini (2004) examined a demand model which takes into account the effect of the age of a medicine in the market. The model examines the non-mandatory substitution reform that took place in Norway in 2001. His model assumes Bertrand competition and he suggests that the reform has a negative effect on generic demand. The author also suggests that his findings support the hypothesis that competition does take place between generics.

There are many different findings concerning the impact of regulation on competition and prices. In this study, we will attempt to fill in a gap by examining whether the phenomenon that originator prices increase post patent expiry (known as the generics paradox) holds in regulated markets. Results may give insight into the pricing behaviour of firms in the presence and absence of these two important factors, and therefore help policy makers make policy decisions concerning prescription, reimbursement and pricing of pharmaceuticals.

4.4 Theoretical Background

4.4.1 Sequential Market Entry

After having reviewed the literature on regulation and competition in off-patent markets, we proceed to study market dynamics. Generics affect the market of a medicine through the impact they have on competition. Generic entry transforms the market from a regulated monopoly to a regulated oligopoly, or monopolistic competition, since some consumers perceive differences between brand name and generic products. It is useful to see how market structure affects prices and quantities in the pharmaceutical market.

Wiggins and Maness (2004) found that the relationship between pharmaceutical prices and the number of sellers is more like that found in other industries. A negative relationship is therefore assumed. Mark Boyer and Michel Moreaux (1987) suggest that "whatever the role (leader, follower, Nash competitor), it is always more profitable to be a quantity (price) setter if the goods are substitutes (complements)" (Boyer and Moreaux 1987). In other words, it is better to fight in a quantity space when goods are substitutes, which is the particular case we are examining in this study, because generics are substitutes of the originator product. This would lead us to the hypothesis that the nature of competition in the pharmaceutical market follows the Stackelberg Model. There is a price leader, which is the producer of the originator product, which is initially patent protected. After patent expiry, generics enter the market. As the producer of the originator has already set his price, generics are price followers.

Although R&D involves significant costs, it does not enter the profit maximizing function, so it does not affect the equilibrium quantity or price. This is due to the fact that it is a sunk cost.

The solution of the Stackelberg model shows that the leader has higher level of sales than each of the followers separately. The model also suggests that the price is the same for all competitors. Empirical data though is not in support of such behaviour. There are explanations for this. Empirical data and previous studies (discussed in section 4.4) have shown that the market share of the originator medicine falls constantly after patent expiry, but a small market share remains, despite the fact that its price is significantly higher than generic prices. This is a consequence of brand loyalty. Although band-name products and generics have the same chemical substance, some consumers may believe that the brand-name product

is better, so products cannot be considered as perfectly homogenous, not because of their actual nature, but because of the perception of some consumers. There is evidence from European countries indicating that generic medicine substitution for some patients is not considered an equal alternative to branded medicines, and these patients may need additional information and support (Kjoenniksen et al, 2006). Alternatively, it is usually the physician (who acts as the patient's agent) who makes decisions on their behalf regarding the medicine which will be consumed. Physicians may be influenced by direct promotional activities by the industry, influencing the his decision regarding which product will be prescribed. Pharmacists also play a role in demand and supply, since in some countries (such as Germany and Denmark) legislation gives them incentives to substitute originator products with generics, in order to reduce government spending for pharmaceuticals (PPRI country profiles 2008).

Market shares of the originator product fall after patent expiry. Mrazek and Frank (2004) suggest that although residual loyalty remains after generic entry, it does not deter generic competition. After patent expiry, prices of generic products fall to a fraction of the originator medicine price. Evidence on prices of generics indicates that they are significantly below those of originator products. Kanavos and Srivastava (2008) point out that the average generic price was 25 percent lower than the originator price at the point of generic entry in the United States, and that as the number of generic competitors increased the price fell to about one-fifth of the initial average generic price. Kanavos, Costa-Font and Seeley (2008) have also illustrated the gradual decrease in generic prices as competition increases.

Although the product is in practice homogenous, the Stackelberg model of sequential entry is possibly not appropriate for the analysis of competition in the

pharmaceutical market post patent expiry. In contrast to the predictions of the Stackelberg Model, prices differ across products due to brand loyalty, the originator product being priced at a higher level than generics. The originator product keeps only a part of the market and does not engage in price war with the generics.

The special nature of pharmaceutical markets make it necessary to set up a conceptual framework that captures the likely effects of brand loyalty and the extent to which it leads to different prices across products in the same market. this framework is outlined in the section that follows.

4.4.2 A prescription medicine market model with (perceived) product differentiation: The importance of Brand Loyalty

The pharmaceutical market is a market of sequential entry, due to patent protection. While the product is in patent, only the branded product is in the market. Post patent expiry, generic competitors enter. Economic theory explains behaviour in markets with sequential entry using the Stackelberg model. The outcome of the Stackelberg model suggests that prices across producers are the same, while the first entrant has a larger market share than the second entrant (Stackelberg 1952). This Model though cannot explain the function of the pharmaceutical market post patent expiry, due to the presence of brand loyalty, which upsets the assumption of a homogenous product, due to consumer perceptions, at least for a significant part of consumers. For this reason we set up a different theoretical model in order to understand how the market works for branded and generic products. This will serve as a framework for the empirical model which will follow. Frank and Salkever's pioneering study on this topic did not provide a theoretical model on the effects of brand loyalty on prices. A discussion on how generic entry could affect branded

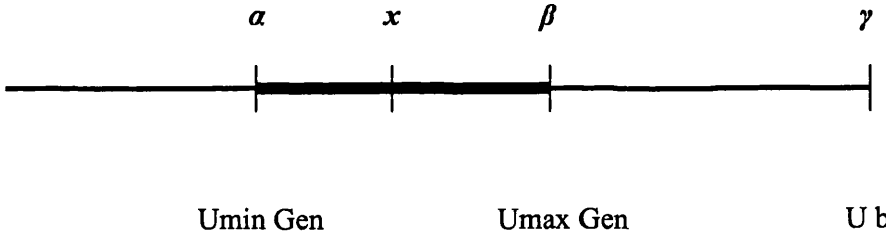
prices was provided instead. In our model, the branded product is perceived by purchasing decision makers (patients or physicians) as a differentiated product. Consumers obtain higher levels of utility when consuming the branded than a generic (although in practice they have the same chemical substance and therefore are identical). This reflects brand loyalty by consumers or physicians, who act as their agents.

Suppose there is a market of a certain chemical substance. There is a branded product, which has gone off- patent, allowing for generic competitors to enter the market. For simplicity, we assume there is only one generic present. The total quantity of medicines sold is fixed and does not depend on prices (we assume fixed demand). It is therefore assumed that all patients will be treated, but they have the choice between the branded and the generic product. This assumption follows universal health coverage in the EU. Thus the total quantity is fixed, but the breakdown among different medicines is not. Whether the branded medicine or a generic is dispensed depends on a number of factors.

Brand loyalty and perceived quality differences influence purchasing decisions. These decisions may be taken either by the physician, which is the one that prescribes the medicines, or the consumer, if he or she is aware of the products available and has a strong preference for the branded medicine. The insurer though may also make this decision, by announcing whether the originator will be reimbursed or not, or whether a co-payment will occur when the branded product is dispensed. The insurer has an incentive to do so as he is interested in paying for the lowest cost medicine, given that they are of the same chemical substance, thus the therapeutic outcomes are the same. Assume there is a density of consumers, which are uniformly distributed among points α and β, as it appears in Figure 4.1. This

distance represents the utility of consumers at each point of the line that is gained from consuming the generic. $\beta > \alpha$, meaning that the utility of people consuming generics increases as we move to the right. In other words, the distance between α and β represents aversion to generics, revealing how brand-loyal each consumer is: Consumers at point β are less averse towards the use of generics, so they are not as brand loyal as patients closer to α. They obtain the maximum possible utility from generic consumption. Consumers at point α are the most averse towards generic use; therefore they are the most brand-loyal. On the right of point β is point γ, which represents the (perceived) utility from using the branded product.

Figure 4.1 Consumer Utility



There is a point x between α and β, where the population of consumers is split into two parts and consumers on the left hand side of x consume the branded product, while the consumers on the right hand side of x consume the generic. The demand for the generic is β-x and the demand for the branded medicine is x-α.

x is the point where consumption switches from the branded to the generic. At that point utility must be the same for purchasing the generic or the branded. Thus:

$$I - p_G + x = I - p_B + \gamma \qquad (1)$$

$$\Rightarrow x = p_G - p_B + \gamma \qquad (2)$$

where I is income, p_G and p_B are prices of the generic and the branded respectively, and x and γ are the utility originating from consuming the generic and the branded respectively.

Profits of generic producer are:

$$\Pi_G = p_G(\beta - x)$$

$$= p_G(\beta - p_G + p_B - \gamma) \qquad (3)$$

The first order conditions for profit maximization are:

$$\Pi'_G = \beta - 2p_G - \gamma + p_B = 0$$

So the price of the generic is:

$$p_G = \frac{1}{2}[\beta + p_\beta - \gamma] \qquad (4)$$

Similarly, profits of branded producer are:

$$\Pi_B = p_B(x - a)$$

$$= p_B(p_G - p_B + \gamma - \alpha) \qquad (5)$$

The first order conditions for profit maximization are:

$$\Pi'_B = p_G - 2p_B + \gamma - \alpha = 0$$

So the price of the branded is:

$$p_B = \frac{1}{2}[p_G + \gamma - \alpha] \qquad (6)$$

Substituting equation (6) into (4) gives us:

$$p_B = \frac{1}{2}\left[\frac{1}{2}(\beta + p_B - \gamma) + \gamma - \alpha\right]$$

$$= \frac{1}{3}[2\beta - \gamma - \alpha] \qquad (7)$$

Similarly, substituting equation (4) into (6) gives us

$$p_G = \frac{1}{2}\left[\frac{1}{2}(p_G + \gamma - \alpha) + \beta - \gamma\right]$$

$$= \frac{1}{3}[\beta + \gamma - 2\alpha] \qquad (8)$$

Differentiating (7) and (8) with respect to brand loyalty (γ) gives us:

$$\frac{dp_B}{d\gamma} = \frac{1}{3} > 0$$

and $$\frac{dp_G}{d\gamma} = -\frac{1}{3} < 0$$

As γ increases, the price of the branded medicine increases and the price of the generic decreases. The reason for this is that γ represents the (perceived) utility from consuming the branded medicine. An increase in this utility moves point x (which is the point at which consumers switch from the branded to the generic) to the right, thus increasing the fraction of consumers purchasing the branded medicine. Therefore the price increases. The effect on the generic is exactly the opposite, meaning that brand loyalty leads to higher prices of the originator products and lower prices of the generics. This is reflected in pharmaceutical markets, where branded products are indeed more expensive than generics.

The market share of the branded product is:

$$MS_B = \frac{x-\alpha}{\beta-\alpha} = \frac{-2\alpha+\beta+\gamma}{3(\beta-\alpha)} \qquad (9)$$

$$\frac{dMS_B}{d\gamma} = \frac{\beta-\alpha}{3} > 0$$

The market share of the generic product is:

$$MS_G = \frac{\beta-x}{\beta-\alpha} = \frac{\alpha-2\beta+\gamma}{3(\alpha-\beta)} \qquad (10)$$

$$\frac{dMS_G}{d\gamma} = \frac{\alpha-\beta}{3} < 0$$

The first derivative of the branded product's market share with respect to γ is positive, showing that the market share of the branded product increases with brand loyalty. The opposite happens to the generic product, as the first derivative is negative.

This analysis gives us results which are in accordance with what we expected. Prices and market share of branded products increase with brand loyalty, while this has exactly the opposite effect on generics (decrease of price and market share).

In a market with insurance, it can be argued that prices do not play a (significant) role in purchasing decisions, so the model discussed previously does not apply to such markets, unless co-payments are present. Nevertheless, even in these markets, there are factors that make prices play a role in dispensing patterns: First, regarding physicians, policies can include penalizing over-spending or rewarding under-spending. These incentives encourage generic prescribing in order to control expenses. Second, in some countries pharmacists are able (or obliged) to substitute a branded for a cheaper generic, if this is available. Pharmacists are

typically remunerated by health insurance. If regressive margins are implemented, these may provide an incentive to dispense the cheapest medicine in some cases. Hence, this remuneration scheme encourages generic dispensing.

We have showed how brand loyalty leads to higher prices, which is the underlying factor and a necessary condition for the hypothesis in the empirical model (which follows in section 4.5.2) that prices of branded medicines may keep on increasing after generic entry. Regarding the direct effect of generic entry on originator prices, consider a branded medicine that has been in the market for a time period equal to its patent. When generics enter the market, they attract a large proportion of the market, while the originator's market share drops continuously (since many consumers or their agents are not brand loyal and do not mind consuming generics), ending up in controlling a small fraction of the market. This small market fraction concerns brand loyal consumers. Since sales have dropped so steeply, the firm's profits decrease. We can assume that the originator's remaining consumers' behaviour is inelastic regarding the originator's price, due to the aversion they have towards generics. This means that total revenue increases with a moderate increase in its price. Hence, increasing prices post patent expiry can be an originator producer's way to gain back part of lost profits.

Unfortunately, this framework cannot be tested empirically, as brand loyalty is unobservable and it is difficult to be quantified. Nevertheless, this model sets a firm background for the very important issue of brand loyalty in pharmaceutical markets and shows how it can lead to higher prices of branded originator products and mirrors other empirical analysis in the field (Frank and Salkever 1997).

4.4.3 Brand loyalty and price elasticity

According to Cunningham (1956), brand loyalty is a "substantial asset" for producers. Its main characteristic is that it varies widely across consumers, but it may be present even if there is no difference between products apart from their brand (Tucker 1964). Higher brand trust leads to positive outcomes for producers, such as market shares (Chaudhuri and Holbrook 2001). In pharmaceutical markets, physicians may become brand loyal as a result of prescribing a particular brand only while the product is in- patent (Grabowski and Vernon 1992).

Some patients prefer branded to generic products, for two reasons. First, they may have the mistaken impression that branded products are better than generics, meaning that they perceive the product as differentiated. Second, their physician, who acts as their agent, may prescribe the branded product, and they follow the physician's decision. It is this particular part of the population that is critical for the originator manufacturer's pricing decisions.

The producer of the originator product is a monopolist for the particular molecule until patent expires and generic competitors enter the market. Generics enter the market at a lower price than the originator product. The producer of the originator has paid for R&D, hence the relatively high prices while the product is in patent. R&D costs are high when compared to the per-unit cost of production. Generic producers however are not subject to R&D costs and the per-unit cost of production of their product is low compared to R&D costs and this allows them to set a lower price than the originator product and still have the possibility to have positive profits. R&D does not play a role in determining prices for either producers post patent expiry due to the fact that R&D is a sunk cost.

Prices of generics enter at a lower price than the branded product due to the absence of a brand name. However, regulatory interventions aiming at generic prices may cause a further decrease in generic prices. This would lead to an even larger difference between the originator product and generic competitors.

If the originator producer chooses to lower his price as a response to generic prices reduction, this will lead generic producers to further lower their prices, as the per-unit cost is very small for pharmaceuticals. If the originator producer follows, they will again lower their prices and this will carry on until the point where generic producers make zero supernormal profits. This price war is not in favour of the branded product producer.

By lowering their prices, the generic producers gain part of the market share of the branded product. This will leave the branded product with a smaller market share, but this part of consumers are now on average even more brand loyal than before. For this part of the consumers it is reasonable to believe that demand is inelastic. Consequently, by increasing its price, the branded product increases its total revenue, as well as total profits (as total production costs are lower for producing lower quantities of product).

The conclusion is that regulatory measures targeting generic prices will have an indirect effect of an increase in the branded price. This is known as the generics paradox in the United States, where price regulation is not present.

Consumers do not pay for medicines out-of-pocket, as long as the price is what health insurance agrees to pay for. Any difference usually has to be paid out-of-pocket by the consumer. Thus, the approach explained previously does not change in the presence of third-party payers. The higher the out-of-pocket payment (due to the price difference between the generics and the originator), the more

consumers will choose the generic instead of the branded product, leaving a smaller and more brand-loyal part of consumers choosing the branded product. Demand originating from these consumers is inelastic, thus increasing the originator's price leads to higher profits for the producer of the originator product.

4.4.4 Why Reference Pricing may reduce Competition Levels

In this section we discuss internal reference pricing, which refers to using prices of other products marketed in the same market as a benchmark, as opposed to international referencing, which includes prices of other countries and is usually applied to in-patent products.

Reference pricing has been implemented as a cost- containment mechanism in generic markets. The reference price takes into account a basket of relatively low prices and set a price at which products of the same molecule (or same class of molecules in certain countries such as the Netherlands) will be reimbursed by health insurance. At a first glance, this appears to be a measure which helps decrease medicines prices post patent expiry and leads to savings. Nevertheless, this regulatory measure may not lead to the most efficient allocation of resources.

According to economic theory, competition reduces prices. The more players participating in the market, the higher competition is and the lower prices are expected to be.

Reference pricing is usually set at the average of the cheapest products of a group. Any product priced at the reference price or at a lower level is reimbursed by health insurance. Products which are priced lower than the reference price have the incentive to increase their prices to the level of the reference price because they will not lose part of their market share since consumers will not be subject to any higher

price burden. New market entrants also have no incentive to price at a level lower than the reference price.

Products which are priced at a higher level than the reference price may adjust their prices and converge at the reference price level. This does not lead to any savings for health insurance, since there are other products available in the market at a lower price, which would be the ones reimbursed, and consumers would have to pay the price difference for any products which are more expensive.

This price level works as an equilibrium from which generic producers will not deviate. Lowering the price will lead to lower profits, as the market share will be the same (due to reimbursement) but the price will be lower. Although this may influence the price basket which determines the reference price, there is still no incentive to deviate, especially since other competitors will follow and a new - lower- reference price will be set. Deviating upwards will lead to a co-payment on behalf of consumers. A generic company would not be better off doing so if it does not have any advantage (from a consumer's point of view) compared to other generics.

Generic prices tend to decrease steadily in the years following patent expiry (Kanavos, Costa-Font, Seeley 2008). The presence of reference pricing though may prevent this from happening, as reference pricing makes prices rigid downwards. Although reference pricing leads to price cuts in the short run, in the long run it may actually keep prices at a relatively high level.

The originator producer does not follow generic prices and does not set its price at the reference price level. Brand loyalty makes some consumers be willing to pay a co- payment in order to get the branded product rather than the generic, due to perceived product differentiation. Besides, lowering its price at the reference price

level would make generics lose a great part of their market share, so they would force their prices down, making the reference price also decrease. Such a price war could keep pushing prices down and eventually the originator price would have to drop to a fraction of the initial price in order to sustain a large market share. This would lead to lower profits than previously, so the originator producer would chose not to involve in a price war and keep the price at relatively high levels.

However, reference pricing has an indirect effect on originator prices. In the short run, if reference pricing reduces generic prices further, this could lead even more consumers to consume generic products rather than the originator, due to the larger price difference. Therefore, at least in the short run, reference pricing may have a spillover effect on originator prices.

The short run is a very important and critical period for cost containment and savings from genericization, as in the first years of generic presence generic uptake is not always large. The originator product may sustain a significant part of the market, so its price has an impact for health insurance spending.. Reference pricing may lead to higher prices and a lower market share for originator products, but also a higher price for the latter. The aggregate effect on savings is ambiguous, as these effects are towards different directions.

In the long run though, the effects of reference pricing on originator medicines are opposite: Generic prices do not decrease further (as they may in the absence of reference pricing) so the market share of the originator will not decrease as rapidly and the patients consuming originators will not be the most averse to generics. Therefore, the originator price will also not increase as steeply.

Nevertheless, there are a number of other parameters that affect prices of pharmaceuticals apart from reference pricing and the number of suppliers.

Advertising and promoting the product may be effective and may lead to price differentiation. Furthermore, cost of production and the presence of other measures of regulation are also very important.

4.5 Descriptive Analysis

4.5.1 Stylized Facts on Generic Entry

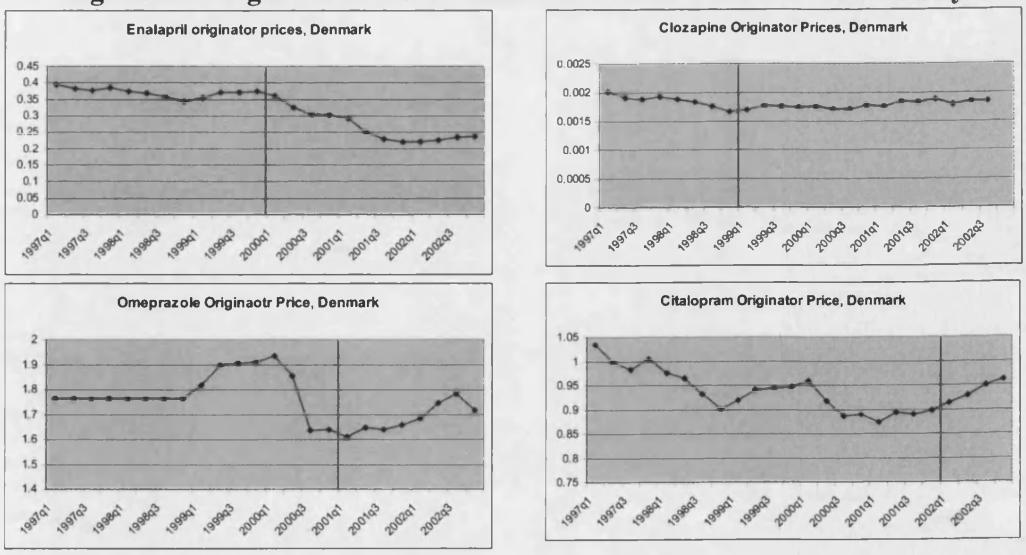
Market shares of the originator product fall after patent expiry. Mrazek and Frank (2004) suggest that although residual loyalty remains after generic entry, it does not completely deter generic competition. After patent expiry, prices of generic products fall to a small fraction of the originator medicine price. Evidence on prices of generics indicates that they are significantly below those of originator products. (Kanavos and Srivastava 2008, Kanavos 2008). The effect of patent expiry on sales and prices of captopril in UK, the Netherlands and Germany have been demonstrated in a study by Kanavos and Srivastava (2008). Originator sales drop dramatically, as generic products move in. Sales drop by 69% in Germany, 51% in the Netherlands and 74% in the UK. Originator prices increase in the UK by 30% following generic entry, but the opposite happens in the Netherlands and Germany, where originator prices drop by 14% and 61% respectively. Data from the UK show that the average difference between branded price and generic price up to 3 years after first entry is 80% and that the average generic penetration up to 3 years after first entry is 55% (Kanavos 2008). Under the reasonable assumption that demand for the branded product is inelastic, the price of the branded product would have to decrease by 80% in order to regain a maximum of 55% of the total generic market, in other words to roughly double its market share (if the originator would regain the

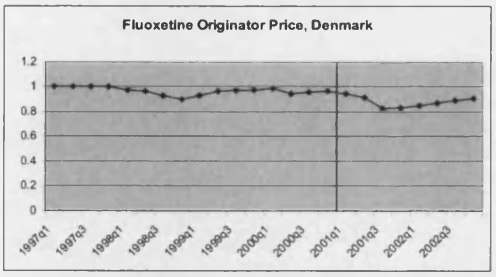
whole market back by decreasing its price down to the level of generics). In Germany, the originator price would have to decrease by 25-40% in order to regain 45% of the market (Kanavos 2008), but generics could potentially respond to this by lowering prices even more, and regain part of the market. Therefore, in the UK and possibly also in Germany, total revenue if deciding to go into price war would be lower than in the case in which the price would remain at high levels, and this strategy would make the originator producer worse off.

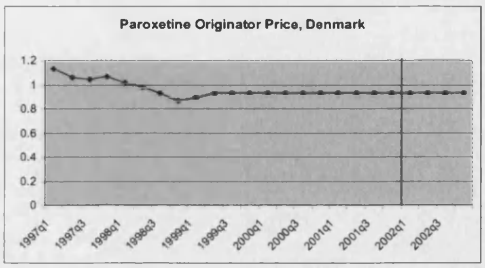
4.5.2 Graphical Representation of Originator Prices Before and After Generic Entry

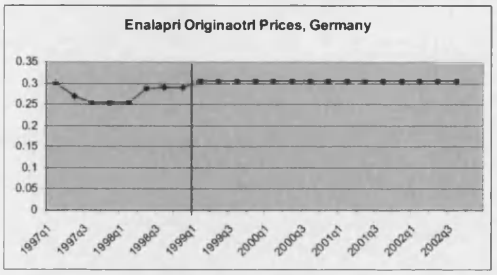
A graphical analysis is the first step to see how the prices of originator products change as a result of generic entry. In Figure 4.2, the price (in real terms) each originator in each country is plotted, while a vertical line indicates the point of generic entry.

Figure 4.2 Originator Price Evolution Before and After Generic Entry




Fluoxetine Originator Price, Denmark


Paroxetine Originator Price, Denmark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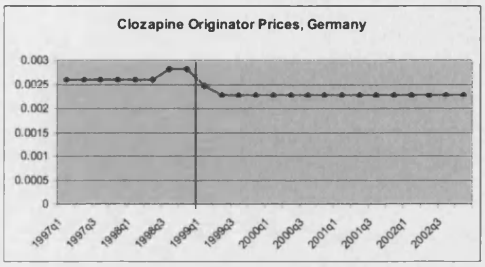
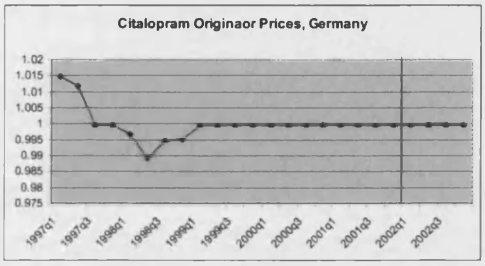

Clozapine Originator Prices, Germany


Omeprazole Originator Prices, Germany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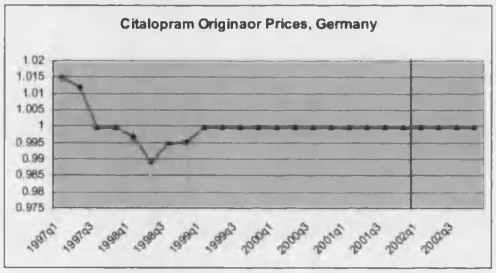
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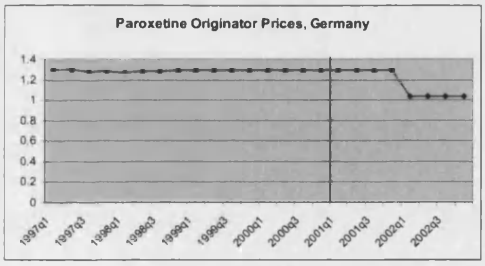
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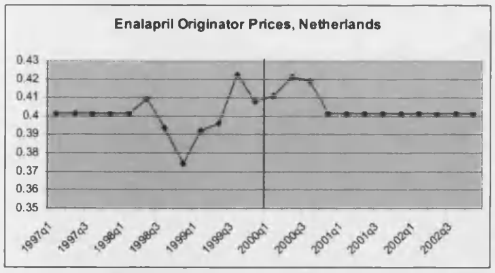
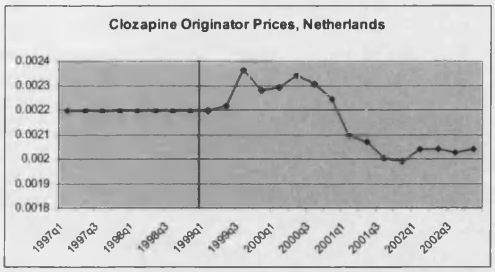

Enalapril Originator Prices, Netherlands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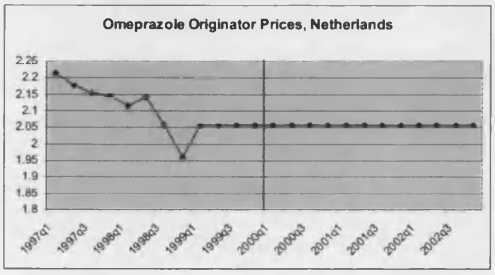
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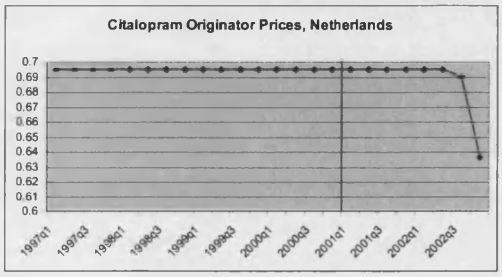
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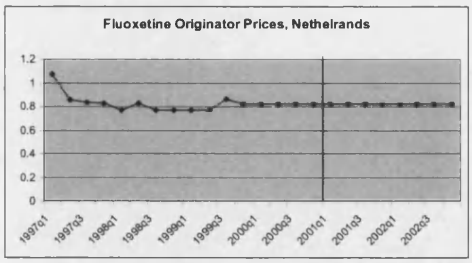
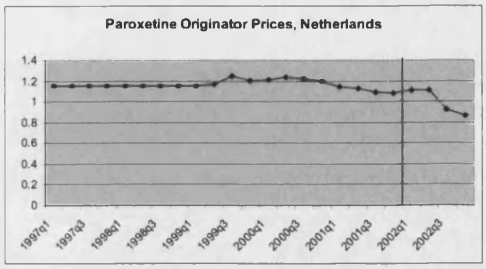

Fluoxetine Originator Prices, Netherlands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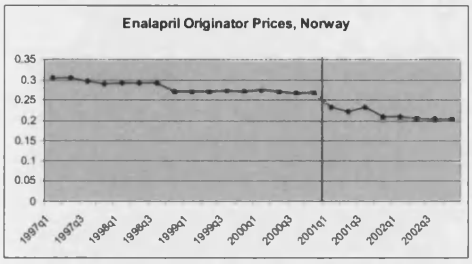
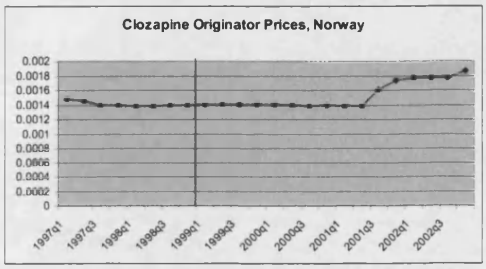
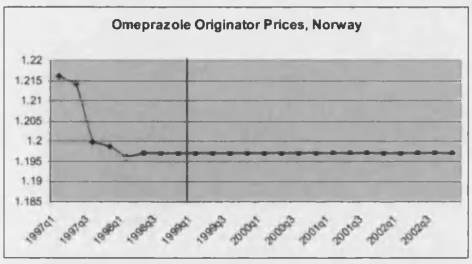
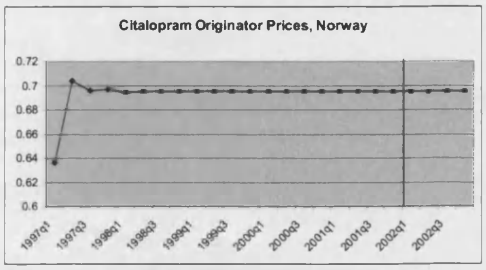
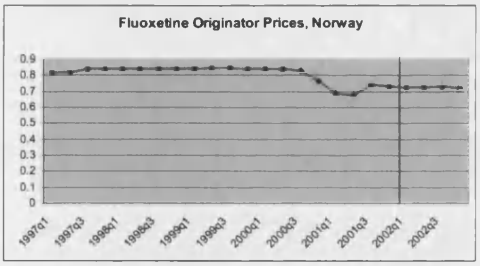
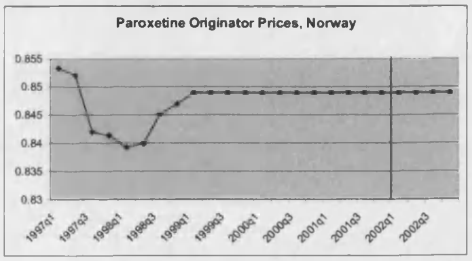

Enalapril Originator Prices, Norway


Clozapine Originator Prices, Norway

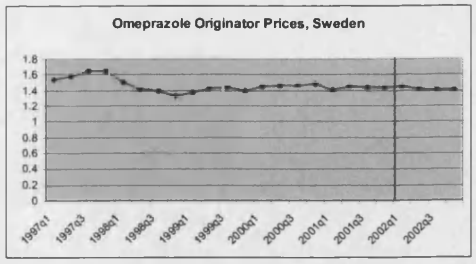

Omeprazole Originator Prices, Norway


Citalopram Originator Prices, Norway


Fluoxetine Originator Prices, Norway


Paroxetine Originator Prices, Norway


Enalapril Originator Prices, Sweden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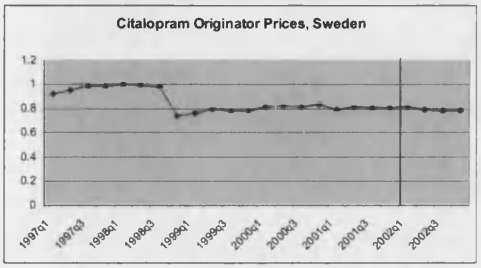
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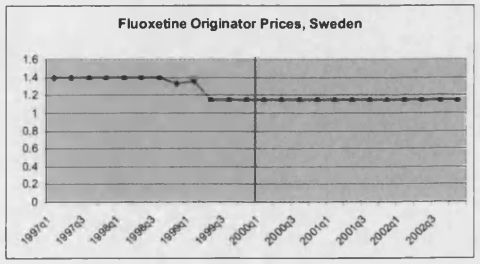
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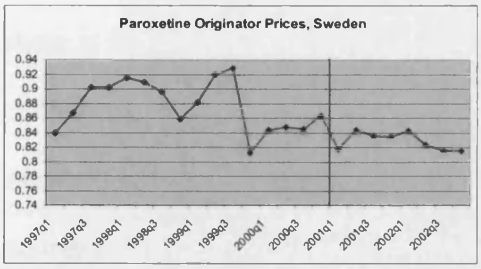
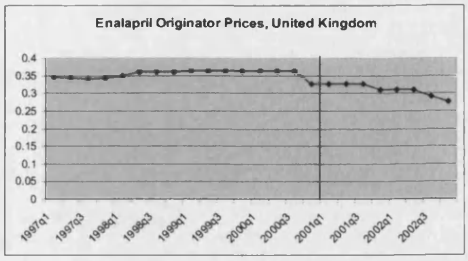
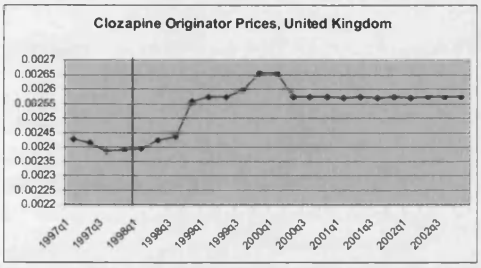
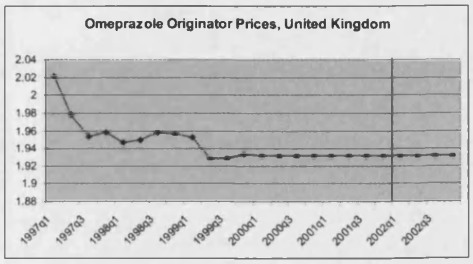
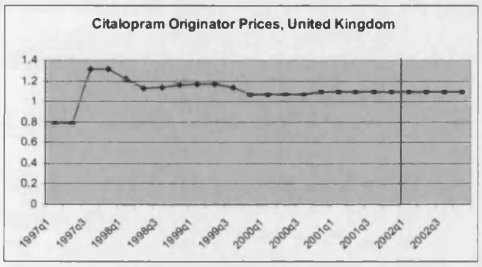
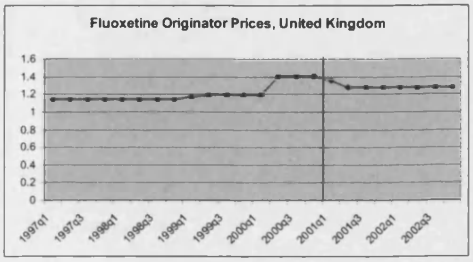


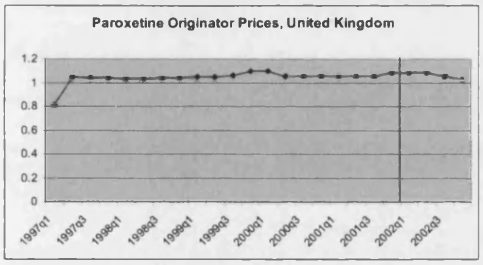












Note: *vertical line indicates generic entry*

In some cases, the price of the originator appears to rise after generic entry. Such examples are omeprazole in Germany and clozapine in the UK. In other cases, prices appear to rise not with generic entry, but with generic penetration (clozapine in Norway). This suggests that the generic paradox may be present. In some other cases, the price of the originator medicine appears to fall after generic entry. Such cases are enalapril in the UK and paroxetine in the Netherlands. In general, markets do not seem to follow a particular pattern after generic entry. Some medicines demonstrate price increase post generic entry and others drop, while in most cases

there is no price change at all. In most cases though, changes are marginal and it is difficult to observe the changes graphically. Furthermore, these graphs do not allow controlling for other factors which influence prices and may be the main reason for changes. Graphs only provide a univariate approach which does not show the whole picture and may be misleading. In other words, a change that graphically demonstrates a negative effect of generic entry on prices, could actually be positive when the factors that affect prices are controlled for. Thus, multivariate econometric analysis is more insightful and will provide more specific and accurate information regarding the causes of the changes of the originators' prices.

4.6 Data and Methods

4.6.1 Data

In order to pursue the analysis we used data from the Intercontinental Medical Statistics (IMS) pharmaceutical sales database. The accuracy of the data ranges between 98 and 99% (IMS 2002). Prescription medicines'prices are actually reimbursed by health insurance. Data were obtained for the 1997-2002 period for 12 medicines from four product categories: Plain ACE inhibitors (Captopril, Enalapril, Quinapril, Ramipril); atypical anti-psychotics (Clozapine); proton pump inhibitors (Lansoprazole, Omeprazole, Pantoprazole); and antidepressants (Citalopram Fluoxetine, Paroxetine, Sertraline) in six European countries (Germany, United Kingdom, the Netherlands, Sweden, Norway, Denmark) for the retail (pharmacy) market in each country. Data was available for originator and generic versions of each molecule. Generic competitors enter the market during the time period

examined for at least on medicine in each therapeutic category in at least one country in the sample.

We have a range of variables in the dataset used in the analysis. All data are reported quarterly. The variables that are most important are the price of the originator and generic penetration and entry (market share and dummy for presence respectively). *p* is the price of each originator product in each country, measured in logs. Prices are in Euros, deflated. *genms* is the market share of generic products, which indicates market penetration. Market shares are calculated based on actual invoiced sales as a proportion of total sales of the particular molecule, both branded and generic. *generic* is a dummy variable for generic penetration in a country (i) on quarterly basis. The dummy takes the value of 1 when generic entry occurs for a product (j) in a country (i); 0 elsewhere. Generic entry is identified and confirmed by (a) patent records for brand product and (b) separate entries of sales, volumes and prices of generics by firms other than holders of the original patent (generic companies).

Further, there are a number of policy dummy variables included in the model. *rp* is a dummy variable for the presence of reference pricing in a country. The dummy takes the value of 1 when reference pricing is present and 0 when there is no such measure in the country. Reference pricing is present in Denmark, Germany, the Netherlands, Sweden over the whole period examined and in Norway until the second quarter of 2001. *hsys* is a dummy variable for health system organized as an NHS-type or an insurance-based system. NHS-type systems have gatekeeper arrangements in place through general practitioners and potentially restrict demand for health services, including pharmaceuticals, compared with social insurance-based systems where access to specialists is still safeguarded. The dummy takes the

value of 1 for the UK, Denmark, Sweden, and Norway (NHS-type system) and 0 for Germany and the Netherlands (insurance-based systems). *pcut* is a dummy variable for price cuts or price freezes. These are command-and-control regulatory measures often implemented by health insurance in order to contain costs, after a product has been introduced; these policies always affect the entire pharmaceutical market in a particular country. This dummy takes the value of 1 in Denmark (from Q1, 1998 to Q1, 2002), and the UK (from Q1, 1999 to Q2, 2001). All 12 products in our sample are affected in the above two countries and for the periods specified. The dummy takes the value of 0 elsewhere. *cap* is a dummy variable indicating the presence of price caps for generics. This takes the value of 1 in Norway for the last two quarters of 2002, in Sweden, in the United Kingdom from the second quarter of 2000, and the value of 0 elsewhere. *preg* is a dummy variable for price regulation. Price regulation defined as the intervention of third party payer (national insurance company) or the government in terms of setting price of each product (j). Price regulation takes value of 1 in Norway, Sweden and the Netherlands from Q1, 1997 onwards; and for Denmark from Q1, 2001 onwards. *ror* is a dummy variable referring to rate of return regulation. This policy is known as 'profit controls'. When this is present, the manufacturer is allowed to make profits up to a certain rate of the capital invested. Any profits exceeding this must be paid back to health insurance. This policy is present in the United Kingdom. Thus, this variable is 1 for the UK and 0 elsewhere. *clawb* is a dummy variable for introduction of clawbacks. Clawbacks are a policy tool whereby health insurance is aware of discounting practices taking place at pharmacy level and retain a proportion of that discount. The dummy takes the value of 1 in the UK and the Netherlands over the 1997-2002 period, and 0 in the other four countries. *er* is the exchange rate, that converts currencies into Euros.

The following variables are used as instruments in the analysis (explained in section 4.5.2): *age* is a measure of time (in quarters) since generic entry for the particular product. *sub* is a policy dummy. It is 1 when obligatory or optional generic substitution policies are present (Denmark, Germany from Q2, 2002, the Netherlands, Norway from Q2, 2001, Sweden, UK from Q3, 2002) and 0 elsewhere. When such policies are present, the pharmacist can or must substitute the branded product mentioned in a prescription with the corresponding generic product, if available. Summary statistics of all variables are in Table 4.1.

Table 4.1 Summary Statistics

Observations: 1728

Variable	Mean	Std. Dev.
p	-0.711	1.697
generics	0.278	0.448
lgenms	19.389	28.443
rp	0.199	0.399
cap	0.250	0.433
pcut	0.139	0.346
preg	0.444	0.497
ror	0.167	0.373
hsys	0.667	0.472
clawb	0.500	0.500
er	1.147	0.964
sub	0.093	0.290
age	2.343	4.933

4.6.2 The Emprical Model

4.6.2.1 Conceptual Framework

The originator producer is a profit maximizing firm. In order to set profit-maximizing prices, it takes market parameters into account. Before generic entry, the firm acts like a monopolist, as there is not other medicine with exactly the same chemical substance in the market. During this period of patent protection, the

constraint that the firm faces is demand. In European markets, where health insurance is present, the consumer is not the payer. The consumer also has a decision-making agent (the physician). Further, regulation affects pricing and the reimbursement list also affects dispensing of the product, as if it is not covered by health insurance, the patients will have to pay out-of-pocket, which would affect sales. Thus the monopolist sets the price as

$$P^O = f(D, R, ins) \qquad (11)$$

where D is demand, R is regulation and *ins* indicates insurance coverage of the particular medicine.

Things change post patent expiry with generic entry. The originator producer is no longer a monopolist as there are other firms which produce and sell the very same chemical substance. Therefore competition is now present in the market due to the presence of generics. In regular markets, the presence of competitors enhances competition and leads to lower prices and the price of an oligopolist is expected to be lower than the price of the monopolist. This has been proven not to happen in the US pharmaceutical market (Frank, Salkever 1993) and is known as the "generics paradox". Whether generic entry and penetration affect originator prices in regulated European markets will be examined in the empirical section of the study. The hypothesis is that prices of the originator decreases after generic entry, as economic theory suggests. Further, prices are affected by regulation, such as reference prices.

$$P^O = f(comp, D, R) \qquad (12)$$

where *comp* indicates the level of competition (generic entry or generic penetration), D is demand, and R indicates regulatory measures.

4.6.2.2 The Ecomometric Model

We consider two empirical models to examine the effect of generics on originator prices. The first empirical model has the following form:

$$p_{i,t} = \alpha_i + \beta_0 + \beta_1 generics_{i,t} + \beta_2 rp_{i,t} + \beta_3 cap_{i,t} + \beta_4 pcut_{i,t} + \beta_5 preg_{i,t}$$
$$+ \beta_6 ror_{i,t} + \beta_7 hsys_{i,t} + \beta_8 clawb_{i,t} + \beta_9 er_{i,t} + \sum_{n=10}^{34} \beta_n time_t + \varepsilon_{i,t} \qquad (13)$$

where *i* indicates the specific product in the specific country and *t* indicates time. In equation (13) the variable capturing the effect of generics on the originator price is *generics*, which is a dummy variable indicating the presence or not of generic alternatives to the originator product. The second empirical model is equation (14):

$$p_{i,t} = \alpha_i + \beta_0 + \beta_1 genms_{i,t} + \beta_2 rp_{i,t} + \beta_3 cap_{i,t} + \beta_4 pcut_{i,t} + \beta_5 preg_{i,t}$$
$$+ \beta_6 ror_{i,t} + \beta_7 hsys_{i,t} + \beta_8 clawb_{i,t} + \beta_9 er_{i,t} + \sum_{n=10}^{34} \beta_n time_t + u_{i,t} \qquad (14)$$

where *i* indicates the specific product in the specific country and *t* indicates time. In equation (14) the variable capturing the effect of generics on originator prices is *genms*, which represents generic penetration.

hsys, *rp*, *cap*, *pcut*, *preg*, *ror* and *clawb* are policy dummy variables for the nature of the health system (how it is financed), the presence of reference pricing, price caps, price cuts, price regulation, rate-of-return regulation and clawbacks respectively. *er* is the exchange rate and is used as a control variable. *time* represents all time dummy variables, one for each quarter.

Generics market share is endogenous in this model because it affects the price of the branded medicine, but the price of the originator also affects generics market share. In order to address this problem we use two instrumental variables: *age* and *sub*. Age does not impact originator drug prices directly, because it does not relate to the overall age of the originator product, but only relates to time post-patent expiry. There is no apparent reason why originator drug prices should drop post-patent expiry other than the introduction of policy/regulatory measures that might influence them. For instance, the implementation of a statutory requirement to reduce originator drug prices post-patent expiry will affect originator prices downwards, but is related to that particular measure of regulation rather than timing since patent expiry. As a result, time since patent expiry, captured by the *age* dummy is unrelated to the originator drug price. Similarly, *sub* is unrelated to the originator drug price post-patent expiry. The originator drug price would be impacted by another regulatory measure, notably reference pricing: should the originator drug wish to maintain a (nominal) market share post-patent expiry, the introduction of a reference pricing system would impact it downwards. By contrast substitution policies do not affect nominal originator drug prices.

For both models we estimate two specifications: Specification 1A and 2A, which include only generic entry or generic penetration, the exchange rate and time dummies, and specifications 1B and 2B which also include all policy dummies as explanatory variables. Generic entry is used to capture a one-off effect of generics on originator prices, while generic market penetration is used to show the gradual effects of generic entry on prices over a period of time.

We use Panel Data analysis in order to estimate the model. Panel data is used because it can give "more informative data, more variability, less collinearity among

variables, more degrees of freedom and more efficiency" (Gujarati 2003). Thus, having a different intercept for each country may allow us to have a better and more efficient model. The constant term, α_i is different for each country *i*. The Hausman test suggests that we follow the random effects approach. The chi-squared statistic is 0.22 with a p-value of 1.00, indicating that coefficients estimated by the efficient random effects estimator are the same as the ones estimated by the consistent fixed effects estimator, so it is safe to use random effects, which are a more efficient estimator than fixed effects. The random effects approach assumes that the intercepts of the individuals are different but that they can be treated as drawings from a distribution with mean μ and variance σ_α^2. The essential assumption here is that these drawings are independent of the explanatory variables. (Verbeek 2005).

The panel identifier in this model is the pharmaceutical product per country. In this way we can distinguish both between countries and between medicines. This is useful since there can be differences not only across countries but also across medicines within the same country.

4.6.3 Relationship between Variables

From economic theory, we expect that competitor entry into the market leads to lower prices. In a regular market, we would expect a negative coefficient for the variables capturing generic entry or penetration. The special nature of the pharmaceutical market though may lead to opposite results. According to the generics paradox, we would expect that generic entry will either not affect the price of the originator products, or that it will push them upwards. Therefore we would expect the coefficient to be statistically insignificant (which would be in accordance to research (Grabowski and Vernon (1992)), or, if statistically significant, to have a

positive value, according to Frank and Salkever (1993), and Rizzo and Zeckhauser (2005). Nevertheless, the data used in this analysis concerns regulated markets (in contrast to the less regulated US market used in previous studies concerning the generics paradox), so our findings could be different.

We use two specifications in order to consider the generics paradox: The market share of generics – or generic penetration (*genms*) and a dummy variable indicating the presence or not of generics on the market – or generic entry (*generics*). We use each variable separately in different models. The results of the regressions for there coefficients will be very interesting for policy makers.

4.7 Results

Table 4.2 shows the results of the regressions for using generic entry or market share in order to test the presence of the generics paradox. Two different random effects models are used. Model 1 uses generic entry (*generics*) in order to capture the effect of generic competition and Model 2 uses generic market share (*genms*). In Model 2, *age* and *sub* are instrumental variables for endogenous variable *genms*. Reference pricing, price caps, price regulation, price cuts, the type of funding of the health system and clawbacks are used in order to explain changes in prices. Both models include two specifications. One with only *generics* or *genms*, *er* and time dummies as explanatory variables (A) and one also including all policy variables (B).

Table 4.2 Random Effects - all countries

Dependent Variable: *p*

	Model 1A	Model 2A	Model 1B	Model2B
generics	0.030***		0.050***	
	(0.008)		(0.014)	
genms		2.67e-04		6.6e-05
		(3.90e-04)		(4.21e-04)
rp			-0.027*	0.015
			(0.015)	(0.011)
cap			0.021**	0.014
			(0.011)	(0.011)
pcut			-0.022**	-0.027***
			(0.009)	(0.009)
preg			-0.016	-0.021*
			(0.011)	(0.012)
ror			0.182	0.168
			(0.678)	(0.680)
hsys			-0.210	-0.243
			(0.680)	(0.682)
clawb			-0.354	-0.414
			(0.569)	(0.571)
er	-0.264***	-0.252***	-0.236***	-0.267***
	(0.043)	(0.044)	(0.053)	(0.053)
constant term	-0.398**	-0.411**	-0.138	-0.050
	(0.196)	(0.202)	(0.747)	(0.750)
Observations	1728	1728	1728	1728
Wald χ sq	290.04	277.75	310.18	295.75
R-squared within	0.152	0.149	0.161	0.155
R-squared between	0.003	0.003	0.004	0.005
R-squared overall	0.003	0.004	0.004	0.005

standard errors in parenthesis.

(***), (**) and (*) refer to significance at 1%, 5% and 10% respectively

Instruments for *genms*: *age* and *sub*

In Model 1A *generics* has a positive and statistically significant coefficient. Prices of originators that face generic competition are on average 3% higher than originators that do not face generic competition. In Model 1B, that includes all other explanatory variables, findings are similar. Prices of originators are 5% higher in markets in which generic products are present (statistically significant at α=1%). *cap* has a positive coefficient that is statistically significant at the 5% level. Originator products sold in markets where generic price caps are present have higher prices by

2.1% compared to those without such policies. The presence of reference pricing leads to lower branded prices by 2.7% compared to those in markets without reference pricing (statistically significant at α=10%). *preg*, *ror*, *hsys* and *clawb* are statistically insignificant.

In Model 2A, the coefficient of *genms* is positive but has a statistically insignificant effect on the prices of the originator medicine. This means that as generic penetration increases, there is no effect on the price of the originator product. The coefficient of *genms* is also positive but insignificant in Model 2B, in which other explanatory variables are included. *pcut* has a statistically significant negative coefficient. The presence of price cuts leads to lower originator prices by 2.7% on average. Originator medicine prices are lower by 2.1% on average when price regulation is implemented. *rp*, *cap*, *ror*, *hsys* and *clawb* are statistically insignificant.

These findings suggest the presence of the generics paradox in regulated markets. Generic entry has a positive and statistically significant effect on originator prices and generic penetration has a positive but insignificant effect. There appears to be a one-off effect of generic entry that pushes originator prices up. In any case, we do not find any evidence that originator prices decrease as a result of generic competition. This suggests that the generics paradox is present in regulated markets.

Regarding the effect of policies, results are robust. Price caps have a positive effect on originator prices. This can be explained. Price caps lead to significant price reductions of generic products. This makes more patients switch to generic products, leaving only the most brand loyal ones buying the originator product, whose demand is inelastic. This gives the originator producer the incentive to increase the medicine's price in order to increase his revenue. This does not hold for reference pricing because this particular policy measure prevents the "race to the bottom",

preventing generic prices from declining further, hence the negative coefficient of *rp* (Reference pricing appears to lead to lower originator prices in both models). Price cuts have a statistically significant negative coefficient in both models, showing that direct price cuts on originator products lead to lower originator prices. Coefficients of price regulation are also negative but not as statistically significant.

Table 4.3 Random Effects – country-specific regressions

Dependent Variable: *p*

	Model 1A	Model 2A	Model 1B	Model2B
		Denmark		
generics	-0.025		-0.024	
	(0.020)		(0.020)	
genms		-0.002		-0.001
		(0.001)		(0.001)
Observations	288	288	288	288
Wald χ sq	136.6	136.08	134.29	134.75
R-squared within	0.348	0.351	0.349	0.353
R-squared between	0.196	0.587	0.196	0.574
R-squared overall	0.008	0.143	0.008	0.134
		Germany		
generics	0.013		0.012	
	(0.026)		(0.026)	
genms		-0.004***		-0.004***
		(0.001)		(0.001)
Observations	288	288	288	288
Wald χ sq	17.54	33.24	19.01	34.58
R-squared within	0.065	0.009	0.065	0.009
R-squared between	0.063	0.001	0.063	0.001
R-squared overall	0.001	0.001	0.001	0.001
		Netherlands		
generics	0.113***		0.113***	
	(0.017)		(0.017)	
genms		-0.001*		-0.003***
		(0.001)		(0.001)
Observations	288	288	288	288
Wald χ sq	250.65	169.13	250.65	218.87
R-squared within	0.498	0.374	0.498	0.408
R-squared between	0.185	0.217	0.185	0.005
R-squared overall	0.024	0.030	0.024	0.003
		Norway		
generics	0.038*		0.038*	
	(0.022)		(0.022)	
genms		0.049		-0.183
		(0.051)		(0.511)
Observations	288	288	288	288
Wald χ sq	75.3	20.42	73.28	1.77
R-squared within	0.221	0.054	0.221	0.017
R-squared between	0.137	0.054	0.137	0.122
R-squared overall	0.005	0.122	0.005	0.115
		Sweden		
generics	-0.008		-0.052	
	(0.020)		(0.019)	
genms		0.004***		0.002***
		(0.001)		(0.001)
Observations	288	288	288	288
Wald χ sq	51.07	44.04	15.96	62.27
R-squared within	0.168	0.057	0.049	0.143

R-squared between	0.020	0.022	0.021	0.028
R-squared overall	0.001	0.012	0.007	0.009
	United Kingdom			
generics	0.041***		0.018***	
	(0.015)		(0.014)	
genms		-3.24e-05		-4.71e-04
		(0.001)		(0.001)
Observations	288	288	288	288
Wald χ sq	53.83	46.56	18.4	50.21
R-squared within	0.180	0.148	0.060	0.106
R-squared between	0.413	0.194	0.413	0.121
R-squared overall	0.079	0.001	0.052	0.026

standard errors in parenthesis.

(***), (**) and (*) refer to significance at 1%, 5% and 10% respectively

Instruments for *genms*: *age* and *sub*

After having considered all countries together, we proceed to examine each country separately (Table 4.3). The models estimated for each country separately are the same as the ones used for the aggregate regressions, but only the coefficients of *generics* and *genms* are reported in Table 4.3.

In the Netherlands, Norway and the United Kingdom, generic entry has a positive and statistically significant effect, indicating that prices of originator products are higher post patent expiry. In Denmark, Germany and Sweden this is statistically insignificant. Generic penetration (*genms*) has a positive and statistically significant effect at the α=1% level in Sweden. In Norway and the United Kingdom it is statistically insignificant. In Denmark, Germany and the Netherlands *genms* has a negative and statistically insignificant coefficient. Thus generics paradox is present in the United Kingdom and Norway and is materialized upon generic entry, indicating a one-off effect. In Sweden, the generic paradox takes place gradually, as it is generic penetration rather than generic entry that leads to an increase in originator prices. In the Netherlands, generic entry leads to an upward shift of originator prices, but generic penetration offsets part of this increase. Neither generic

entry nor penetration have any effect on originator prices in Denmark. In Germany, generic entry does not have any effect on originator prices, but generic penetration leads to marginal decreases in originator prices. A 1% increase in generic market share leads to a decrease in originator prices by 0.004%.

4.8 Policy Implications

The findings of studies on the generics paradox are important for policy makers as they provide evidence that price competition (following generic entry) does not necessarily lead to a decrease in the prices of originator products in environments where prices of medicines are not explicitly regulated. As generic presence does not trigger price competition with the originator product, no direct savings occur for health insurance by dispensing originator products. Thus, for generic policies to be effective, genericization needs to be swift and a switch to generic alternatives (generic substitution) must take place immediately after patent expiry, otherwise it is likely that continued use of a genericized originator is in itself unable to deliver savings to health insurance. In regulated pharmaceutical markets, it is possible that the generics paradox may be called into question and it is also possible that regulation may cause prices of originator medicines to decline, rather than increase, although this is dependent on market dynamics, the extent of regulation and the nature of competition within the product therapeutic class.

4.9 Concluding Remarks

This study examined whether the generics paradox holds in European markets with some level of regulation. A conceptual model was outlined in order to

explain how brand loyalty influences the price of originator products. Market dynamics were explained and elasticity of demand was taken into account to explain why prices of originators do not decline post patent expiry. The empirical model demonstrated empirical evidence that the generics paradox holds in markets with a considerable degree of regulation. When including all 6 countries in panel data models, we find strong evidence that prices of originators rise with generic entry. When considering each country separately, we find evidence that the generics paradox is present in the United Kingdom, Norway and Sweden, as originator prices increase post patent expiry. In Sweden prices increase post patent expiry but part of this increase is offset as generic penetration takes place, while in Denmark generic entry does not affect originator prices. The only country in which generics lead to lower originator prices is Germany.

The findings of studies on the generics paradox are important for policy makers as they provide evidence that competition due to generic entry does not necessarily lead to a decrease in the prices of originator products in environments where prices of medicines are regulated.

The results of this study are subject to limitations: The countries considered in the analysis have a relatively more regulated pricing for pharmaceuticals, in contrast to the United States, which was the market considered by Frank and Salkever in the main study in the literature concerning the Generics Paradox. Nevertheless, there are some elements of flexible pricing arrangements, since the price may increase after permission from the authorities in all countries of the sample (in some other EU countries prices cannot increase in any way). Therefore, the results concern markets with these particular properties and cannot be generalized for all countries. Also, Brand loyalty is difficult to be quantified, so the

effect of this important variable on originator prices could not be empirically tested, although it was included in the theoretical framework. Instruments were used in the econometric analysis to address endogeneity problems. Although they appear to be good instruments, is it difficult to say for sure that an instrumental variable works perfectly well.

Another limitation of this study is that the study period is probably too short to allow dynamic effects. Further research could use a longer time period with a longer period of post-genericization in order to observe the long-term dynamics of pricing of originator products and how the prices evolve until they reach their long-term steady state. Further research could also consider countries with strict regulation such as France and Spain, which regulate very strictly increases in prices, to determine wheather the generics paradox would hold under strict regulation.

5. Switching Behaviour Post Patent Expiry: Empirical Evidence from the EU

5.1 Background

Patent expiry is typically associated with generic entry, and the market share of the branded product declines as generic uptake takes place (Kanavos et al. 2008). This leads to a significant drop in the branded product's producer's revenue and could make him lose interest in that particular market. He may then focus on other patented products from other therapeutic classes which generate higher profits. This could be expressed by abandoning promotion and advertising of the product whose patent has expired and focusing these promoting efforts on other newer, patented products, in the market of which the firm acts like a monopolist.

This "abandonment" of a product produces an opportunity for the introduction of indirect patented substitutes, which are products with different chemical substance but within the same therapeutic category, to attract part of the off-patent molecule's market share. The efforts of the indirect competitor (whose product has gone off-patent) concerning advertising is much weaker, so the other branded product that is still on patent with the same or less advertising efforts can secure higher sales.

Advertising intensity influences the choice of pharmaceutical products in an environment of product differentiation pre-patent expiry, where products are considered to be either broadly comparable or simply substitutes. Empirical evidence suggests that advertising, by means of detailing, has a powerful effect and systematically lowers price sensitivity because it increases brand loyalty, in addition

to the effect of increasing a product's sales (Rizzo, 1999), as well as having spillover effects, such that advertising by one firm in a therapeutic category increases demand for other medicines in the same category (Berndt el al, 1995). In a study conducted by Berndt, Danzon and Kruse (2007), it is empirically concluded that total promotion effects on medicine utilization is positive. The authors also suggest that promotion of new medicines positively affects their market share, which is also negatively affected by promotion of old medicines.

Dispensing dynamics of the market are of great importance for this analysis. There are policy elements that affect these dynamics. The more generic dispensing is encouraged, the lower the profits for the off-patent branded medicine and therefore the more likely is its producer to focus promotion efforts on other products.

Generic substitution policies targeting pharmacists aim to control costs. In some countries pharmacists are able to substitute a branded for a cheaper generic, if this is available. Pharmacists are typically remunerated by health insurance through fixed fees per prescription, progressive margins or regressive margins. The first two do not encourage generic dispensing, because in the case of the fixed fee they receive the same amount of money, no matter what is dispensed, while in the case of progressive margins they clearly have an incentive to dispense the most expensive medicine. It is regressive margins that may provide an incentive to dispense the cheapest medicine. Hence, this remuneration scheme encourages generic dispensing. Discounts provided to pharmacists from wholesalers though must not be neglected. These give an incentive to dispense the medicine that offers the highest discount to them and are beyond government control.

Policies targeting patients may also be present. Such policies are co-payments and reference pricing. Co- payments that are a flat fee per prescription do

not promote generic use. This can be promoted by percentage co-payments, though these are very modest in Europe. Reference pricing leaves the choice to the consumer, as under reference pricing the cheaper medicine is reimbursed, while patients willing to purchase the more expensive medicine will have to pay the difference.

Previous research has focused on competition between different molecules prior to generic entry or generic competition within the same molecule, but not on the effect generic entry has on the switch from one branded product to another. Studies suggesting the presence of competition within a therapeutic category give an indication that the switch effect may take place because they show that the chemical substances of the branded products are substitutes. Since generics of each product have the same chemical substance as the branded product, this switch in consumption may be encouraged by generic entry.

Kanavos, Costa-Font and McGuire (2007) studied competition between in-patent statins in France, UK, Germany and the Netherlands. They examined the volume and price patterns of pravastatin and simvastatin, which were the first to enter the market, followed by the effects of entry of atorvastatin, cerivastatin and fluvastatin. Empirical evidence showed that price competition is present and has an impact on the first three entrants.

Danzon and Chao (2000) found no evidence of competition within therapeutic class in the US, but small negative effect on the price in France, Italy, Germany and the UK. In another study, the same authors got inconclusive results about the effect of substitution across therapeutic class and the first-mover advantages on product price. Finally, Ellison et al (1997) found small and not

universally significant elasticities between therapeutic substitutes for the case of cephalosporins.

Regarding generic entry dynamics, empirical evidence from the USA suggests that innovator firms do not attempt to deter generic entry through their pricing strategies and this may lead to a significant reduction in market share of the originator medicine post generic entry (Grabowski and Vernon, 1992; Grabowski and Vernon, 1986). Frank and Salkever found empirical evidence from the United States that prices of originator products increase post patent expiry. Another study (Rizzo and Zeckhauser, 2005) provides empirical evidence that producers of brand-name products do not decrease prices after generic market entry. Finally, Caves, Whinston and Hurwitz (1991) conclude that generic entry only leads to a slow-down in the increase of originator medicine prices.

5.2 Objectives

Most studies concerning pharmaceutical competition has focused on the impact of generics on prices, market shares and sales. Significantly fewer studies have looked into competition on in-patent markets. No research has been done though on the effect of generic entry on a switch in consumption towards the market of a different medicine of the same therapeutic class. This study fills in this gap in the literature, giving insight into this element of competition. Presence of such a switch would lead to higher pharmaceutical costs, as in-patent medicines do not have generic alternatives. Generic policies can be completely ineffective when dealing with such a phenomenon. This should trigger the implementation of policies in order to discourage such a switch in consumption from off-patent to in-patent markets.

Section 5.2 discusses advertising and its effects on the pharmaceutical market; section 5.3 provides a conceptual framework; section 5.4 provides information on ACE inhibitor markets and section 5.5 discusses regulatory measures implemented in the countries included in the study. Section 5.6 discusses data and methods and section 5.7 explains empirical results. Section 5.8 discusses policy implications and concludes.

5.3 The importance of Advertising

The switching effect discussed in this chapter is possibly a result of changes in promotional efforts on behalf of the firm whose molecule loses its patent, so we start the analysis by discussing how advertising can influence markets. The reason why advertising is chosen to be included in this context of switching and competition between molecules of the same therapeutic class is that, as can be seen in the next sub-sections, it influences volume of sales of both the advertiser and his competitors.

5.3.1 Advertising and Industrial Organization

Advertising is a means of increasing sales or market share in a particular market. Tirole discussed the economics of advertising in his book "Industrial Organization" (Tirole 1988). Advertisements inform consumers (or proxy-consumers such as doctors) about prices, distribution locations, product properties, and reduce product differentiation which originates from lack of information. Perception of quality increases due to advertising because firms producing high quality products can communicate information on quality (Tirole 1988). Theory

suggests that there is a degree of substitutability of product characteristics such as quality and advertising. It is possible that advertising may increase competition by increasing elasticity of demand, but it may also lead to the opposite results by creating differences across products which seem identical. In the latter case it decreases elasticity of demand. In certain industries, firms may choose to compete in terms of advertising rather than pricing.

Increased advertising efforts are associated with higher sales, according to a review of the literature on advertising since the early 20th century conducted by Bagwell (2005). This association is considered to be "short lived". Further, an increase in advertising by a competitor may decrease sales of a rival, which may, in turn, trigger a reciprocal reaction, by increasing his advertising efforts and gaining back his market share.

5.3.2 Sales promotion and the Pharmaceutical Market

Promotion expenditure accounts for a significant part of the total pharmaceutical industry expenditure. According to the Pharmaceutical Research and Manufacturers of America (PhRMA) report on marketing and promotion in the pharmaceutical industry, an IMS industry related study for 2006 concluded that the research-based U.S. pharmaceutical industry spent $56.1 billion on R&D and $12.0 billion on promotional activities (PhRMA, 2010).

A study conducted by Gagnon and Lexchin (2008) disputed available figures on the cost of pharmaceutical promotional activities for 2004. The authors claim that their findings indicate that the U.S. pharmaceutical industry spends almost twice as much on promotion than on R&D. The industry spent 24.4% of their sales on promotion, while for the same year the spending on R&D accounted for 13.4% of

sales. According to the authors, these findings contradict the figures that the IMS and the CAM Group (two market research companies) reported. The IMS had reported $33.5 billion spending on promotional activities by the U.S. pharmaceutical industry, while the CAM Group had reported $27.7 for 2004. The authors used both reports, which studied expenditure on promotional activities from a different point of view, in order to reach their conclusions. IMS studied promotion from an industry point of view, while the CAM Group studied promotion from a physician point of view. The authors concluded that the total expenditure on promotion was $57.5 billion in 2004. No matter which figure is the actual one, it is clear that promotion accounts for a significant part of the pharmaceutical industry's activities and is an important determinant of market dynamics.

5.3.3 Competition and Sales Promoting Activities

A therapeutic class includes medicines of similar but not identical chemical substances which are meant to target the same disease. They differ in terms of side effects and efficacy, but there may be a certain degree of substitutability. Each medicine of the class is subject to patent protection. The first entrant actually starts the whole therapeutic class, and acts as a monopolist, as there is no other medicine in the same therapeutic class and no generic versions due to patent protection. The monopolist has more bargaining power with health insurance when setting the price at which the product will be reimbursed, and also a lot of power when it comes to the question whether the product will be reimbursed at all or not, since there are no close substitutes. A monopoly is a market in which the price is higher than socially optimal and the quantity is lower than socially optimal (Mas– Collel et al. 1995).

Eventually, the so called "me-too" medicines enter the therapeutic class with new products, also protected by patents. This triggers competition between the different medicines of the same class. This can now be considered as a monopoly market, as there is interaction between producers, and one producer's decisions and actions influence other producers' strategies. Research on the exact nature of competition between medicines of the same class is very limited. Kanavos et al (2007) suggest that for the case of statins, after product entry has been materialized, producers follow a Cournot competition model. It could be argued that producers follow a monopolistic competition type of market structure. This is because the product is not homogenous as it has some degree of differentiation, with regards to the chemical substance. The most important element though is that it is perceived as a differentiated product. Each producer puts some advertising and promotional efforts into his product, in order to achieve a larger market share of the therapeutic class.

Generic entry creates new market dynamics. The off- patent product now faces competition not only from other medicines of the same class, but also from generic products. Post patent expiry, the physician, who acts as the patient's agent, loses his power to determine that a particular branded product will be consumed. Generic prescribing and substitution policies eventually lead to the dispensing of a generic product rather than the branded one. A way to determine exactly which product and brand will be consumed by a patient which is covered by health insurance, is to prescribe a product which is still in- patent. This can be done by prescribing a medicine of the same therapeutic class, which is a close substitute (although not exactly the same chemical substance) and is still patent protected. This product will be the one that will be dispensed because it is the only available product of that

particular chemical substance. Also, it cannot be substituted at the pharmacy because there is no generic substitute.

While the medicine was in- patent, it was competing against other molecules of the same therapeutic class under the same conditions. Advertising helps sustain market share if competitors are putting in equivalent advertising efforts, or increase it, if competitors choose to put in weaker advertising efforts. But patent expiry changes the environment and makes the market much more complicated for the off-patent molecule. Competition originates from both generics and in- patent medicines and the market share shrinks rapidly in favour of generics. With generic substitution and dispensing policies present, and facing competitors which are still in- patent, a monetary unit invested in an off- patent product has a smaller expected return than a monetary unit invested in an in- patent product. Therefore it is more profitable for the pharmaceutical firm producing the off- patent product to focus on (and advertise in) medicine markets of other in- patent products that it produces.

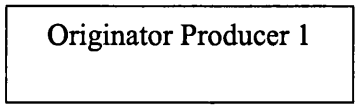
Bagwell's findings (2005), discussed in section 5.2.1 are in accordance with the hypothesis that a decrease in advertising on behalf of the firm whose molecule lost its patent may lead to a switch in consumption to other medicines. First, advertising is considered to be "short lived", meaning that the effects of advertising which happened in previous periods have a small impact on current sales. Thus even if previously the molecule was communicated extensively to consumers or their agents, the impact is small on future consumption which takes place long after advertising decreases or ceases (after generic entry). Second, advertising may reduce rivals' sales at the same time that it increases own sales. Thus, by decreasing advertisement efforts, sales of other (rival) molecules are expected to increase, while own sales will decrease.

5.4 Conceptual Framework

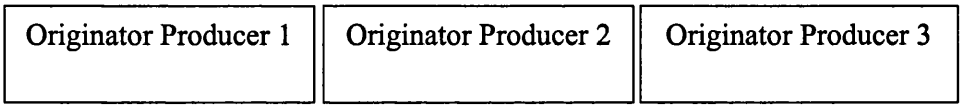
Consider a therapeutic class characterised by an originator molecule, and other molecules which follow in the same class and are also under patent protection. New innovative pharmaceutical products are subject to patent protection for 20 years. During their effective patent life they are, in effect, the monopolist provider of the molecule in question. If they are the only product in the class they have even more market power, because any substitutes are less close to the product in question, because they will belong to another therapeutic class. Eventually, other products enter the therapeutic class so the first molecule faces competition from other molecules of the same therapeutic class which target the same illness. A description of these market dynamics at class level is shown in Figure 5.1. Eventually, the patent of the first provider expires and generic versions of the first molecule enter the market. Gradually patents of other medicines also expire and generics of other molecules also enter the market. This in principle intensifies competition and puts existing originators under greater pressure in terms of volume due to the presence of more competitors. Depending on regulation, this pressure may be more or less intense. Reference pricing at the therapeutic class level makes in- patent molecules subject to reimbursement at prices of generic versions of off- patent molecules, hence creating more competition and more savings for health insurance.

Figure 5.1 Competition in the Pharmaceutical Market

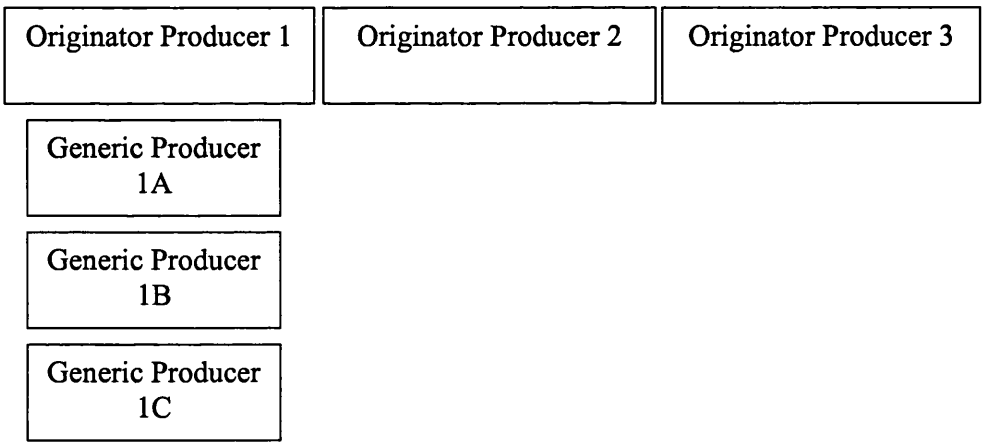
Stage 1. New Class. One molecule. Monopoly at class level



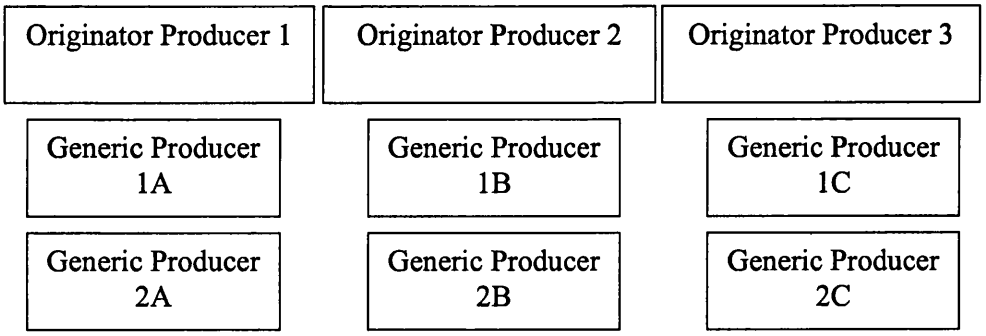
Stage 2. New molecules in class. Monopoly only at molecule level



Stage 3. Generic entry. A producer loses monopoly at molecule level; all others still have monopoly power at molecule level



Stage 4. Patent expiry of another molecule. Another producer loses monopoly at molecule level; Others still have monopoly power at molecule level



Assume there is a firm which has developed an originator medicine (medicine A). The cost of R&D is a fixed cost, which is a sunk cost. In addition, there is a unit cost of production, c. Before the development of this medicine, other medicines were used for the treatment of the particular disease. In order to help the new medicine penetrate the market, promotional strategies are implemented. This involves a unit cost of promotion efforts. Promotion should lead to higher.

Medicine A is sold at price p_A . Total sales are Q_A . Post patent expiry, generics enter the market and gain part of the market. When generic competitors are present, advertising has a smaller effect on volume than before entry. First, the originator has a smaller market share, which constantly decreases due to higher generic prescribing, dispensing and use. Second, there is a spillover effect to generic producers, "not only by increasing the number of prescriptions written for generics, but also through generic substitution of brand-written prescriptions" (Caves, Whinston, Hurwitz, 1991). Therefore advertising does not have as positive effect as prior to generic entry.

Profits from medicine A while it is still on-patent are:

$$\Pi_A = p_A Q_A(1+\alpha) - c_A Q_A - k\alpha \qquad (1)$$

Where α is the net promotion multiplier, indicating how sales increase due to the originator producer's promotional activities, and k indicates the cost of advertising.

Profits from medicine A post generic entry are:

$$\Pi_A = p_A q_A(1+\alpha) - c_A q_A - k\alpha \qquad (2)$$

Where $q_A < Q_A$, as part of the market is taken over by generics with sales q_G, and $q_A + q_G = Q_A$

It is common though that the originator producer has other branded in-patent products in other therapeutic class markets. Suppose medicine B is such a medicine. Profits from in-patent medicine B are:

$$\Pi_B = p_B Q_B (1+\alpha) - c_B Q_B - k\alpha \qquad (3)$$

Differentiating profits with respect to α for product A and B respectively gives us:

$$\frac{\partial \Pi_A}{\partial \alpha} = p_A q_A - k \qquad (4)$$

$$\frac{\partial \Pi_B}{\partial \alpha} = p_B Q_B - k \qquad (5)$$

Economic theory suggests that prices in a monopolistic market are higher than prices in an oligopolistic or competitive market, thus $p_B > p_A$. Even if this is not the case though, and prices in the two markets are the same, sales are not expected to be the same after generic entry in market A. Market B is an in-patent market, thus generic products do not have any market share, contrary to market A, which faces generic competition. Therefore, in most cases it is reasonable to expect that $Q_B > q_A$.

If this holds, then $p_B Q_B - k > p_A q_A - k \qquad (6)$

$\Rightarrow \frac{\partial \Pi_B}{\partial \alpha} > \frac{\partial \Pi_A}{\partial \alpha}$, which means that the marginal return to promotion in an in-patent market is higher then the marginal return to promotion in an off-patent market. The immediate implication is that it pays more for a pharmaceutical firm to focus on new products than to focus on old ones. Thus it is expected that a firm which has a patented product will focus its promoting efforts on that particular product rather than on one that has gone off patent. If one of the determinants of demand is advertising, assuming a positive effect of promotional efforts on sales, then generic

entry has a negative effect on sales. This is when producers of other products of the same therapeutic class may attract part of the market of the molecule which went off-patent (regardless of if they were already in the market or just entered), assuming that medicines of the same class may be close substitutes. Unfortunately, data on expenditure for promotional activities are not announced at product level. Further, aggregate data on promotional activities of the pharmaceutical industry have been disputed (Gagnon and Lexchin, 2008). Therefore in the empirical model we will not be able to take this important factor into account. However, les advertising would have a volume effect on the off-patent molecule and its competitors. Data on volume of the off-patent molecule and other molecules that are still in- patent can show whether such a switch in consumption from the off- patent product to in- patent products does take place, regardless of the source of the switch.

5.5 The Case of ACE Inhibitors

ACE (angiotensin-converting enzyme) Inhibitors are used for the treatment of hypertension and congestive heart failure (NICE 2004). The first ACE inhibitor to enter the market was Captorpril, followed by many other products (Enalapril, Lisinopril, Quinapril, Ramipril, Trandalopril, Periodinopril, Moexipril, Fisinopril, Benazepril, Cilazapril, Cilazapril, Zofenopril, Imidrapril, Spriapril). The study period is 1991-2006, where in total there were 14 ACE inhibitors on the market. It is generally accepted that they are interchangeable for the conditions they are used for (Salvetti 1990). In a double blind comparison between Captorpil and Enalapril (Vlasses et al 1986), the authors conclude that the two ACE inhibitors have similar antihypertensive effects and mechanisms of action. Similar findings occurred from a double blind multicentre comparison of captopril and enalapril (Rumboldt et al.

1988). According to the findings, these two ACE inhibitors demonstrate "comparable effectiveness within the used dose range", although enalapril was more potent, longer acting, and possibly safer. In a comparison of enalapril versus captopril on left ventricular function and survival three months after acute myocardial infarction (Foy et al 1994), results showed that the benefit to patients was similar with both ACE inhibitors and was in excess of the benefits of optimal conventional therapy.

In a comparison of treatment with lisinopril (the third ACE inhibitor to enter the market) versus enalapril for congestive heart failure (Zannad et al 1992), the results indicate that lisinopril 5-20 mg once daily is at least as effective and well tolerated as enalapril 5-20 mg once daily. Dews et al (1989) conducted a study with limitations due to the small number of patients, but found that lisinopril is as effective as enalapril in lowering blood pressure. Similar findings occurred from a study by Enstrom et al (1992). The authors conclude that "no difference was found in blood pressure lowering efficacy between enalapril and lisinopril even though the blood pressure changes were evaluated in a more comprehensive way than in earlier studies of these medicines".

Rumboldt et al (1993) compared the antihypertensive efficacy and safety of lisinopril to those of captopril. The results showed that both medicines demonstrated similar efficiency and safety, although lisinopril was marginally more potent and longer acting. Morisco et al (1997) conducted a comparison study between captopril and lisinopril for the treatment of congestive heart failure in elderly patients. The results showed that "lisinopril 5-20 mg once daily is at least as effective and well tolerated as captopril 12.5-50 mg daily in the treatment of elderly patients with congestive heart failure".

These studies indicate that there is a high level of interchangeability between ACE inhibitors and allows us to make the hypothesis that there is competition between medicines of this therapeutic class. This interchangeability may concern new patients, but may also apply to existing patients.

Health insurance practice also provides some evidence on how ACE inhibitors are perceived by social planners. In the Netherlands, all ACE Inhibitors are subject to the same reference price, as the reference price is set at the therapeutic class level (Kanavos and Gemmill 2005). In the United Kingdom, in the outpatient guidance for hypertension, the National Institute for Clinical Excellence (NICE) does not distinguish between ACE inhibitors (NICE 2004), but simply refers to the whole class, showing that according to NICE they are considered as similar treatments.

If the result of an ACE inhibitor going off patent has a positive effect on volume of other molecules of the same class, while total volume for both the originator and generics of the off patent molecule decrease, this would indicate a switch in consumption from the off-patent molecule to molecules that are still on patent. The effect would be clear on medicine expenditure. The off- patent originator can be substituted by a generic alternative, which is cheaper than the originator. In- patent medicines though have no generic alternative, so the originator has to be dispensed, unless there is "therapeutic" substitution in place which, strictly speaking, is not allowed, unless all ACE inhibitors are clustered together in the same reference cluster and reference pricing system exists. Thus a product going off patent may not lead to as much savings for health insurance as it could potentially lead to if the switching in consumption did not take place.

5.6 Pharmaceutical Policies

Regulation plays a significant role in pharmaceutical markets in the European Union. Policies heavily influence volume and quantity of medicines sold, as well as the choice between alternative products, e.g. the choice between an originator medicine and its generic alternative. Policies also play a significant role in the significant price differences observed across countries within the European Union. Consequently it is imperative that policies are taken into consideration in this analysis. This section provides a brief overview of the main policies implemented in the countries studied in this chapter. These policies are discussed in detail in the Appenix, with reference to all countries studied in this dissertation.

Tables 5.1, 5.2, 5.3, 5.4, 5.5 and 5.6 indicate the presence or not of different policies in pharmaceutical markets in Denmark, France, Germany, the Netherlands, Sweden and the United Kingdom. Policies included in the tables are: Reference pricing (*rp*), clustering all molecules of the same therapeutic class for the purpose of reference pricing (*clust*), mandatory generic substitution at pharmacy (*ms*), optional generic substitution at pharmacy (*os*), generic price controls (*gcont*), regressive pharmacy markups (markup), profit controls (*pc*), clawbacks (*clawb*), tax funded health insurance (*tax*), contribution-based health insurance (*contrib*) and the explicit use of cost effectiveness analysis in the reimbursement approval process (*cea*).

5.6.1 Reference Pricing

A reference price is the maximum price that health insurance will pay for a particular molecule. Molecules are grouped together and a price is determined for each group. The price is usually based on the average of the prices of the cheapest medicines. Cross country reference pricing is also common. In this case, prices of

other countries from the European Economic Area are taken into account when defining the reference price. Medicines may be grouped at the molecule level or at the therapeutic class level. Health insurance reimburses the reference price while the price difference for any medicine whose price exceeds the reference price will have to be paid out-of-pocket by the patient (Lopez-Casasnovas, Puig 2000, PPRI pharma profiles 2008).

5.6.2 Generic Substitution

Generic substitution refers to the pharmacists' right or obligation (depending on regulation) to substitute a branded prescription medicine with its generic, when the medicine has been prescribed by brand name (PPRI pharma profiles 2008). Such policies help generic penetration.

5.6.3 Generic price controls

In some countries, generic medicines are subject to a price cap or a maximum price as a percentage of the price of the corresponding originator product. This percentage is usually gradually reduced with time (PPRI pharma profiles 2008).

5.6.4 Regressive Pharmacy margins

Depending on regulation, pharmacists are remunerated based on flat fees per prescription, fixed margins, progressive margins or regressive margins. Under flat fee schemes, pharmacists are indifferent with regards to the cost of the medicine dispensed. Fixed margins and progressive margins actually provide an incentive for pharmacists to dispense the most expensive medicine. It is more profitable for them

to dispense the originator than the (cheaper) generic. It is regressive pharmacy margins which actually provide an incentive to pharmacists to dispense (cheaper) generic medicines rather than the (more expensive) originator. In an effort to contain costs, pharmacists are remunerated based on regressive margins in many European countries (PPRI pharma profiles 2008).

5.6.5 Profit controls

Profit controls are a form of rate-of-return regulation (OFT 2007,DoH 2008). When this policy measure is present, the manufacturer is allowed to make profits up to a certain rate of the capital invested. Any profits exceeding this must be paid back to health insurance. This policy is present in the United Kingdom.

5.6.6 Explicit use of Cost Effectiveness Analysis (CEA)

Cost Effectiveness Analysis is explicitly used in determining pricing/reimbursement rates of pharmaceutical products in some countries. This is a form of regulation applied to medicines prior to their entry into the market and used as an implicit means of quality assurance in that products requesting a price premium over similar products have to prove they are better than their competitors in clinical terms.

5.6.7 Clawbacks

When clawbacks are implemented, health insurance may retrieve part of the discounts given to pharmacists by wholesalers (PPRI pharma profiles 2008, Kanavos and Costa-Font 2005).

5.6.8 Tax funded or NHS-type health insurance

Health systems may be organized as an NHS-type or an insurance-based system. NHS-type systems have gatekeeper arrangements in place through general practitioners and potentially restrict demand for health services, including pharmaceuticals, compared with social insurance-based systems where access to specialists is still safeguarded.

Table 5.1 Policy Measures 1992-2006, Denmark

Year	*rp*	*clust*	*sm*	*so*	*gcont*	*markup*	*pc*	*clawb*	*tax*	*contrib*	*cea*
1992	no	no	no	yes	no	yes	no	no	yes	no	no
1993	yes	no	no	yes	no	yes	no	no	yes	no	no
1994	yes	no	no	yes	no	yes	no	no	yes	no	no
1995	yes	no	no	yes	no	yes	no	no	yes	no	no
1996	yes	no	no	yes	no	yes	no	no	yes	no	no
1997	yes	no	yes	no	no	yes	no	no	yes	no	no
1998	yes	no	yes	no	no	yes	no	no	yes	no	no
1999	yes	no	yes	no	no	yes	no	no	yes	no	no
2000	yes	no	yes	no	no	yes	no	no	yes	no	no
2001	yes	no	yes	no	no	yes	no	no	yes	no	no
2002	yes	no	yes	no	no	yes	no	no	yes	no	no
2003	yes	no	yes	no	no	yes	no	no	yes	no	no
2004	yes	no	yes	no	no	yes	no	no	yes	no	no
2005	yes	no	yes	no	no	yes	no	no	yes	no	yes
2006	yes	no	yes	no	no	yes	no	no	yes	no	yes

Table 5.2 Policy Measures 1992-2006, France

Year	*rp*	*clust*	*sm*	*so*	*gcont*	*markup*	*pc*	*clawb*	*tax*	*contrib*	*cea*
1992	no	no	no	no	yes	yes	no	no	no	yes	no
1993	no	no	no	no	yes	yes	no	no	no	yes	no
1994	no	no	no	no	yes	yes	no	no	no	yes	no
1995	no	no	no	no	yes	yes	no	no	no	yes	no
1996	no	no	no	no	yes	yes	no	no	no	yes	no
1997	no	no	no	no	yes	yes	no	no	no	yes	no
1998	no	no	no	no	yes	yes	no	no	no	yes	no
1999	no	no	no	yes	yes	no	no	no	no	yes	no
2000	no	no	no	yes	yes	no	no	no	no	yes	no
2001	no	no	no	yes	yes	no	no	no	no	yes	no
2002	no	no	no	yes	yes	no	no	no	no	yes	no
2003	yes	no	no	yes	yes	no	no	no	no	yes	no
2004	yes	no	no	yes	yes	yes	no	no	no	yes	no
2005	yes	no	no	yes	yes	yes	no	no	no	yes	no
2006	yes	no	no	yes	yes	yes	no	no	no	yes	no

Table 5.3 Policy measures 1992-2006, Germany

Year	*rp*	*clust*	*sm*	*so*	*gcont*	*markup*	*pc*	*clawb*	*tax*	*contrib*	*cea*
1992	yes	no	no	no	no	yes	no	no	no	yes	no
1993	yes	no	no	no	no	yes	no	no	no	yes	no
1994	yes	no	no	no	no	yes	no	no	no	yes	no
1995	yes	no	no	no	no	yes	no	no	no	yes	no
1996	yes	no	no	no	no	yes	no	no	no	yes	no
1997	yes	no	no	no	no	yes	no	no	no	yes	no
1998	yes	no	no	no	no	yes	no	no	no	yes	no
1999	yes	no	no	no	no	yes	no	no	no	yes	no
2000	yes	no	no	no	no	yes	no	no	no	yes	no
2001	yes	no	no	no	no	yes	no	no	no	yes	no
2002	yes	no	no	yes	no	yes	no	no	no	yes	no
2003	yes	no	no	yes	no	no	no	no	no	yes	no
2004	yes	no	yes	yes	no	no	no	yes	no	yes	no
2005	yes	no	yes	no	no	no	no	yes	no	yes	no
2006	yes	yes	yes	no	no	no	no	yes	no	yes	no

Table 5.4 Policy Measures 1992-2006, Netherlands

Year	*rp*	*clust*	*sm*	*so*	*gcont*	*markup*	*pc*	*clawb*	*tax*	*contrib*	*cea*
1992	yes	yes	no	no	no	no	no	no	no	yes	no
1993	yes	yes	no	no	no	no	no	no	no	yes	no
1994	yes	yes	no	no	no	no	no	no	no	yes	no
1995	yes	yes	no	no	no	no	no	no	no	yes	no
1996	yes	yes	no	yes	no	no	no	no	no	yes	no
1997	yes	yes	no	yes	no	no	no	no	no	yes	no
1998	yes	yes	no	yes	no	no	no	yes	no	yes	no
1999	yes	yes	no	yes	no	no	no	yes	no	yes	yes
2000	yes	yes	no	yes	no	no	no	yes	no	yes	yes
2001	yes	yes	no	yes	no	no	no	yes	no	yes	yes
2002	yes	yes	no	yes	no	no	no	yes	no	yes	yes
2003	yes	yes	no	yes	no	no	no	yes	no	yes	yes
2004	yes	yes	no	yes	no	no	no	yes	no	yes	yes
2005	yes	yes	no	yes	no	no	no	yes	no	yes	yes
2006	yes	yes	no	yes	no	no	no	yes	no	yes	yes

Table 5.5 Policy Measures 1992-2006, Sweden

Year	*rp*	*clust*	*sm*	*so*	*gcont*	*markup*	*pc*	*clawb*	*tax*	*contrib*	*cea*
1992	no	no	no	no	yes	yes	no	no	yes	no	no
1993	yes	no	no	no	yes	yes	no	no	yes	no	no
1994	yes	no	no	no	yes	yes	no	no	yes	no	no
1995	yes	no	no	no	yes	yes	no	no	yes	no	no
1996	yes	no	no	no	yes	yes	no	no	yes	no	no
1997	yes	no	no	no	yes	yes	no	no	yes	no	no
1998	yes	no	no	no	yes	yes	no	no	yes	no	no
1999	yes	no	no	no	yes	yes	no	no	yes	no	no
2000	yes	no	no	no	yes	yes	no	no	yes	no	no
2001	yes	no	no	no	yes	yes	no	no	yes	no	no
2002	no	no	yes	yes	yes	yes	no	no	yes	no	yes
2003	no	no	yes	yes	yes	yes	no	no	yes	no	yes
2004	no	no	yes	yes	yes	yes	no	no	yes	no	yes
2005	no	no	yes	yes	yes	yes	no	no	yes	no	yes
2006	no	no	yes	yes	yes	yes	no	no	yes	no	yes

Table 5.6 Policy Measures 1992-2006, United Kingdom

Year	*rp*	*clust*	*sm*	*so*	*gcont*	*markup*	*pc*	*clawb*	*tax*	*contrib*	*cea*
1992	no	no	no	no	no	no	yes	no	yes	no	no
1993	no	no	no	no	no	no	yes	no	yes	no	no
1994	no	no	no	no	no	no	yes	no	yes	no	no
1995	no	no	no	no	no	no	yes	no	yes	no	no
1996	no	no	no	no	no	no	yes	no	yes	no	no
1997	no	no	no	no	no	no	yes	yes	yes	no	no
1998	no	no	no	no	no	no	yes	yes	yes	no	no
1999	no	no	no	no	no	no	yes	yes	yes	no	no
2000	no	no	no	no	yes	no	yes	yes	yes	no	yes
2001	no	no	no	no	yes	no	yes	yes	yes	no	yes
2002	no	no	no	no	yes	no	yes	yes	yes	no	yes
2003	no	no	no	no	yes	no	yes	yes	yes	no	yes
2004	no	no	no	no	yes	no	yes	yes	yes	no	yes
2005	no	no	no	no	yes	no	yes	yes	yes	no	yes
2006	no	no	no	no	yes	no	yes	yes	yes	no	yes

5.7 Data and Methods

5.7.1 Data

Data used are obtained from the Intercontinental Medical Statistics (IMS) – MIDAS database. Collected and reported data are based on actual invoiced prices and sales. Within the European context, list of prices of prescription medicines are actually reimbursed by health insurance. Data are quarterly and concern the 1991-2006 period for 14 Plain ACE inhibitors (Captopril, Enalapril, Lisinopril, Quinapril, Ramipril, Trandalopril, Periodinopril, Moexipril, Fisinopril, Benazepril, Cilazapril, Cilazapril, Zofenopril, Imidrapril, Spriapril) in six European countries (Germany, United Kingdom, the Netherlands, Sweden, France, Denmark) for the retail

(pharmacy) market in each country. Data were available for originator and generic versions of each molecule.

5.7.2 The Empirical Model

As expenditure data on promotional activities for each product separately are not available, it was not possible to include this important variable in the empirical model. However, the use of advertising as an explanatory variable would be endogenous and thus not suitable for the model, as it would be difficult to find a good instrumental variable for this. Without advertising data, the empirical model can show a possible switch in consumption volume using price, sales, competition and regulation data. The source of this possible switch can be theoretically attributed to a drop in promotional activities for the off- patent product and the constitution of promotional activities for those products in the same class that are still in-patent. The purpose of the empirical model is to explain the variation in volume as a function of generic presence, the number of competitors, regulatory measures and time. The empirical model is shown in equations (7) (8) and (9).

$$\ln Q_{it}^{OP} = \beta_i + \beta_0 + \beta_1 off_{it} + \beta_2 N_{it} + \beta_3 Nsq_{it} + \beta_4 sub_{it} + \beta_5 rp_{it} + \beta_6 gcont_{it}$$

$$+ \beta_7 markup_{it} + \beta_8 pc_{it} + \beta_9 clawb_{it} + \beta_{10} tax_{it} + \beta_{11} cea_{it} + \sum_{k=12}^{72} \beta_k time_{it} + \varepsilon_{it} \quad (7)$$

$$\ln Q_{it}^{IP} = \beta_i + \beta_0 + \beta_1 off_{it} + \beta_2 N_{it} + \beta_3 Nsq_{it} + \beta_4 sub_{it} + \beta_5 rp_{it} + \beta_6 gcont_{it}$$

$$+ \beta_7 markup_{it} + \beta_8 pc_{it} + \beta_9 clawb_{it} + \beta_{10} tax_{it} + \beta_{11} cea_{it} + \sum_{k=12}^{72} \beta_k time_{it} + u_{it} \quad (8)$$

$$\ln\left(\frac{Q_{it}^{OP}}{Q_{it}^{IP}}\right) = \beta_i + \beta_0 + \beta_1 off_{it} + \beta_2 N_{it} + \beta_3 Nsq_{it} + \beta_4 sub_{it} + \beta_5 rp_{it} + \beta_6 gcont_{it}$$

$$+ \beta_7 markup_{it} + \beta_8 pc_{it} + \beta_9 clawb_{it} + \beta_{10} tax_{it} + \beta_{11} cea_{it} + \sum_{k=12}^{72} \beta_k time_{it} + \mu_{it} \quad (9)$$

where i indicates the specific product in a specific country and t indicates time. ε_{it}, u_{it} and μ_{it} are the error terms in equations (7), (8) and (9) respectively. The dependent variable in equation (9) can be expressed as the difference of the logs of Q_{it}^{IP} and Q_{it}^{OP}. This follows the mathematical properties of logarithms, according to which $\log\left(\frac{\alpha}{\beta}\right) = \log\alpha - \log\beta$. Consequently, the dependent variable of equation (9) can be expressed as $\log Q_{it}^{IP}$ - $\log Q_{it}^{OP}$.

Q_{it}^{OP} indicates volume of the product which goes off patent measured in number of milligrams. Q_{it}^{IP} indicates volume of all other products in the same therapeutic class which are in patent when the study medicine goes off patent (also measured in milligrams). *off* is a dummy variable, indicating generic entry. The dummy takes the value of 1 when generic entry occurs for a product (j) in a country (i); 0 elsewhere. Generic entry is identified and confirmed by (a) patent records for the branded product and (b) separate entries of sales, volumes and prices of generics by firms other than the holders of the original patent (generic companies). *N* is the number of generic competitors on the market. *Nsq* is the square of the number of generic competitors. This is included because the number of competitors as a determinant of volume competition is not linear. The effects are diminishing, therefore we assume a quadratic effect of competition. There is also a number of policy dummies included in the model: *sub* indicates the presence of generic

substitution policies. *rp* indicates the presence of reference pricing. *gcont* represents generic price controls. *markup* indicates markup regulation. *pc* indicates price controls. *clawb* is the presence of clawbacks and tax indicates that the health system is tax funded. and *cea* indicates the use of cost effectiveness analysis in pharmaceutical policy. Finally, time dummies are included for each of the 61 quarters (time observations) in the data. Summary statistics for captopril, enalapril and lisinopril, which are the first ACE inhibitors on the market for the 6 study countries, which also went off- patent in this order, are shown in Tables 5.7, 5.8 and 5.9 respectively.

Table 5.7 Summary Statistics, Captopril

Variable	Obs	Mean	Std. Dev.
$\ln Q_{it}^{OP}$	366	12.522	1.480
$\ln\left(Q_{it}^{OP} \Big/ \sum_{i=1}^{n} Q_{it}^{IP}\right)$	366	-2.392	1.591
$\ln Q_{it}^{IP}$	3089	9.235	2.324
off	3632	0.620	0.485
N	3632	3.375	6.618
Nsq	3632	55.169	169.420
sm	3632	0.149	0.356
rp	3632	0.608	0.488
gcont	3632	0.398	0.490
markup	3632	0.526	0.499
pc	3632	0.168	0.374
clawb	3632	0.222	0.416
tax	3632	0.446	0.497
cea	3632	0.188	0.391

Table 5.8 Summary Statistics, Enalapril

Variable	Obs	Mean	Std. Dev.
$\ln Q_{it}^{OP}$	366	11.912	1.006
$\ln\left(Q_{it}^{OP} \Big/ \sum_{i=1}^{n} Q_{it}^{IP}\right)$	366	-2.396	0.997
$\ln Q_{it}^{IP}$	2723	8.875	2.213
off	3266	0.438	0.496
N	3266	2.386	5.183
Nsq	3266	32.550	114.088
sm	3266	0.147	0.354
rp	3266	0.607	0.489
gcont	3266	0.398	0.490
markup	3266	0.524	0.499
pc	3266	0.168	0.374
clawb	3266	0.222	0.415
tax	3266	0.440	0.496
cea	3266	0.186	0.389

Table 5.9 Summary Statistics, Lisinopril

Variable	Obs	Mean	Std. Dev.
$\ln Q_{it}^{OP}$	366	10.927	1.543
$\ln\left(Q_{it}^{OP} \Big/ \sum_{i=1}^{n} Q_{it}^{IP}\right)$	366	-2.751	1.502
$\ln Q_{it}^{IP}$	2357	8.556	2.129
off	2900	0.255	0.436
N	2900	1.385	3.575
Nsq	2900	14.697	67.712
sm	2900	0.144	0.351
rp	2900	0.605	0.489
gcont	2900	0.398	0.490
markup	2900	0.522	0.500
pc	2900	0.168	0.374
clawb	2900	0.221	0.415
tax	2900	0.432	0.495
cea	2900	0.183	0.387

Equation (7) shows the effect of generic entry on the evolution of total volume (originator and generic after patent expiry) for the product which goes off-patent. Equation (8) shows how volume of other products in the same therapeutic class is affected by generic entry in the product which goes off-patent. Equation (9) is introduced in order to capture the effect of generic entry on the relative volume of the product which goes off-patent compared to all other medicines in the same class.

Although equations (7) and (8) are useful as they demonstrate the effect of patent expiry on the total volume (originator and generic) of the particular molecule, their findings do not necessarily confirm or contradict the presence of a switching effect. Total volume of the off-patent molecule may increase as a result of patent expiry but at a slower rate or not as much as the total volume of in patent ACE inhibitors. Similarly, the total volume of the off-patent molecule may decrease, but at a slower rate than the total volume of the in patent ACE inhibitors. Therefore, equations (7) and (8) separately do not provide evidence regarding the presence or not of the switching effect.

This is why equation (9) is introduced. This equation helps overcome possible problems which would occur due to a shock in demand for ACE inhibitors and changes in total market size. Equation (9) shows whether the switching effect of consumption from off patent molecules to in patent ACE inhibitors does or does not occur. A negative and statistically significant coefficient would suggest that the ratio of the volume of the off patent molecule over the volume of in patent molecules decreases post patent expiry. this would, in turn, suggest that the switching effect is

present. Separate estimates are run for each of the three first ACE inhibitors that went off patent, namely captopril, enalapril and lisinopril, in this order.

The coefficient of *off* shows the effect of generic entry on volume of either the ACE inhibitor which goes off patent (equation 7), or the sum of all other ACE inhibitors. A negative coefficient for *off* in equation (7) would show that generic entry in the market of a particular ACE inhibitor leads to a decrease in the sum of originator and generic volume. A positive coefficient for *off* in equation (8) would suggest that volume of in-patent ACE inhibitors increases following generic entry in another ACE inhibitor. A negative coefficient for *off* in equation (9) would indicate that the volume of the molecule which goes off patent decreases relative to the volume of in-patent ACE inhibitors. All three cases mentioned above would suggest the presence of a switch in consumption.

Recent studies have emphasized the importance of pharmaceutical regulation whether on the supply- or the demand-side (Lopez-Casasnovas and Puig 2000, Kanavos et al, 2008; Kanavos and Costa-Font, 2005). The presence of generic substitution policies is expected to encourage switching behaviour (Kanavos et al 2008). Generic substitution policies put pressure on the branded product's market share, leading to lower revenue, and in practice limiting the effect of promotional activities. Thus, the producer has an incentive to promote other products in his portfolio which are on patent rather than focus on ACE inhibitors anymore. This would lead producers of in-patent ACE inhibitors to increase their market share by attracting a part of the off-patent molecules market share.

A higher number of generic competitors is also expected to encourage switching behaviour for the same reason. More generic competitors implies a higher price competition between generics, and, consequently, lower generic prices and a

smaller market share for the originator. Again, the producer of the originator will "abandon" promotion effects in the particular market, allowing other ACE inhibitors to gain part of its market share.

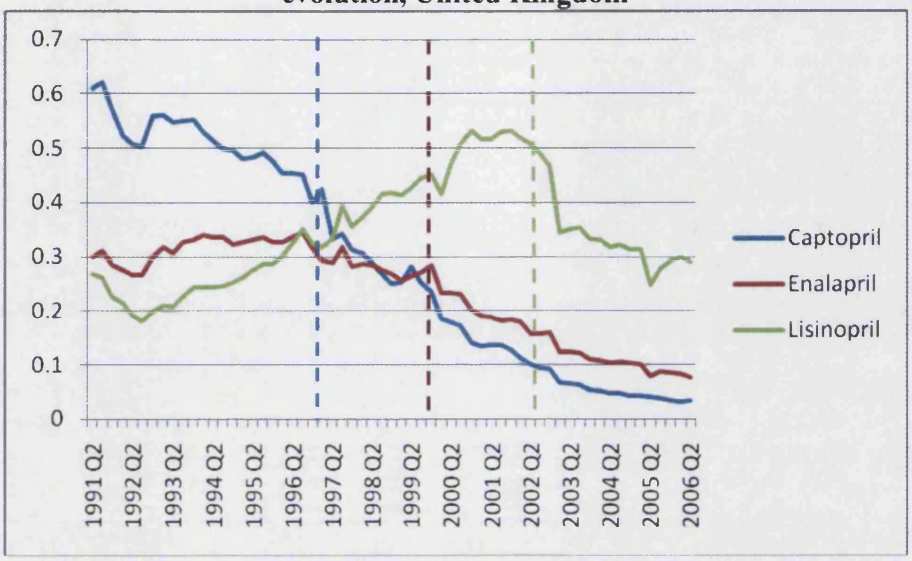
Panel data is used to complete the analysis because it can give more informative data estimates, greater variability, less collinearity among variables, more degrees of freedom and higher efficiency (Gujarati 2003). Having a different intercept for each country and product allows us to have a more efficient model. The constant term, β_i is different for each molecule in each country and is determined using either fixed or random effects. We assume heterogeneity between countries due to the fact that different policies apply. Based on this assumption, the constant term that is different for each country captures the effects of those variables that are peculiar to the *i*-th individual and that are constant over time. The error term is assumed to be independent and identically distributed over products and time, with mean zero and variance σ_ε^2. Alternatively, the random effects approach assumes that the intercepts of the individuals are different but that they can be treated as drawings from a distribution with mean μ and variance σ_α^2. The essential assumption here is that these drawings are independent of the explanatory variables. Apart from the analysis including all six countries, regressions are also run for each country separately. However, in the latter case ordinary least squares are used instead of panel data, because of the presence of only one group per regression.

In estimating equations (7), (8) and (9), we have used panel data random effects. The Hausman Test suggests that we follow the random effects approach: The Chi-squared statistic is 0.32, indicating that the difference between the consistent fixed effects and the random effects estimator is statistically insignificant. Therefore, it is safe to use random effects (which provides a more efficient estimator

compared to fixed effects) as, according to the Hausman test, they give consistent results.

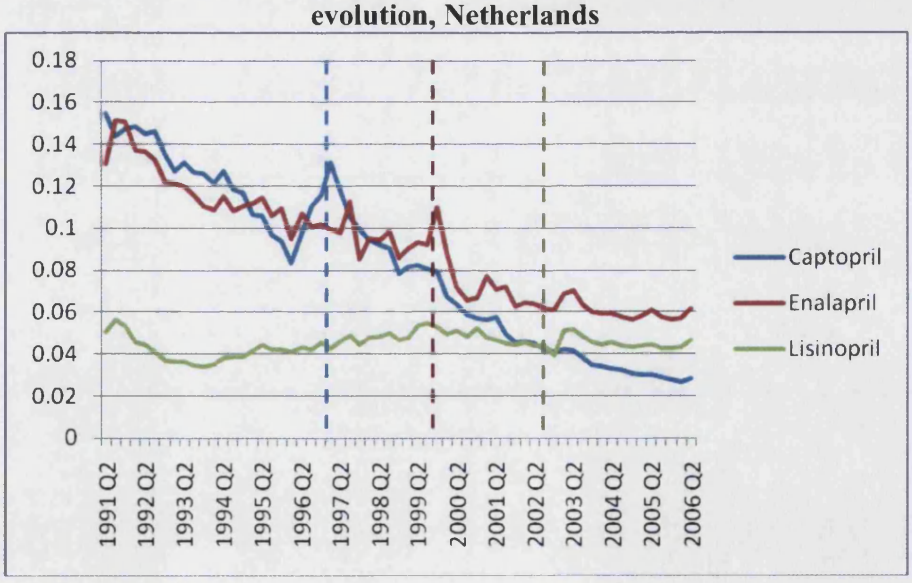
Figure 5.2 shows the evolution of the ratio of captopril, enalapril and lisinopril volume over all in- patent ACE inhibitor volume in the United Kingdom. The vertical line indicates the point at which each molecule goes off patent. The graph shows that the ratio declines at a faster rate post patent expiry for captopril and enalapril. In the case of lisinopril, although the ratio increases prior to patent expiry, it decreases sharply after generic entry. Figure 5.3 shows the evolution of the ratio of captopril, enalapril and lisinopril volume over all in- patent ACE inhibitor volume in the Netherlands. The vertical line indicates the point at which captopril goes off patent Results are not as clear as in the case of the United Kingdom. The rate of enalapril over other ACE inhibitors appears to decline at a faster rate, and the ratio of captopril over other molecules decreases sharply post patent expiry, but this only follows another period of sharp decrease that was interrupted by a short period of steep increase. No effect seems to be present in the case of lisinopril. Figure 5.4 demonstrates the case of France, where there is no evident sign of a switch post patent expiry. These figures are indicative only, and the analysis does not rely on graphical representations. Graphs show a two- dimension relationship only and do not include other factors which may affect volume. This is why we focus on econometric analysis which allows controlling for many other factors, such as number of generic competitors and regulation, which plays a primary role in pharmaceutical markets.

Figure 5.2 Ratio of captopril, enalapril and lisinopril volume (originator and generics) over volume of all in- patent ACE Inhibitors (originators and generics) evolution, United Kingdom



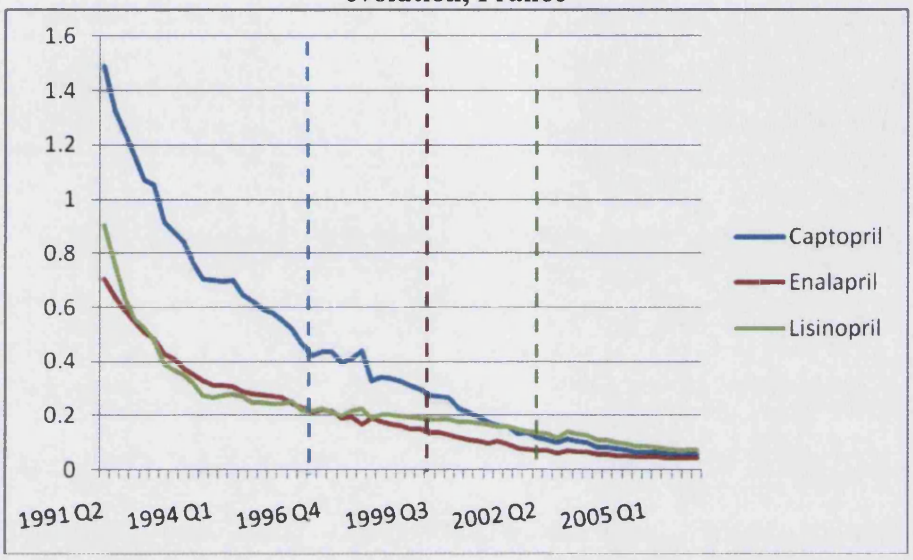
Note: Vertical line indicates generic entry

Figure 5.3 Ratio of captopril, enalapril and lisinopril volume (originator and generics) over volume of all in- patent ACE Inhibitors (originators and generics) evolution, Netherlands



Note: Vertical line indicates generic entry

Figure 5.4 Ratio of captopril, enalapril and lisinopril volume (originator and generics) over volume of all in- patent ACE Inhibitors (originators and generics) evolution, France



***Note**: Vertical line indicates generic entry*

5.8 Results

Equations (7) and (9) could be estimated simultaneously. This could potentially lead to a more efficient estimator, but would not lead to any gains in terms of consistency. In order to see if estimating the two equations simultaneously would improve efficiency, the correlation between the residuals in the two equations was observed. Correlation between residuals is small, thus there is no need to estimate them jointly.

5.8.1 Results at the aggregate level

Table 5.10 shows the regression results for equation (7), for the cases of captorpil, enalapril and lisinopril. In the case of captopril, the coefficient of *off* is negative (-0.702) and statistically significant (α=5%). This indicates a decrease in

the total volume, originator and generic, of captopril post patent expiry. The number of generic competitors in the captopril market of each country has a negative and statistically significant effect. s*ub* has a positive and statistically significant coefficient. This result suggests that when generic substitution policies are present the volume of the off patent ACE inhibitor increases post patent expiry. Generic price controls, regressive pharmacist markups and profit controls all have a positive and statistically significant effect on total captopril volume. Reference price, clawbacks and the use of CEA do not appear to have a significant effect on volume.

In the estimation results for enalapirl, *off* has a positive and statistically significant coefficient (α=1%). Generic substitution policies have a positive and weakly statistically significant effect. The effect of reference pricing is statistically insignificant. Generic price controls and profit controls have a positive and significant effect (α=1%) on enalapril volume post patent expiry. The coefficients of regressive pharmacist markups and clawbacks are negative and statistically significant.

The coefficient of *off* in the regression results for lisinopril is positive and statistically significant (α=1%). The calculation is made in the same way as for captopril and enalapril. Generic substitution policies lead to lower volume of lisinopril when it goes off patent. Reference pricing has no effect, as in the case of captopril and enalapril. Generic price controls, regressive pharmacist markups, profit controls and clawbacks have a positive and statistically significant effect on lisinopril volume.

The findings for captopril markets are different than enalapril and lisinopril markets. In the case of captopril, the coefficient of *off* is negative, demonstrating a decrease in total captopril volume post patent expiry. The opposite holds for

enalapril and lisinopril. These findings alone do not say much about the presence or not of a switch in consumption from an off patent ACE inhibitor to an in patent one as a result of generic entry. An increase in enalapril and lisinopril volume does not necessarily contradict the switching effect, as the volume of the in patent ACE inhibitors may increase at a faster rate post patent expiry. This would be the result of an increasing market of ACE inhibitors, out of which the molecules that go off patent gain a relatively smaller share. Consequently, the effect on the volume of captopril, enalapril and lisinopril post patent expiry has to be taken into consideration together with the effect on the volume of the in patent ACE inhibitors, as well as the relative changes compared to these other molecules. Estimation results of equations (8) and (9) will help draw a clear picture.

Table 5.10 Random Effects Panel Data Estimation, off patent molecule volume six countries

Dependent Variable: $\ln Q_{it}^{OP}$			
	Captopril	Enalapril	Lisinopril
off	-0.702**	1.265***	1.338***
	(0.299)	(0.316)	(0.357)
N	-0.076***	-0.101***	-0.082***
	(0.009)	(0.007)	(0.011)
Nsq	0.002***	0.004***	0.005***
	(1.39e-04)	(1.54e-04)	(2.88e-04)
sub	0.415***	0.120*	-0.288***
	(0.089)	(0.073)	(0.075)
rp	-0.035	-0.068	0.002
	(0.087)	(0.078)	(0.082)
gcont	0.719***	0.551***	0.922***
	(0.084)	(0.063)	(0.050)
markup	0.535***	-0.574***	0.340***
	(0.116)	(0.107)	(0.125)
pc	3.353***	1.228***	3.637***
	(0.174)	(0.174)	(0.159)
clawb	-0.100	-0.161***	0.258***
	(0.067)	(0.062)	(0.070)
tax	-3.047***	-1.024***	-2.105***
	(0.119)	(0.103)	(0.081)
cea	-0.129	-0.075	-0.280***
	(0.095)	(0.084)	(0.089)
constant	13.023***	11.749***	10.054***
	(0.227)	(0.257)	(0.237)
Observations	366	366	366
Rsq within	0.428	0.641	0.781
Rsq between	0.992	0.994	0.998
Rsq overall	0.948	0.909	0.966
Wald chi sq	9568.03	7055.33	27116.58

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively.

Standard errors in parenthesis

After having estimated the effect of generic entry on the volume of the molecule which goes off-patent, we examine the effect on volume of all other ACE

inhibitors. Estimation results of equation (8) are shown in Table 5.11. Captopril generic entry leads to an increase in volume of other molecules in the same class (statistically significant at α=5%). When captopril goes off patent, the total volume of all in patent ACE inhibitors increases. Generic substitution policies, generic price controls, profit controls and clawbacks lead to an increase in the volume of all in patent ACE inhibitors. Reference price has no effect, while regressive pharmacist markups have a negative effect on volume.

In the case of enalapril, *off* has a positive and statistically significant coefficient, indicating that generic entry leads to an increase in the total volume of all in patent ACE inhibitors. Generic substitution policies, generic price controls, profit controls and clawbacks lead to an increase in the volume of all in patent ACE inhibitors in the case of enalaril. Reference price has no effect and regressive pharmacist markups have a negative effect on volume.

Lisinopril patent expiry leads to an increase in the total volume of all other in-patent ACE inhibitors. This follows the estimation of the coefficient of *off* after controlling for the variables included in the econometric model. In the case of lisinopril, generic substitution policies, generic price controls, profit controls and clawbacks lead to an increase in the volume of all in patent ACE inhibitors. Reference price has no effect while regressive pharmacist markups have a negative effect on volume. The findings which occur from the estimation of equation (9) show the impact of generic entry in each of the three molecules considered in the study on the total volume of the other ACE inhibitors which remain in patent. Evidence is clear and shows that generic entry in captopril, enalapril and lisinopril leads to an increase in the volume of the in patent ACE inhibitors. This itself does not confirm the presence of a switch in consumption. When considered together

with the estimation results of equation (7), the findings suggest that the switching effect is present in the case of captorpril because captopril generic entry leads to a decrease in the total volume of captorpil (occurring from the estimation results of equation (7)) and an increase in the total volume of all in patent ACE inhibitors (occurring from the estimation results of equation (8)). We cannot conclude the same for enalapril and lisinorpil. Generic entry for each of these two medicines leads to both an increase in volume of the molecule which goes off patent (findings from the estimation of equation (7)) and an increase in the volume of all in patent ACE inhibitors (findings from the estimation of equation (8)). In order to make things clear, we proceed to estimate equation (9), which considers the effect of patent expiry on the ration of the volume of the product which goes off patent over the total volume of all other in patent ACE inhibitors.

Table 5.11 Random Effects Panel Data Estimation, in patent molecule volume, six countries

Dependent Variable: $\ln Q_{it}^{IP}$

	Captopril	Enalapril	Lisinopril
off	1.542***	1.700***	1.965***
	(0.252)	(0.278)	(0.315)
N	-0.017***	0.002	0.040***
	(0.006)	(0.009)	(0.011)
Nsq	0.003***	0.003***	0.002***
	(1.80e-04)	(2.95e-04)	(3.90e-04)
sub	0.136**	0.129*	0.258***
	(0.068)	(0.077)	(0.087)
rp	-0.058	-0.053	-0.052
	(0.064)	(0.072)	(0.078)
gcont	0.483***	0.641***	0.686***
	(0.074)	(0.081)	(0.091)
markup	-0.486***	-0.547***	-0.686***
	(0.075)	(0.080)	(0.088)
pc	1.400***	1.448***	1.359**
	(0.538)	(0.513)	(0.582)
clawb	0.392***	0.405***	0.327***
	(0.051)	(0.055)	(0.062)
tax	-1.837***	-2.032***	-2.203***
	(0.396)	(0.388)	(0.447)
cea	0.024	0.002	0.025
	(0.062)	(0.068)	(0.075)
constant	7.898***	7.403***	6.970***
	(0.303)	(0.314)	(0.358)
Observations	3089	2723	2357
Rsq within	0.426	0.451	0.462
Rsq between	0.163	0.205	0.211
Rsq overall	0.177	0.216	0.212
Wald chi sq	1889.91	1908.81	1760.04

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Equation (9) is the most important of all three equations estimated in this study. It does not only show the effects on the off patent molecule or on all in patent

ACE inhibitors separately, but also the joint effect on the relative volume of these two categories. Results are in Table 5.12. The findings of this equation are not distorted by an increase or decrease of total market size, as what matters is how the market is distributed between the molecule which goes off patent and all other ACE inhibitors, rather than the absolute volume of each of these categories.

In the case of captopril, the ratio of the total volume of captopril over the total volume of all other ACE inhibitors decreases post patent expiry. The coefficient of *off* is negative and statistically significant. Generic substitution policies have a positive effect on the ratio, meaning that the volume of the molecule that goes off patent increases compared to the volume of the other in patent ACE inhibitors. The effect of generic price controls, regressive mark-ups for pharmacists and price controls is positive and statistically significant. Clawbacks, reference pricing and the explicit use of cost effectiveness analysis for reimbursement purposes do not have a statistically significant effect on the ratio of volumes.

The coefficient of *off* in the regression for enalapril is also negative, suggesting that the switching effect is also present for the second ACE inhibitor which faces generic entry. Post enalapril generic entry, the ratio of the total volume of enalapril over the total volume of all other ACE inhibitors decreases. Similar to the case of captopril, generic substitution policies have a positive effect on the ratio. The effect of generic price controls, regressive mark-ups for pharmacists and price controls is positive and statistically significant. Clawbacks have a negative and statistically significant effect. Reference pricing and the explicit use of cost effectiveness analysis for reimbursement purposes do not have a statistically significant effect on the ratio of volumes.

Finally, the estimation results of equation (9) also indicate the presence of a switching in consumption towards patent protected ACE inhibitors after lisinopril generic entry. On average the ratio of the total volume of lisinopril over the total volume of all other ACE inhibitors decreases post patent expiry. Substitution policies have a negative and statistically significant effect on the volume ratio. Generic price controls, regressive pharmacist mark-ups, price controls and clawbacks have a statistically significant positive effect on the volume ratio. Once again reference pricing has an insignificant effect.

Table 5.12 Random Effects Panel Data Estimation, ratio of volumes, six countries

Dependent Variable: $\ln\left(Q_{it}^{OP} \Big/ \sum_{i=1}^{n} Q_{it}^{IP}\right)$

	Captopril	Enalapril	Lisinopril
off	-2.213***	-0.859***	-0.841***
	(0.287)	(0.308)	(0.264)
N	-0.076***	-0.101***	-0.082***
	(0.009)	(0.007)	(0.011)
Nsq	0.002***	0.004***	0.005***
	(1.39e-04)	(1.54e-04)	(2.88e-04)
sub	0.415***	0.120*	-0.288***
	(0.089)	(0.073)	(0.075)
rp	-0.035	-0.068	0.002
	(0.087)	(0.078)	(0.082)
gcont	0.719***	0.551***	0.922***
	(0.084)	(0.063)	(0.050)
markup	0.535***	-0.574***	0.340***
	(0.116)	(0.107)	(0.125)
pc	3.353***	1.228***	3.637***
	(0.174)	(0.174)	(0.159)
clawb	-0.100	-0.161***	0.258***
	(0.067)	(0.062)	(0.070)
tax	-3.047***	-1.024***	-2.105***
	(0.119)	(0.103)	(0.081)
cea	-0.129	-0.075	-0.280***
	(0.095)	(0.084)	(0.089)
constant	-0.990***	-1.391***	-2.154***
	(0.227)	(0.257)	(0.237)
Observations	366	366	366
Rsq within	0.808	0.612	0.655
Rsq between	0.992	0.994	0.998
Rsq overall	0.955	0.908	0.964
Wald chi sq	10984.91	5243.41	20842.94

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

The results indicate the presence of a switch in consumption, in particular for captopril, the first ACE inhibitor which went off patent. The findings of all three regressions for this particular molecule point towards the same direction. The sum of volumes of originator and generic captopril decreases post patent expiry. The effect of captopril patent expiry on the volume of all other ACE inhibitors is positive. The ratio of volumes of captopril over all other ACE inhibitors decreases post patent expiry. Thus there is strong evidence that there is a switch in consumption from captopril to other ACE inhibitors after generic captopril enters the market. There is evidence that this switching effect is also present for enalapril and lisinopril, although it is not as strong as in the case of captopril. Enalapril volume increases after generic entry. The volume of other products of the same class also increases, though the ratio of volumes increases, which provides evidence that a switch in consumption from off patent enalapril to patented ACE inhibitors does occur post enalapril patent expiry. Results for lisinopril are similar to those for enalapril.

Empirical evidence suggests that the larger the number of generic competitors, the more intense the switch effect. This is what was expected: A higher number of competitors means lower profits for the producer of the originator, and therefore a stronger incentive for the producer to focus on another market.

5.8.2 Results at the country level

Tables 5.13 – 5.30 show the results of the econometric analysis for each country separately. Due to the small number of observations for each country, we used the ordinary least squares approach instead of panel data analysis. Clustered standard errors were used though when different products were present (estimation of equation (8)). Tables 5.13, 5.14 and 5.15 show the estimation results of equations

(7), (8) and (9) respectively for Denmark. The effect of patent expiry on the volume of the off patent molecule is different for captopril, enalapril and lisinopril. The effect of generic entry on the total volume of originator and generic captopril is statistically insignificant. In the case of enalapril, generic entry leads to an increase in total enalapril volume, while the effect of lisinopril generic entry on total lisinopril volume is negative. The effect of captopril, enalapril, or lisinopril generic entry on the volume of other on patent ACE inhibitors in Denmark is much more clear. In all three cases generic entry has a positive effect on the volume of other ACE inhibitors. The most important findings though are those of the estimation of equation (9), as the results are unaffected by any changes in total demand for ACE inhibitors. The coefficient of *off* is negative for all three medicines examined, and strongly statistically significant for captopril and lisinopril. The coefficient of enalapril is insignificant. Empirical results suggest the presence of a switching effect in Denmark.

In France (Tables 5.16, 5.17 and 5.18), the effect of generic entry for captopril and enalapril has a negative and statistically significant effect on the total volume of each of these two ACE inhibitors. In the case of lisinopril the effect of generic entry on total lisinopril volume is positive but statistically insignificant. In the estimation results of equation (8), the coefficient of *off* is negative for all three medicines studied, although in the case of captopril the effect is statistically insignificant. These findings alone do not provide a full picture without taking into account the estimation results of equation (9). For all three medicines, the coefficient of *off* is negative and statistically significant, meaning that the ratio of total volume (originator and generic) of the product that goes off patent over the volume of all other in patent ACE inhibitors decreases post patent expiry. The results for France

suggest the presence of a switching effect in consumption of ACE inhibitors once they go off patent, towards patented ACE inhibitors.

The estimation results of equations (7), (8) and (9) for Germany are shown in Tables 5.19, 5.20 and 5.21, respectively. Post patent expiry, total volume of captopril, enalapril and lisinopril appears to increase (Table 5.19). The effect is not that clear regarding the effects on the volume of all other ACE inhibitors which remain in patent (Table 5.20). The coefficient of *off* is positive and statistically significant for captopril, whilst insignificant for enalapril and lisinopril. Results for the ratio of volumes are also not clear (Table 5.21). The volume ratio decreases post patent expiry in the case of captopril, but increases in the cases of enalapril and lisinopril. Thus we cannot draw conclusions about the presence or not of a switch in consumption post patent expiry for ACE inhibitors in Germany.

In the Netherlands, total volume of captopril appears to increase post patent expiry. The effect of patent expiry on total volume of enalapril and lisinopril is insignificant (Table 5.22). Results are different for each molecule, regarding the effects on all other in patent ACE inhibitors (Table 5.23). The effect is positive when captopril goes off patent, negative when enalapril goes off patent and insignificant when generic lisinopril enters the market. The estimation results of equation (9) for the Netherlands are clear though. The effect of patent expiry on the volume ratio is negative and statistically insignificant for captopril, enalapril and lisinopril (Table 5.24), suggesting the presence of a switch in consumption post patent expiry for all three ACE inhibitors included in the study.

In Sweden, the coefficient of *off* in the estimation of equation (7) is positive and statistically significant for captopril and enalapril, while the coefficient is insignificant for lisinopril (Table 5.25). The coefficient of *off* in the estimation

results of equation (8) is negative and statistically significant for captopril, but statistically insignificant for enalapril and lisinopril (Table 5.26). The effect of patent expiry on the ratio of volumes, as described in equation (9), is statistically insignificant for all three medicines, in the case of Sweden. Thus there is no empirical evidence that the switching effect is present in this particular country.

In the United Kingdom, the effect of patent expiry on the total volume (originator and generic) of the medicine that goes off patent is negative and statistically significant for captopril and enalapril, and negative but statistically insignificant for lisinopril (Table 5.28). The coefficient of *off* in the estimation results of equation (8) for the United Kingdom is positive and statistically significant for captopril, positive but insignificant for enalapril and negative and significant for lisinopril (Table 5.29). The estimation results of equation (9) demonstrate a negative and statistically significant effect of generic entry on the volume ratios for captopril, enalapril and lisinopril. Therefore, there is strong empirical evidence that the switch in consumption from off patent ACE inhibitors to in patent ones is present in the United Kingdom.

According to the country - specific results, there is strong empirical evidence that the switch in consumption post patent expiry is present in Denmark, France, the Netherlands and the United Kingdom. No empirical evidence in support of the switch exists in Germany or Sweden.

Table 5.13 Ordinary Least Squares Estimation, off patent molecule volume, Denmark

Dependent Variable: $\ln Q_{it}^{OP}$

	Captopril	Enalapril	Lisinopril
off	0.097	0.369***	-0.130*
	(0.061)	(0.046)	(0.076)
N	-0.686***	-0.025	-0.021
	(0.073)	(0.026)	(0.074)
Nsq	0.073***	0.002	0.002
	(0.007)	(0.002)	(0.008)
sub		0.321***	0.270***
		(0.044)	(0.042)
rp	0.073	0.411***	0.204***
	(0.073)	(0.057)	(0.053)
cea	-0.230***	0.114*	-0.081
	(0.085)	(0.060)	(0.056)
constant	9.863***	9.492***	8.353***
	(0.063)	(0.079)	(0.039)
Observations	61	61	61
Rsq	0.843	0.930	0.710
Adj - Rsq	0.829	0.923	0.678
F statistic	59.08	119.96	22.01

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.14 Ordinary Least Squares Estimation, in patent molecule volume, Denmark

Dependent Variable: $\ln Q_{it}^{IP}$

	Captopril	Enalapril	Lisinopril
off	0.361***	0.689***	0.422**
	(0.127)	(0.152)	(0.181)
N	0.345***	0.448***	0.527***
	(0.040)	(0.047)	(0.050)
Nsq	-0.007**	-0.022***	-0.027***
	(0.003)	(0.004)	(0.004)
sub		-0.067	0.437***
		(0.164)	(0.156)
rp	-0.265	-0.201	0.031
	(0.202)	(0.218)	(0.243)
cea	-0.075	-0.231	-0.191
	(0.176)	0.199)	(0.236)
constant	6.521***	6.389***	5.829***
	(0.175)	(0.189)	(0.213)
Observations	464	403	342
Rsq	0.566	0.427	0.421
Adj - Rsq	0.562	0.418	0.411
F statistic	119.73	49.11	40.66

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.15 Ordinary Least Squares Estimation, ratio of volumes, Denmark

Dependent Variable: $\ln\left(Q_{it}^{OP} \Big/ \sum_{i=1}^{n} Q_{it}^{IP}\right)$

	Captopril	Enalapril	Lisinopril
off	-0.309***	-0.064	-0.498***
	(0.104)	(0.042)	(0.087)
N	-1.140***	-0.163***	-0.044
	(0.124)	(0.024)	(0.084)
Nsq	0.117***	0.011***	0.002
	(0.012)	(0.002)	(0.009)
sub		-0.029	-0.078
		(0.041)	(0.048)
rp	-0.315**	-0.053	-0.411***
	(0.124)	(0.053)	(0.061)
cea	-0.282*	0.002	-0.292***
	(0.145)	(0.056)	(0.063)
constant	-4.255***	-3.672***	-4.246***
	(0.107)	(0.073)	(0.044)
Observations	61	61	61
Rsq	0.8377	0.765	0.939
Adj - Rsq	0.823	0.738	0.933
F statistic	56.79	29.23	139.19

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.16 Ordinary Least Squares Estimation, off patent molecule volume, France

Dependent Variable: $\ln Q_{it}^{OP}$

	Captopril	Enalapril	Lisinopril
off	-0.563***	-0.279***	0.042
	(0.052)	(0.044)	(0.051)
N		0.005	
		(0.015)	
Nsq	0.016***	-0.002	-2.89E-04
	(0.005)	(0.001)	(0.001)
sub			
rp	-0.317**	-0.143*	-0.129**
	(0.137)	(0.076)	(0.054)
constant	10.482***	12.624***	12.076***
	(1.021)	(0.017)	(0.010)
Observations	61	61	61
Rsq	0.893	107.640	0.329
Adj - Rsq	0.887	0.885	0.294
F statistic	158.06	0.88	9.32

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.17 Ordinary Least Squares Estimation, in patent molecule volume, France

Dependent Variable: $\ln Q_{it}^{IP}$

	Captopril	Enalapril	Lisinopril
off	-0.456	-0.305**	-0.380*
	(0.132)	(0.130)	(0.216)
N	0.683	1.221***	0.982***
	(0.080)	(0.108)	(0.120)
Nsq	-0.039	-0.096***	-0.074***
	(0.006)	(0.011)	(0.016)
sub			
rp	-0.648	-0.446***	-0.133
	(0.147)	(0.154)	(0.236)
constant	10.551	10.005***	9.856***
	(0.107)	(0.089)	(0.079)
Observations	598	537	476
Rsq	0.211	0.268	0.158
Adj - Rsq	0.206	0.263	0.151
F statistic	39.63	48.70	1.29

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.18 Ordinary Least Squares Estimation, ratio of volumes, France

Dependent Variable: $\ln\left(Q_{it}^{OP} \Big/ \sum_{i=1}^{n} Q_{it}^{IP}\right)$

	Captopril	Enalapril	Lisinopril
off	-1.164***	-0.881***	-0.684**
	(0.110)	(0.158)	(0.285)
N		-0.065	
		(0.054)	
Nsq	0.026***	0.002	0.001
	(0.010)	(0.004)	(0.004)
rp	-0.453	-0.339	-0.408
	(0.288)	(0.273)	(0.302)
constant	-6.202***	-1.277***	-1.384***
	(2.153)	(0.061)	(0.059)
Observations	61	61	61
Rsq	0.8562	0.821	0.536
Adj - Rsq	0.849	0.808	0.512
F statistic	113.17	64.04	21.98

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.19 Ordinary Least Squares Estimation, off patent molecule volume, Germany

Dependent Variable: $\ln Q_{it}^{OP}$

	Captopril	Enalapril	Lisinopril
off	0.467***	1.441***	1.704***
	(0.032)	(0.103)	(0.359)
Nsq		0.001***	2.63E-04
		(2.08E-04)	(0.001)
sub	-0.097	0.055	-0.009
	(0.117)	(0.334)	(0.524)
markup	0.043		
	(0.060)		
clawb	-0.110	0.004	0.050
	(0.124)	(0.355)	(0.556)
constant	14.084***	11.557***	11.461***
	(0.023)	(0.161)	(0.466)
Observations	61	61	61
Rsq	0.806	0.8941	0.7436
Adj - Rsq	0.792	0.887	0.7253
F statistic	58.020	118.240	40.61

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.20 Ordinary Least Squares Estimation, in patent molecule volume, Germany

Dependent Variable: $\ln Q_{it}^{IP}$

	Captopril	Enalapril	Lisinopril
off	0.366***	0.110	-0.199
	(0.107)	(0.120)	(0.264)
N	0.150***	0.190***	0.297***
	(0.015)	(0.021)	(0.026)
Nsq	-0.001*	-0.002***	-0.005***
	(4.72e-04)	(0.001)	(0.001)
sub	0.022	0.019	0.022
	(0.340)	(0.368)	(0.381)
markup	-0.638***	-0.657***	-0.818***
	(0.177)	(0.202)	(0.316)
clawb	-0.062	-0.064	-0.065
	(0.361)	(0.390)	(0.404)
constant	9.078***	9.249***	9.291***
	(0.091)	(0.077)	(0.066)
Observations	628	567	506
Rsq	0.6094	0.489	0.391
Adj - Rsq	0.606	0.484	0.384
F statistic	161.47	89.30	53.35

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.21 Ordinary Least Squares Estimation, ratio of volumes, Germany

Dependent Variable: $\ln\left(Q_{it}^{OP} \Big/ \sum_{i=1}^{n} Q_{it}^{IP}\right)$

	Captopril	Enalapril	Lisinopril
off	-0.134**	0.660***	0.978***
	(0.055)	(0.038)	(0.232)
Nsq		4.25E-04***	3.75E-04
		(7.59E-05(	(0.001)
sub	-0.157	-0.031	-0.166
	(0.197)	(0.122)	(0.339)
markup	-0.299***		
	(0.101)		
clawb	-0.143	-0.070	-0.060
	(0.209)	(0.129)	(0.360)
constant	-0.363***	-2.210***	-2.057***
	(0.039)	(0.059)	(0.302)
Observations	61	61	61
Rsq	0.6674	0.934	0.677
Adj - Rsq	0.644	0.930	0.654
F statistic	28.09	198.89	29.40

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.22 Ordinary Least Squares Estimation, off patent molecule volume, Netherlands

Dependent Variable: $\ln Q_{it}^{OP}$

	Captopril	Enalapril	Lisinopril
off	0.260***	0.098	0.110
	(0.053)	(0.087)	(0.207)
N		-1.802***	
		(0.448)	
Nsq	0.001***	0.059***	0.004
	(0.000)	(0.015)	(0.003)
clawb	-0.190***	0.010	0.623***
	(0.069)	(0.096)	(0.147)
cea	-0.086	0.059	0.245
	(0.054)	(0.104)	(0.155)
constant	11.868***	25.040***	9.315***
	(0.059)	(3.299)	(0.677)
Observations	61	61	61
Rsq	0.74	0.760	0.790
Adj - Rsq	0.721	0.738	0.775
F statistic	39.84	34.74	0.27

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.23 Ordinary Least Squares Estimation, in patent molecule volume, Netherlands

Dependent Variable: $\ln Q_{it}^{IP}$

	Captopril	Enalapril	Lisinopril
off	0.478*	-0.796***	-0.249
	(0.254)	(0.302)	(0.232)
N	0.526***	0.548***	0.561***
	(0.040)	(0.046)	(0.057)
Nsq	-0.014***	-0.018***	-0.018***
	(0.002)	(0.003)	(0.004)
clawb	0.089	0.533**	0.479
	(0.325)	(0.270)	0.314
cea	-0.593**	0.088	-0.676**
	(0.244)	(0.378)	0.327
constant	6.307***	6.367***	6.486***
	(0.115)	(0.111)	(0.126)
Observations	470	409	348
Rsq	0.7428	0.680	0.577
Adj - Rsq	0.740	0.676	0.571
F statistic	268.04	171.08	93.27

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.24 Ordinary Least Squares Estimation, ratio of volumes, Netherlands

Dependent Variable: $\ln\left(Q_{it}^{OP} \Big/ \sum_{i=1}^{n} Q_{it}^{IP}\right)$

	Captopril	Enalapril	Lisinopril
off	-0.071***	-0.257***	-0.163**
	(0.099)	(0.076)	(0.077)
N		1.234***	
		(0.390)	
Nsq	0.002	-0.040***	0.002
	(0.000)	(0.013)	(0.001)
clawb	-0.243*	-0.054	0.143**
	(0.129)	(0.084)	(0.054)
cea	-0.424***	-0.016	0.005
	(0.102)	(0.091)	(0.058)
constant	-3.021***	-11.491***	-3.471***
	(0.111)	(2.878)	(0.252)
Observations	61	61	61
Rsq	0.901	0.853	0.300
Adj - Rsq	0.8935	0.840	0.250
F statistic	126.87	64.01	6.01

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.25 Ordinary Least Squares Estimation, off patent molecule volume, Sweden

Dependent Variable: $\ln Q_{it}^{OP}$

	Captopril	Enalapril	Lisinopril
off	0.903**	0.258**	0.192
	(0.416)	(0.108)	(0.282)
N	-0.179**	0.023***	-0.055*
	(0.083)	(0.007)	(0.029)
sub	0.512***	0.350***	0.782*
	(0.178)	(0.118)	(0.410)
rp	0.820***	0.697***	0.856***
	(0.072)	(0.088)	(0.115)
constant	10.802***	10.544***	9.300***
	(0.060)	(0.077)	(0.202)
Observations	61	61	61
Rsq	0.8339	0.771	0.561
Adj - Rsq	0.822	0.7546	0.529
F statistic	70.28	47.13	17.86

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.26 Ordinary Least Squares Estimation, in patent molecule volume, Sweden

Dependent Variable: $\ln Q_{it}^{IP}$

	Captopril	Enalapril	Lisinopril
off	-0.761***	-0.065	0.032
	(0.249)	(0.204)	(0.679)
N	0.404***	0.625***	0.298***
	(0.057)	(0.046)	(0.097)
Nsq	-0.007	-0.024***	0.014
	(0.004)	(0.004)	(0.012)
sub		1.091***	1.339*
		(0.379)	(0.780)
rp	1.480***	1.728***	2.015***
	(0.370)	(0.300)	(0.355)
cea	0.543		
	(0.440)		
constant	6.252***	4.781***	4.528***
	(0.322)	(0.285)	(0.343)
Observations	379	318	257
Rsq	0.4293	0.544	0.439
Adj - Rsq	0.422	0.537	0.428
F statistic	56.12	74.47	39.35

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.27 Ordinary Least Squares Estimation, ratio of volumes, Sweden

Dependent Variable: $\ln\left(Q_{it}^{OP} \Big/ \sum_{i=1}^{n} Q_{it}^{IP}\right)$

	Captopril	Enalapril	Lisinopril
off	0.379	-0.089	-0.334
	(0.597)	(0.119)	(0.308)
N	-0.165	-0.001	-0.063**
	(0.118)	(0.008)	(0.031)
sub	-0.356	-0.565***	-0.320
	(0.256)	(0.131)	(0.447)
rp	0.403***	0.074	-0.162
	(0.104)	(0.097)	(0.125)
constant	-3.355***	-2.814***	-3.251***
	(0.087)	(0.085)	(0.221)
Observations	61	61	61
Rsq	0.8677	0.669	0.735
Adj - Rsq	0.858	0.645	0.716
F statistic	91.79	28.30	38.85

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.28 Ordinary Least Squares Estimation, off patent molecule volume, United Kingdom

Dependent Variable: $\ln Q_{it}^{OP}$

	Captopril	Enalapril	Lisinopril
off	-2.049***	-1.287***	-0.181
	(0.149)	(0.417)	(0.147)
N	0.209***	0.205***	
	(0.015)	(0.048)	
gcont	-0.100	0.078	0.351
	(0.115)	(0.181)	(0.269)
clawb		0.399***	1.018***
		(0.086)	(0.121)
cea	-0.299**	-0.150	0.267
	(0.114)	(0.286)	(0.260)
constant	13.779***	12.580***	11.730***
	(0.031)	(0.049)	(0.071)
Observations	61	61	61
Rsq	0.937	0.461	0.813
Adj - Rsq	0.933	0.412	0.799
F statistic	208.18	9.41	60.76

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.29 Ordinary Least Squares Estimation, in patent molecule volume, United Kingdom

Dependent Variable: $\ln Q_{it}^{IP}$

	Captopril	Enalapril	Lisinopril
off	0.646***	0.110	-0.692**
	(0.245)	(0.643)	(0.306)
N	0.754***	1.303***	1.202***
	(0.048)	(0.310)	(0.363)
Nsq		-0.087	-0.077
		(0.074)	(0.079)
gcont	0.001	-0.151	0.288
	(0.473)	(0.451)	(0.544)
clawb		0.908***	0.886***
		(0.246)	(0.273)
cea	-0.323	0.119	0.214
	(0.494)	(0.750)	(0.529)
constant	8.732***	7.977***	8.005***
	(0.155)	(0.158)	(0.176)
Observations	550	489	428
Rsq	0.3222	0.389	0.161
Adj - Rsq	0.317	0.382	0.149
F statistic	64.78	51.21	13.49

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

Table 5.30 Ordinary Least Squares Estimation, ratio of volumes, United Kingdom

Dependent Variable: $\ln\left(Q_{it}^{OP} \Big/ \sum_{i=1}^{n} Q_{it}^{IP}\right)$

	Captopril	Enalapril	Lisinopril
off	-2.765***	-2.085***	-0.458***
	(0.173)	(0.196)	(0.065)
N	0.245***	0.300***	
	(0.018)	(0.023)	
gcont	-0.403***	-0.250***	0.162
	(0.134)	(0.085)	(0.119)
clawb		-0.116***	0.452***
		(0.040)	(0.054)
cea	-0.466***	-0.201	0.121
	(0.132)	(0.135)	(0.115)
constant	-0.668***	-1.155***	-1.386***
	(0.036)	(0.023)	(0.031)
Observations	61	61	61
Rsq	0.970	0.951	0.759
Adj - Rsq	0.968	0.946	0.741
F statistic	455.89	211.36	43.98

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively

Standard errors in parenthesis

5.9 Discussion and Policy Implications

Our findings show that the effect of generic entry on demand and consumption is not limited to just the product that has gone off patent, but also to other products within the same therapeutic category. Aggregate results for all six countries together show that post patent expiry there is a switch in consumption from the molecule that goes off patent to other molecules of the same therapeutic class which remain patent protected. Results from each country separately show that

this phenomenon is present in the United Kingdom, Denmark, France and the Netherlands, but not in Germany or Sweden.

This switch in consumption can increase health spending significantly: When such a switch takes place, the market share of in-patent molecules would be larger than what it would be in the absence of this switch. Purchasing a molecule which is still in-patent means there is no generic alternative, so the product cannot be substituted by a cheaper generic. Therefore pharmaceutical expenditure for a therapeutic class which undergoes such market dynamics would increase, ceteris paribus.

This is a cause for concern for countries which experience switching effects. Since the challenge is to contain spending for health, appropriate policies should be implemented in order to tackle switching in consumption from off-patent to in-patent products, which leads to higher costs. Stricter barriers to new medicines entering the same class as different products could also be part of the solution, in order to make sure that the new product is indeed differentiated at a sufficient level.

From a policy perspective, making the off-patent molecule a first-line treatment would help prevent this switch in consumption. Physicians would have to prescribe the off- patent molecule as a first choice for a patient, before considering another ACE inhibitor. The off- patent molecule has generic alternatives, so generics which are cheaper than the branded product can be dispensed, leading to savings for health insurance. This occurs despite the presence of supply and demand side generic policies, and reveals the weak enforcement of generic policies.

Further, reference pricing at the therapeutic class level could help achieve this goal. By setting a reference price at the class level, the price covered by health insurance would be a price that would take into account cheap generics of the off-

patent molecule. This reference price would apply not only to the off-patent molecule, but also to the in-patent products of the same class. The price covered by health insurance would be at the level of the reference price, and anyone wishing to purchase any of the branded products with a higher price would have to pay the difference out-of-pocket. This policy though would not have the desired effects unless patients are well informed of their alternative choices.

5.10 Conclusions

We have found empirical evidence that a switch in consumption from a medicine which goes off patent towards other in-patent medicines of the same therapeutic class occurs after generic entry. The econometric analysis explored three dimensions of the market. First, the effect of patent expiry on the total volume (both originator and generic) of the molecule which goes off patent, then the effect on the volume of all other molecules of the same therapeutic category which remain in-patent and, finally, the ratio (or differences, as the volume is measured in logarithms) of volumes. The latter approach is the most reliable, as it shows the relative volumes and the results are not affected by any shocks in the total demand of ACE inhibitors.

The effect of patent expiry on the volume of the molecule which goes off patent is not the same for captopril (decrease in volume), enalapril (increase) and lisinopril (increase). The effect on the total volume of all other ACE inhibitors, when each of them loses its patent, is consistently positive though. Most importantly, results show that the relative total volume (both originator and generic) of the molecule which goes off patent decreases compared to the volume of other molecules of the same therapeutic category which remain in- patent. This is strong evidence indicating that the switch in consumption does take place post patent

expiry. The effect is very strong for captopril, enalapril and lisinopril. When considering each country separately, the results suggest that there is a switch in consumption present in Denmark, France, the Netherlands and the United Kingdom, but we do not find evidence of such a phenomenon in Germany or Sweden.

6. The Impact of Parallel Trade on Pharmaceutical Competition: A Game Theoretic Approach and Empirical Evidence from the European Union

6.1 Introduction

The differential regulation of pharmaceutical prices in the European Union (EU), resulting in significant price differences among EU Member States, alongside the development of the single European market has created arbitrage opportunities through pharmaceutical parallel trade (PT). Parallel trade is the practice of purchasing a product in one country and selling it in another country where its price is higher. The agent who is involved in parallel trade gains rent from the difference in prices. The manufacturer of the product supplies the product in both markets, but this practice reduces his profits because, for the part of the market which is covered by parallel trade, this is equivalent to selling in the high-priced market at the prices of the low-priced market. As both the manufacturer and the parallel trader sell in the importing market, they can be considered as competitors. However, differences in packaging and labelling across countries are often perceived as real differences and frequently differentiate locally sourced from parallel traded products.

Parallel trade has been viewed upon as an opportunity to enhance competition in in- patent markets due to its close relationship with the originator medicine. Whilst price competition in in-patent markets is in principle scarce due to product differentiation (Kanavos, Costa-Font, McGuire 2007), cultural issues in prescribing, dispensing and consumption, as well as differences in the features of different products in the same therapeutic class, parallel trade avoids such problems because the product is the same and is produced by the same manufacturer. The only differences which may occur are different languages used on the packaging and in

the patient leaflet, which is usually solved by applying a sticker on the package and inserting a new leaflet in the language of the importing country in the box.

As the EU is a single market, and in accordance with the principle of regional exhaustion of intellectual property rights, no formal permission from the rights holder is necessary for parallel trade to take place, so long as it takes place within EU boundaries. The doctrine of regional exhaustion of intellectual property rights within the context of a single market in the EU postulates that once a product has been legitimately put on the market in one Member State it is in breach of competition laws, governed by articles 28, 81 and 82 of the Treaty of the EU, to prevent the product to be resold in another Member State even if the product is protected by the exclusivity granted by a patent or other intellectual property right in the latter state. In the EU, exhaustion of intellectual property rights is by first sale; however, Article 30 allows a trademark holder to exercise his rights to block the sale of an imported product bearing his trademark, if its original packaging has been modified in a way that is not necessary to permit its sale in the importing Member State.

The only regulatory requirement to allow a parallel traded medicine to be sold in a country other than the one in which it was originally intended for is a Parallel Import Product License, which is issued by the national regulatory authority of the destination country or the European Medicines Agency (EMEA), on condition that parallel distributors conform to national and EU regulations. In order to establish that quality is not undermined, the competent regulatory authority in the import country will contact its counterpart in the exporting country to receive documentation on the product in question.

Parallel trading in medicines is largely, but not exclusively, confined to the movement of patented products from lower-priced to higher-priced EU markets. The volumes of product moved are influenced by the extent of price variability between exporting and importing countries, currency fluctuations and product availability in export markets, among others. The share of products supplied via parallel traders in key import countries is between 10 and 20 per cent of the European in-patent prescription medicines market (Kanavos and Costa-Font 2005).

The aim of this chapter is to study the effect of parallel trade on prices of locally sourced products, the presence or not of a price spread between locally sourced and parallel traded medicines, and whether there is a downward or upward price convergence following parallel importation. For this purpose both theoretical and empirical means are used.

Section 6.2 discusses the legal background concerning parallel trade in the European Union and the various judgments which allow this practice to take place in the EU. Section 6.3 discusses the literature; section 6.4 provides a game theoretic approach about the market equilibria in the presence of parallel trade; section 6.5 provides descriptive statistics on the price spread between locally sourced and parallel traded medicines; section 6.6 provides econometric results on the determinants of prices of locally sourced and parallel traded medicines; finally, section 6.7 discusses policy implications and concludes.

6.2 Legal Background

Parallel trade is based on the free movement of goods and the exhaustion principle of intellectual property rights that underpin the establishment of one free common internal market in the EU. The endeavour to assure a single intra-EU

market is further reflected in numerous, continuous decisions by the European Court of Justice (ECJ) that are implemented and protected by the Commission. These judgments form the ongoing jurisprudence and define the legal framework for parallel trade of medicinal products in the EU Member States. Over the past 30 years the ECJ has ruled on numerous occasions on cases related to parallel trading of goods with the majority of these cases being on pharmaceuticals (ECJ, 1978, 1987, 1996, 1997, 1999, 2000, 2002, 2008). In a similar spirit, national authorities have legislated on certain aspects of pharmaceutical parallel trade, particularly in what concerns competition (White and Case, 2008). Key sources of dispute on pharmaceutical parallel trading activities have been trademarks, repackaging, re-boxing, relabeling and dual pricing. Namely, the ability of manufacturers to charge one price for the domestic market and another for the proportion of their sales that is parallel exported.

Complex litigation has arisen with respect to trademarks, and the rights of the original manufacturer to defend its trademark where parallel importers have repackaged a product sold under a particular trademark in one country and resell it under the current trademark in another country. The ECJ has developed consistent case law on the subject of trademarks and repackaging which are of central importance for parallel trade. Trademark owners may not use their trademarks to try and prevent parallel importation of their products within the European Economic Area including, the EU Member States plus Iceland, Norway, and Switzerland. However, this is dependent on the 'specific subject matter' of the trademark in question.

Repackaging has also been a key issue in pharmaceutical parallel trading. Since language barriers exist across the EU, medicines must be accompanied by

detailed information for the end-user in the language of the country where the product is put on the market. This means that the leaflet must also be in the language of the destination country. The characteristic design of the external packaging is important in pharmaceutical markets so that products are recognizable by patients. Furthermore, medical insurance rules can make reimbursement of pharmaceutical expenses dependent on certain packaging, and some well-established medical prescription practices are based on standard sizes recommended by professional groups or sickness insurance organizations. The Treaty of the EU (article 30) allows a trademark holder to exercise his rights to block the sale of an imported product bearing his trademark, if its original packaging has been modified in a way that is not necessary to permit its sale in the importing Member State.

Repackaging guidelines can also be applied in the situation when an importer attempts to modify the packaging size under market authorization. In many cases parallel traders repackage medicines in such a way that the number of tablets is different than that in the original package.

Two further practices have been addressed in litigation in recent years: the first, is dual pricing, a practice whereby manufacturers supply wholesalers at the price of the country the latter sell at and at higher prices if the same wholesalers export their supplies to other EU countries, and the second relates to the practice of manufacturers managing their supplies to wholesalers. Both practices relate to whether or not they restrict competition within the European single market. Dual pricing has been repelled on the grounds that it impedes competition and interferes with the single market principle. In the case of manufacturers managing their supplies, however, it appears that pharmaceutical companies can legitimately employ systems to limit PT in certain circumstances providing that there be no

agreement between themselves and wholesalers, no outright ban on exports from the side of manufacturers, and no monitoring of the final destination of the product.

As a result of the evolving jurisprudence and the single market principle within the EU that favours it, parallel trade has grown as a share of the total prescription pharmaceutical market in some EU countries, although there is significant variability on its amplitude and intensity at product and country level (EFPIA, 2005; Kanavos and Costa-Font, 2005; Kanavos and Kowal, 2008). Simultaneously, product homogeneity across countries has improved while medicine presentations are increasingly standardised since the establishment of the European Medicines Evaluation Agency (EMEA), thus reducing barriers to entry across Member States. Pressures on the distribution chain in terms of lower margins over time (Kanavos and Gemmill, 2005) also provide an incentive to seek other markets by identifying profitable arbitrage operations that only have to face minimal transaction costs, maximum price differences and adequate market size in destination countries. The parallel distributor chooses a source country, where the target product has a low price relative to the same product sold by the original manufacturer in the destination country. The target product is, in most cases, a new, innovative medicine offering a high price differential and therefore a high profit margin in the destination country. Other factors determining the choice of the target product include patient population, (market size), formulation, transport, re-labelling and storage requirements. The market share of parallel traded products in six countries (Denmark, Germany, Netherlands, Norway, Sweden, UK) has risen from 10% in 1997 to almost 20% in 2002 (Kanavos and Costa-Font, 2005). Subsequent research has shown that parallel trade market penetration has remained stable in these countries (18.44% in 2003 and 18.40% in 2006) (Kanavos and Kowal, 2008).

Many European countries, particularly those where prescription medicine prices are high, encourage parallel trade – often explicitly, with incentives to pharmacies to dispense parallel traded goods - as they view this as an opportunity to introduce competition in their markets and, potentially, achieve savings on their medicine budgets, through the price competition between close substitutes that may ensue.

Although some evidence exists on price competition associated with pharmaceutical parallel trade in a single country (Ganslandt and Maskus, 2004), other research finds that competition effects are mainly associated with generic medicine introduction rather than parallel trade per se (Kanavos and Costa-Font, 2005, Linnosmaa et al, 2003). This may, in part, explain why price dispersion across countries may not necessarily be influenced by PT penetration, which in turn implies that parallel trade might not produce the intended competition effects that one might attribute to arbitrage as clearing price differences (Malueg and Schwartz, 1994). If parallel trade led to price equalisation across countries, then the same product would be sold at the same price everywhere and profits would be eliminated.

Under lack of competitive effects, one should expect that PT would not be able to reduce medicine prices on a sustainable basis. If this holds, very limited price convergence across European Union countries should be observed. However, the evidence pointing towards these effects is limited. Moreover, one might well argue that health insurance in destination countries might benefit from parallel trade if prices are lower than those of locally-sourced originator medicines. Although some studies have examined the potential savings to health systems from parallel trade (West and Mahon, 2003; Kanavos and Costa-Font, 2005; Enemark et al, 2006), only one study demonstrates evidence on the determinants of the price gap between

originator and parallel imported prices in destination countries (Kanavos and Vandoros 2010). Kanavos and Vandoros (2010) also studied the impact of competition in the distribution chain, and found some empirical evidence that a higher number of wholesalers and pharmacists leads to lower prices for the locally sourced originator product. However they found no empirical evidence of an impact on the prices of parallel traded products. This finding, however, should be put in the context of parallel trade and should not be used for policy recommendations for pharmaceutical markets in general, as according to Taylor, Mrazek and Mossialos (2004), increased competition in distribution and retail pharmacy may undermine social solidarity, hence outweighing any benefits for poorer service users. Furthermore, very limited evidence exists on the determinants of price differences between parallel traded and locally-sourced originator medicines. However, this question has only been examined empirically, without any theoretical predictions of the outcome of a market game between a parallel trader and a manufacturer.

In light of the intense legal and economic debate on the effects, costs and benefits of pharmaceutical PT, this chapter uses a game theoretic approach to analyse how the market works and how prices of locally sourced and parallel traded products evolve in a market open to parallel trade. In addition, it provides a theoretical explanation of whether parallel trade leads to a decrease in social welfare. The conceptual framework that is developed is subsequently used to investigate empirically whether there is a price gap between locally sourced and parallel traded products and whether prices of locally sourced products respond to competition from parallel trade. Finally, the analysis takes place from a comparative perspective by drawing on evidence from four countries where parallel trade has been prevalent and, often, extensive. .

The study advances the literature by providing a thorough approach of the effects of parallel trade on market dynamics, notably the impact on competition and prices of locally sourced products. Predictions of theory are used to find the outcome of a game between rational agents. The game theoretic approach helps understand why the market works in a particular way in the presence of parallel trade. As a result, the fact that parallel trade often does not trigger competition is no longer a paradox which cannot be explained by economic theory. The predictions of theory are followed by thorough empirical evidence. Both econometrics and descriptive statistics are combined to show whether there is a price gap between locally sourced and parallel traded products, and whether a possible price convergence is upward or downward. Previous studies have not considered both aspects simultaneously. Using only descriptive statistics would only show whether a price gap exists or not and would not show if the price of the locally sourced product decreases as a result of parallel trade. Econometric analysis alone shows whether parallel trade leads to price cuts for the locally sourced product, but does not reveal much on any price gap between locally sourced and parallel traded products, hence the combination of both methods to provide a spherical view of the issue. Further, this is a multi-country analysis, and results are reported both at the aggregate level as well as the country level.

6.3 Parallel Trade and the Pharmaceutical Market

Theoretically, in the presence of arbitrage, the same product will be sold at the equilibrium prices in all markets, profits will be eliminated and consumers capture the rent. The impact of parallel trade on (price) convergence and

competition, innovation and overall welfare across countries, have been discussed mostly from a theoretical perspective but the literature often remains inconclusive.

Standard economic theory would predict that in unregulated markets and in the absence of product differentiation, arbitrage would give rise to Bertrand-type competition leading to a "race towards the bottom" where price equalization would be achieved in destination countries. This would contribute to pharmaceutical cost containment and, through that, consumer welfare could be improved. Unlike pure arbitrage, pharmaceutical PT arises for markets subjected to heterogeneous regulation and price fixing of prescription medicines. Due to price fixing policies, PT would not necessarily lead to price equalization, and thus the extent to which PT becomes a welfare-improving phenomenon across countries from a pricing point of view is questionable.

Key in the conduct of PT is the distribution chain in source countries, as PT results, in part, from a lack of barriers to arbitrage such as the lack of total vertical control in the distribution chain of pharmaceuticals by the originator rights holder. Other than risking being characterized as anti-competitive, maintaining vertical restraints implies substantial transaction and information costs for the originator manufacturer, and thus weak distribution control leads to some wholesalers in low price (source) countries diverting part of their stock to parallel distribution in high price (destination) countries. A likely explanation for this behaviour rests in the incentives associated in the medicines distribution chain, and, more specifically, the existence of observed and unobserved (price and volume) discounts within the distribution chain. The existence of parallel imports can cause retail prices both to diverge between markets and to increase in high cost locations due to the existence of vertical restraints, which are some times envisaged as a natural extension of IPR

owners to vertically control the product chain (Barfield and Groombridge, 1998). Even if competition results in price uniformity across countries, then in the presence of increasing returns to scale, such uniformity can affect negatively all countries (Hausman and Mackie-Mason, 1988).

While the impact of pharmaceutical PT on prices has produced ambiguous results, there is greater consensus on its impact on innovation at theoretical level. The dynamic effects on innovation suggest that PT could lead to significant welfare losses (Ganslandt and Maskus, 2004; Rey, 2003; Szymanski and Valletti, 2005; Danzon, 1998; Bordoy and Jelovac, 2003). Parallel trade could reduce welfare if consumer willingness to pay in different countries is sufficiently dispersed, the reason being that when dispersion is high, some markets are dropped by the monopolist who prefers to concentrate only on richer markets (Malueg and Schwartz, 1994).

In most countries pharmaceuticals are not directly purchased by consumers but are supplied at prices negotiated between the government (or health insurance organisations) and the manufacturer. Arguably, parallel trade reduces the ability of government or health insurance to make a conscious choice to invest in R&D by paying high prices while permitting foreign governments to negotiate lower prices (Rey, 2003). In this view parallel trade limits the ability of government to make its own policy choices. This challenges the medicine market due to the possible negative effects on future R&D investment as PT grows, despite short-term pecuniary benefits to health insurance, however, small these may be.

It is also argued that price uniformity in the form of average prices might benefit some customers but might affect the equilibrium balance between prices and quality (Rey, 2003). Product quality will, in fact, fall because lower investment will

be devoted to those products under PT, and therefore global welfare could fall (Valletti and Szymanski, 2005).

Overall, the normative implications of increasing parallel trade on welfare are ambiguous as some models employing horizontal arbitrage models suggest (Malueg and Schwarz, 1994; Knox and Richardson, 2002). A regime of uniform retail pricing would be globally inferior to one in which firms could price-discriminate on the basis of countries grouped by demand elasticity (Malueg and Schwartz, 1994). On the other hand, by reducing prices in high income countries parallel trade reduces the incentives for innovative companies to put forward innovations. Finally, a policy leading to the international exhaustion of IPR would enhance welfare by enabling consumers everywhere to take advantage of lower prices, simultaneously would lower welfare of many, especially those in poor countries, because it would actually raise prices in those markets to the international average price (Maskus, 2000).

The theoretical literature and empirical evidence examining price competition effects, the impact on innovation and welfare across countries, is often ambiguous, inconclusive, or, simply, incomplete. In addition, little evidence exists on the impact that parallel trade has on price competition, innovation and welfare, within the destination country. In the section that follows we develop a conceptual framework that attempts to explain and analyse the price behaviour of the originator manufacturer and the parallel distributor as well as the likely determinants of the price difference between locally-sourced originator and parallel traded medicine in destination countries for parallel imports.

Table 6.1 Comparison of Previous studies with present study

	LS vs PT				Imp vs Exp Countries
	Theoretical Solution	empirical evidence on PT triggering competition	Empirical evidence on price convergence	Multi-country analysis	Empirical Evidence on price diff
Kanavos Vandoros 2010		X		X	
Kanavos Font 2005				X	X
Ganslandt Maskus 2004		X			
Linnosmaa et al 2003		X			
Present study	X	X	X	X	

6.4 A Game Theoretic Approach

In this section, a game theoretical approach is made in order to explain pharmaceutical market dynamics in the presence of parallel trade. This is an attempt to formalise the market strategies into a game theoretic model. Assuming the presence of rational producers, a game between a producer and a parallel trader is explored in order to see the predictions of theory on price evolution and whether parallel trade has an effect on competition or not.

6.4.1 4.1 Conceptual Framework

Parallel distributors, just as originator medicine companies, are profit maximisers. The product sold by manufacturers and parallel traders is homogenous, produced by the same manufacturer and sold in two separate markets, the exporting market and the importing market. Suppose the originator medicine is sold at price P_{it}^{LS} in the importing country and at price P_{it}^{exp} in the exporting country by the

manufacturer of the product. In order for parallel trade to be profitable, the price in the exporting country must be lower than the price in the importing country, and this difference must be lower than all associated transactions which may include re-packaging, relabeling, different language patient leaflets and other costs. If transaction costs per unit are k_{it}, then the condition for parallel trade to take place is

$$P_{it}^{LS} > P_{it}^{\exp} + k_{it} \qquad (1)$$

In principle, parallel traders cannot serve a large part of the local market on a sustainable basis (although there have been few cases of parallel trade supplying significant parts of the importing market (Kanavos and Costa-Font 2005)). The challenge for parallel traders is how to acquire larger quantities of the parallel traded product, as it may be the case that the authorities in exporting countries have the option to restrict exports if the local supply is threatened. That is the public health cause, which has not been enforced in any country yet. These are facts that are used as basic assumptions for the game theoretic approach.

Suppose $q_{it}^{\exp}$ is the amount of product in the exporting country which covers domestic demand in the exporting country. q_{it}^{T} is the amount of product that can be imported from the exporting country to the importing country, if $P_{it}^{LS} > P_{it}^{\exp} + k_{it}$ holds, which implies that parallel trade is profitable. The amount of product exported equals the amount imported into the destination country; q_{it}^{imp} is the total amount of product that covers demand in the importing country, whether this is satisfied only by locally sourced product (in the absence of parallel trade) or partially by parallel trade. q_{it}^{LS} is the amount of locally sourced product in the importing market if parallel trade is present (assuming, as explained above, that parallel traders can sell all quantities they can get hold of). Therefore

$$q_{it}^{imp} = q_{it}^{LS} + q_{it}^{T} \tag{2}$$

Profits for the parallel trader equal:

$$\pi_{it}^{PI} = \left(P_{it}^{PI} - P_{it}^{\exp}\right)q_{it}^{T} - k_{it}^{PI} q_{it}^{T} =$$

$$= \left(P_{it}^{PI} - (P_{it}^{\exp} + k_{it}^{PI})\right)q_{it}^{PI} \tag{3}$$

where q_{it}^{T} is the volume of parallel imports and P_{it}^{PI} is the price that the parallel trader sets in the local market. *i* and *t* subscripts refer to product and time, respectively. The manufacturer has a large R&D sunk cost. The per-unit production cost of medicines is *c*, assumed to be the same across countries. In the absence of parallel trade, the originator manufacturer's profits are the sum of profits in the importing and exporting country:

$$\pi_{it}^{LS} = \left(P_{it}^{LS} q_{it}^{imp} - cq_{it}^{imp}\right) + \left(P_{it}^{\exp} q_{it}^{\exp} - cq_{it}^{\exp}\right) =$$

$$= \left(P_{it}^{LS} - c\right)q_{it}^{imp} + \left(P_{it}^{\exp} - c_{it}\right)q_{it}^{\exp} \tag{4}$$

In the presence of parallel trade, the originator producer will sell fewer units of the medicine in the importing market, as a proportion of the market will be covered by parallel trade. Assuming that total demand remains constant in each market, the producer's sales will increase in the exporting market by the amount of product exported. Total profits for the originator manufacturer in both markets in the presence of parallel trade are:

$$\pi_{it}^{LS} = \left(P_{it}^{LS} q_{it}^{LS} - cq_{it}^{LS}\right) + \left(P_{it}^{\exp} q_{it}^{T} - c_{it} q_{it}^{T}\right) + \left(P_{it}^{\exp} q_{it}^{\exp} - cq_{it}^{\exp}\right) \tag{5}$$

From (2), as $q_{it}^{imp} = q_{it}^{LS} + q_{it}^{T}$, the difference between profits for the manufacturer in the absence and presence of parallel trade is:

$$\Delta\pi_{it}^{LS} = \left(P_{it}^{LS} - P_{it}^{\exp}\right) q_{it}^{T} \mathrm{P} \tag{6}$$

Parallel trade causes a drop in the manufacturer's profits by the difference in price between the importing and exporting country times the volume of parallel trade. This occurs because the manufacturer sells the product in the low-price exporting country at the price of that market, but this ends up in the importing country.

Total demand (the sum of locally sourced and imported products) for a particular product can be assumed to be fixed over time. This assumption is made based on the fact that there is universal health insurance for patients, because patients with full insurance will consume the medicines prescribed and covered by health insurance regardless of prices. Thus the same total quantity will be dispensed, regardless of prices, unless there is a real price difference and patients pay significant co- payments and are incentivised to select the cheaper product. Although co-payments are only a small fraction of the price, they could make patients show preference for the cheapest available medicine. If parallel traders enter a market due to profit opportunities, they will sell the whole amount of product they can get hold of. This happens for two reasons. First, they provide discounts to pharmacists. These are undisclosed and not recorded and local manufacturers do not always have the flexibility to provide such discounts. These discounts provide a great incentive for pharmacists to dispense parallel traded products rather than locally sourced ones. The manufacturer of the product is the same in any case, so which of the two is dispensed should not matter to the patient. Second, quantities of parallel traded products are limited. They depend on availability of sufficient

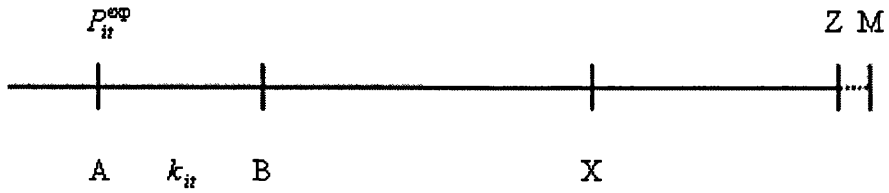
quantities in low-price countries. Parallel traders cannot always get hold of large quantities, as medicine supply is accounted for and monitored by manufacturers.

The previous paragraphs have set the background of a game, explaining profit functions of the manufacturer and the parallel trader, who are the two agents involved in this game. A decisive difference between the two agents, which makes the game special, is that they have different cost functions and have different break even- points. The parallel trader buys the product at the price that the manufacturer sets in the exporting market, and is also subject to transportation costs. The manufacturer's unit cost is lower than the price he sets in the exporting market. Other factors which move this game away from a standard two- agent game is the presence of discounts only on behalf of one of the agents and the fact that the manufacturer does not want to signal that parallel trade triggers competition, as such a development would encourage policy makers to consider more intense promotion of parallel trade, or press for further price cuts for branded products.

6.4.2 Parallel trade markets in the absence of policies targeting parallel trade

After discussing the properties of the agents involved in the game, we now develop the game between the manufacturer and the parallel trader. Assuming both agents are profit maximizers, the question is what strategies manufacturers and parallel traders will follow in order to maximise their profits. Parallel traders wish to maximise their profits by selling imported products. For manufacturers, parallel trade is a source of a decrease in profits, so they would like to eliminate it, if the cost of fighting it out of the market would be lower than that of accommodating. Alternatively, manufacturers would have to accommodate it, as the latter strategy may lead to higher profits rather then fighting it.

Figure 6.1 Price setting in the presence of parallel trade



Consider a plane where the parallel trader buys the product at price P_{it}^{exp} in the exporting country and is subject to transportation and distribution costs k_{it} per unit (Figure 6.1). A is the price level at which the product is priced in the export market. B is the price of the export market plus transaction costs that the parallel trader would undergo in order to sell in the import market, thus B is the break even price for the parallel trader. Z is the level at which the locally sourced product is initially priced, before facing parallel trade. M is a point higher than Z, and X is a price between B and Z. The break-even point of the parallel trader is $P_{it}^{PI} = P_{it}^{exp} + k_{it}$, thus the price that he will set in the import country must cover the price in the exporting country and transportation and distribution costs, and ideally provide a return. Otherwise profits are zero (if price is B) or negative (if the price is lower than B). Any point beyond B to the right leads to profits.

Branded pharmaceutical products enter the market at a price which is negotiated and agreed upon with health insurance. Price increases are very difficult to take place due to regulatory practices. Upward changes in medicine prices are usually sticky in import countries because of the involvement of insurance in the negotiation resulting in price fixing for reimbursement purposes. Prices though are

usually more flexible downwards. Thus, when a parallel trader enters the import market, an "anchor" price is already defined, as the price at which the locally sourced product was priced before parallel trade took place. This makes it difficult for any of the two players to set a price higher than the initial price of the locally sourced product. Thus, setting a price for the parallel trader product P_{it}^{PI}=M > Z $= P_{it}^{LS}$ would not be feasible. If the trader sets price X, with B<X<Z, he may increase profits by moving closer to Z (which is the manufacturer's initial price). His price will still be lower than P_{it}^{LS}, having an advantage in the market, and the profits will rise by the difference in the price times the quantity sold $\left(q_{it}^{PI} * \Delta P_{it}^{PI}\right)$. Since the product is homogenous, the parallel trader will have the incentive to set a price which is not lower than Z= P_{it}^{LS}. It could be argued that the manufacturer of the originator could decrease its price in order to force the parallel trader out of the market. If he decreases the price to say price X (with B<X< P_{it}^{LS}), the parallel trader's best response is to lower his price too, close to the same price. Both will still have positive profits, but smaller than in the previous case, making them both worse off. In order to force the parallel trader out of the market, the manufacturer will have to lower his price to $P_{it}^{\exp} + k_{it}$. At that point the parallel trader will have to leave the market, as by setting price $P_{it}^{PI} = P_{it}^{\exp} + k_{it}$ he will have no profits, and by setting a price higher than that, his product will be more expensive than that of the manufacturer, and will thus occur no sales. The manufacturer though will have a much lower price in the local market than previously and, as pricing agreements are currently structured in most (regulated) countries, once a product's price is discounted, it is difficult to be risen again within a short period of time. Concerning the part of the market that is parallel traded, his per-unit profits will be higher by k_{it}

(as it will be sold at the local market at price $P_{it}^{exp} + k_{it}$ instead of the exporting market at price P_{it}^{exp}), but for the previously locally sourced part of the market he will have a lower per-unit revenue by $P_{it}^{LS} - P_{it}^{exp} + k_{it}$.

Parallel traders usually cannot serve a large part of the local market and their main challenge is how to acquire larger quantities of the parallel traded product. Hence, in order for a price war on behalf of the manufacturer to be profitable, it must hold that the manufacturer's profits with a price war are larger than without such a pricing strategy. This is expressed by inequality (7).

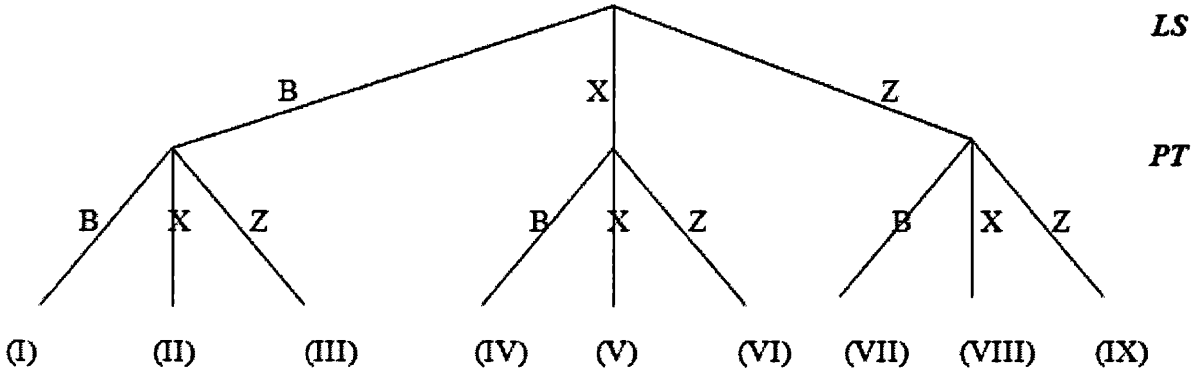
$$\left(P_{it}^{LS} - P_{it}^{exp}\right)q_{it}^{PI} > \left(P_{it}^{LS} - \left(P_{it}^{PI} + k_{it}^{PI}\right)\right)\left(q_{it}^{PT} + q_{it}^{LS}\right) \quad (7)$$

Inequality (6) is highly unlikely to hold in most cases due to the relatively small market share of parallel trade. We therefore assume that inequality (7) does not hold, so instead:

$$\left(P_{it}^{LS} - P_{it}^{exp}\right)q_{it}^{PI} < \left(P_{it}^{LS} - \left(P_{it}^{PI} + k_{it}^{PI}\right)\right)\left(q_{it}^{PT} + q_{it}^{LS}\right) \quad (8)$$

Taking this assumption into account, Figure 6.2 shows all possible pricing strategies for the manufacturer and all possible responses from the parallel trader. We assume that for any strategy which leads to zero profits for the parallel trader, the parallel trader does not enter the market at all. We also assume that the two players do not form a cartel and do not fix prices or agree on how to split the market.

Figure 6.2 Price Setting for the Manufacturer and the Parallel Trader



The different outcomes of the game between the manufacturer and the parallel trader described in Figure 6.2 are:

I. (B, B): $\Pi_{it}^{LS} = (B-c)q^{imp} + q^{\exp}(p^{\exp}-c)$, $\Pi_{it}^{PI} = 0$

II. (B, X): $\Pi_{it}^{LS} = (B-c)q^{imp} + q^{\exp}(p^{\exp}-c)$, $\Pi_{it}^{PI} = 0$

III. (B, Z): $\Pi_{it}^{LS} = (B-c)q^{imp} + q^{\exp}(p^{\exp}-c)$, $\Pi_{it}^{PI} = 0$

IV. (X, B): $\Pi_{it}^{LS} = (X-c)q^{imp} + q^{\exp}(p^{\exp}-c)$, $\Pi_{it}^{PI} = 0$

V. (X, X): $\Pi_{it}^{LS} = (X-c)q^{LS} + (q^{\exp}+q^{T})(p^{\exp}-c)$, $\Pi_{it}^{PI} = q^{T}(X-p^{\exp}-k)$

VI. (X,Z): $\Pi_{it}^{LS} = (X-c)q^{imp} + q^{\exp}(p^{\exp}-c)$, $\Pi_{it}^{PI} = 0$

VII. (Z,B): $\Pi_{it}^{LS} = (Z-c)q^{imp} + q^{\exp}(p^{\exp}-c)$, $\Pi_{it}^{PI} = 0$

VIII. (Z, X): $\Pi_{it}^{LS} = (Z-c)q^{LS} + (q^{\exp}+q^{T})(p^{\exp}-c)$, $\Pi_{it}^{PI} = q^{T}(X-p^{\exp}-k)$

IX. (Z,Z): $\Pi_{it}^{LS} = (Z-c)q^{LS} + (q^{\exp}+q^{T})(p^{\exp}-c)$, $\Pi_{it}^{PI} = q^{T}(Z-p^{\exp}-k)$

where Π_{it}^{LS} is the profit of the manufacturer and Π_{it}^{PI} is the profit of the parallel trader.

This is an infinitely repeated game of perfect information for both players. In each period players can choose another strategy. We put forward that outcome (IX) is the only Subgame Perfect Nash Equilibrium.

A profile of strategies $\sigma = (\sigma_1, \ldots, \sigma_I)$ in an I-player extensive form game Γ_E is a Subgame Perfect Nash Equilibrium (SPNE) if it induces a Nash Equilibrium in every subgame of Γ_E. (Mas Collel, Whinston and Green, 1995). Any subgame perfect Nash equilibrium is also Nash equilibrium.

Assuming that inequality (8) holds, setting price at level B is strictly dominated by setting price at level X or Z, regardless of the reaction of the parallel trader. If the manufacturer sets price Z, the best response of the parallel trader is to also set price Z. The payoffs in this case are:

$$(\Pi_{it}^{LS}, \Pi_{it}^{PI}) = ((X-c)q^{LS} + (q^{exp} + q^{T})(p^{exp} - c),\ q^{T}(X - p^{exp} - k)) \quad \text{(IX)}$$

The parallel trader's best response to the manufacturer's decision to set price Z is to also set price Z, as the payoff for him is higher than to respond by setting price B or X. The manufacturer knows the rational moves that the parallel trader will make as a response to his price setting. Consequently, he chooses to set price Z, as this will lead to equilibrium (Z, Z) with a higher payoff than equilibrium (X, X). Taking trigger strategies into account, each player knows he will be punished if he deviates from an equilibrium which suits both players, and is also ready to punish if the other player deviates. This holds if the discount factor $\delta = e^{-rt}$ is close enough to 1, which means that future payoffs do not lose much of their value due to time preference. The implication of a low discount factor is that each player cares about future payments, so he is hurt if the other player punishes him in the next period. Therefore, in the present round of the game an agent will take into account possible future punishments when making a move. If the discount factor would be very large,

it would make the present value of future payments small, thus making any punishments in future periods less painful for the agent that is punished, and punishment threats would be less credible.

The reason why equilibrium (Z, Z) is a Subgame Perfect Nash Equilibrium is as follows. The manufacturer knows that setting a price lower than Z will make him worse off. Setting price B will lead to lower profits, and setting price X would generate a reaction from the parallel trader, who would set price X. The parallel trader also knows the manufacturer's payoffs for each pricing strategy, and does not lower his price below Z as this would make him worse off: If the manufacturer would not respond with a price cut, the parallel trader would be worse off by the difference in price times the quantity, and would increase his profits by increasing his price back to Z again. This follows the assumption that the parallel trader has access to limited quantities of the product, and sells all quantities he imports if the price he sets is not higher than the price of the manufacturer.

If the manufacturer would also lower his price, this would make the parallel trader (as well as the manufacturer) worse off, given that the parallel trader can sell all quantities he can import if his price is not strictly higher than the manufacturer's price. A possible price war could eventually even drive him out of the market, if prices decline down to the level of the parallel trader's break-even point. It is not in the parallel trader's best interest to provoke the manufacturer by setting a lower price, because if the manufacturer follows, the parallel trader may have to exit the marker, as a result of having a higher break even point than the manufacturer.

Consequently, either of the two players choosing to deviate from (Z, Z) would, eventually, be worse off. Both rational players observe that they are better off by simultaneously setting prices $P_{it}^{LS} = P_{it}^{PI}$ =Z, rather than setting any price = X

$\in [P_{it}^{exp} + k_{it}, Z)$. This is the unique outcome of the game in the absence of any regulation, particularly targeting parallel trade. In this equilibrium the price of the parallel imported product will equal the price of the locally sourced product prior to the presence of parallel trade.

According to this equilibrium, manufacturers accommodate parallel traders as this strategy is more profitable than fighting them out of the market through price competition. Once they are accommodated, parallel traders will manage to sell all the quantities of imported medicines.

In the presence of discounting, the parallel trader would preferably give discounts to pharmacists, rather than lower the official price of the parallel traded product. Lowering the price would make pharmacists' profits decrease, while with unofficial discounts pharmacists receive the same mark-up but benefit directly from discounts.

Otherwise, in the absence of any discounts on behalf of parallel traders, a parallel trader would avoid setting a price lower than that of the locally sourced product. The reason is that lower prices would lead to lower profits for pharmacists, as pharmacist mark-ups are fixed, at least for the United Kingdom, Sweden and Germany. In Sweden there is some form of regressive nature of mark-ups, but this only applies for medicines with significant differences in price, and is partially or fully offset by an extra fee per medicine dispensed, which actually increases rather than decreases as the price goes up. Consequently, also in Sweden, pharmacists usually gain more by dispensing more expensive medicines, especially when price differences are relatively small. Therefore, if the pharmacy purchase price is smaller for the parallel traded than the locally sourced product, pharmacists would prefer to dispense locally sourced products, as their profit would be larger, making it obvious

that parallel traders would avoid setting a price lower than that of the locally sourced product.

The difference in the cost functions between the two agents plays a very important role in this game. Clearly, the parallel trader has a higher unit cost than the manufacturer and any price lower than this would force him out of the market. The difference in the break even point prevents a price war. The parallel trader knows that by triggering a price war he may eventually be forced to exit the market, so he prices at the same point as the manufacturer. The manufacturer also knows that if he reduced his price, in order to eventually kick the parallel trader out of the market, the parallel trader would follow, but the price war would stop only after the parallel trader leaves the market, at his break even point. At this point the manufacturer would be worse off anyway due to the large reduction in price he would have to make compared to the market share he would actually gain and the inability to increase prices quickly due to stickiness.

If inequality (8) $\left(P_{it}^{LS} - P_{it}^{\exp}\right)q_{it}^{PI} < \left(P_{it}^{LS} - \left(P_{it}^{PI} + k_{it}^{PI}\right)\right)\left(q_{it}^{PI} + q_{it}^{LS}\right)$ did not hold, meaning that the quantities imported by the parallel trader do not represent only a small fraction of the importing market, a manufacturer could drive the parallel trader out of the market through a price war. Even in this case, however, a manufacturer may still not wish to be engaged in a price war with a parallel trader. Manufacturers are large multinational firms with strong brand names, large sales worldwide and care about their reputation. Being engaged in a price war against a parallel trader selling a product manufactured by them is controversial and counter-intuitive and would most certainly damage the brand's reputation and by extension the firm's reputation. Such damage to the firm's image would jeopardise future revenue in all aspects of the firm's activities. Another factor is the sustainability and continuity of

the parallel trade supply chain. The volume of parallel traded products is not constant and also depends on the prices in the export countries. By lowering his price, the manufacturer may find himself in the situation of a low price which cannot be increased quickly, while parallel trade has stopped or decreased due to other reasons.

Importantly, lowering prices of medicines which are subjected to parallel trade could have a very negative effect on prices of medicines which do not face parallel trade, predominantly for two reasons:

First, a price reduction as a result of competition from parallel trade would lead to large savings for health insurance. Parallel trade would no longer be a controversial activity of which effects on competition are ambiguous. It would provide clear evidence that parallel trade lowers prices of locally sourced products almost down to the level of exporting countries. Thus more aggressive policies encouraging parallel trade could be implemented.

Second, lowering the price of the locally sourced product would indicate that the manufacturers can indeed manage with lower prices in import countries. This would lead to tougher negotiations and overall tougher stance by health insurance when pricing and reimbursement decisions are made upon the launch of new medicines, resulting in lower future profits.

Therefore, it would be better for manufacturers not to engage in a price war and somehow acquiesce to parallel trading activity. Manufacturers' efforts could instead focus on exporting countries, where their local offices could try to limit quantities to only what is needed in the local market, so that there is no space for parallel traders to perform their activities.

The above analysis generates an important question regarding parallel trade penetration in importing countries. If the price of the parallel imported product is the same or almost the same as the locally sourced product pharmacies would not necessarily be interested in dispensing parallel traded products. The reason why they do lies in discounts which parallel traders give to pharmacists and any incentives or enforcement mechanisms by health insurers. Even when discounts are officially allowed, they are not recorded. Branded product manufacturers usually do not have the flexibility to make discounts on top of what they are allowed to give through regulation. Thus, there is a strong financial incentive for pharmacists to dispense parallel traded products. Another factor contributing to the dispensing of parallel traded products by pharmacies is government intervention, as discussed in the next sub-section. In some cases, policies may provide incentives encouraging pharmacies to dispense parallel traded products, or may force them to do so through disincentives.

6.4.3 The effect of Policies targeting Parallel Trade on equilibrium prices

In the previous section we analysed how prices of locally sourced and parallel imported medicines evolve as a result of parallel trade. The equilibrium in game outcome (IX) assumed no regulatory interventions targeting parallel trade. However, policy makers in importing countries are aware of price differences across countries and the possibilities to reduce costs through parallel imports. As a result of this perception, explicit policies aiming at the dispensing of parallel imported medicines have been implemented in Germany, the Netherlands, Sweden and the United Kingdom.

6.4.3.1 Price Spread sharing

A policy aiming directly at encouraging parallel imports is sharing the price difference between the locally sourced and the parallel traded product with pharmacists. Any price difference which occurs between the locally sourced product and the parallel imported product leads to savings for health insurance. When this policy is implemented, health insurance shares these savings with pharmacies. This is a very strong incentive for pharmacists to dispense parallel traded products, as this leads to additional rents. This measure has been implemented in the Netherlands, where the pharmacists gain a third of the price difference. The remaining two thirds accrue to health insurance.

Pharmacists do not compete against the manufacturer or the parallel trader. They simply work as a channel through which the product reaches patients. Thus they are treated as an exogenous factor, rather than an agent in this model.

The main difference between this case and the case of the absence of any policies encouraging parallel trade is that the parallel trader is pressed by a third party to lower prices. The third party (the pharmacist), has some bargaining power and can choose not to dispense parallel traded products if their price is not lower than locally sourced products, as they benefit from a price gap. The argument to do so is reinforced by parallel traded and locally sourced products not always being considered to be identical due to different packaging or labelling, which can potentially confuse patients.

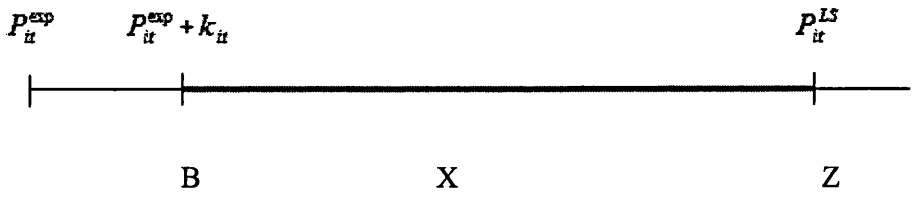
The parallel trader enters at a price lower than that of the locally sourced product, but the manufacturer does not follow. By following, he would not increase his market share, as parallel traders can sell all the (limited) quantities that they can import. In order to gain more than this, the manufacturer would have to lower his

price further down than the level of the parallel imported product. The parallel trader would have to respond by reducing his price down to the level of the locally sourced product, or even lower, as pharmacists would demand a price gap in order to benefit from it. This would trigger a game which would again lead to a "race to the bottom", and would force the parallel trader to exit the market and the price being set at the break- even point of the parallel trader. This would leave both sides worse off.

In summary, the manufacturer would not gain a larger part of the market by lowering the price down to the level of the parallel trader and lowering the price even further would lead to a price war.

The parallel trader would not have set a price lower than that of the manufacturer, in the absence of this policy because this would not necessarily lead to an increase in his market share. He only does so due to pressure from the pharmacist.

Figure 6.3 Pricing with Price Spread Sharing Policies



In the presence of this policy, there are infinite equilibria. These are between the break-even point of the parallel trader $P_{it}^{exp} + k_{it}$ and the price of the locally sourced product P_{it}^{LS} (Figure 6.3). The outcome depends on the negotiating powers of the parallel trader and the pharmacist. The price of the locally sourced product remains unchanged at its initial level because, again, in order to drive the parallel

trader out of the market he would have to reduce prices down to $P_{it}^{exp} + k_{it}$. Also, if the price of the parallel traded product is set below P_{it}^{LS}, even if the manufacturer reduced his price to that level, the parallel trader would still be able to sell all quantities he imports due to discounts, as explained in section 6.2.2. When examining whether the manufacturer would have an incentive to set a price that is lower than the price that the parallel trader sets, the game will be reduced to the simple game without policy interventions. Thus, the manufacturer would not set a price lower than P_{it}^{exp} either. Consequently, the price of the locally sourced product will remain unchanged at its initial level.

In this particular case (in the presence of price spread sharing), the different outcomes of the game described in Figure 6.2 are:

X. (B, B): $\Pi_{it}^{LS} = (B-c)q^{imp} + q^{exp}(p^{exp} - c)$, $\Pi_{it}^{PI} = 0$

XI. (B, X): $\Pi_{it}^{LS} = (B-c)q^{imp} + q^{exp}(p^{exp} - c)$, $\Pi_{it}^{PI} = 0$

XII. (B, Z): $\Pi_{it}^{LS} = (B-c)q^{imp} + q^{exp}(p^{exp} - c)$, $\Pi_{it}^{PI} = 0$

XIII. (X, B): $\Pi_{it}^{LS} = (X-c)q^{imp} + q^{exp}(p^{exp} - c)$, $\Pi_{it}^{PI} = 0$

XIV. (X, X): $\Pi_{it}^{LS} = (X-c)q^{LS} + (q^{exp} + q^{T})(p^{exp} - c)$, $\Pi_{it}^{PI} = 0$

XV. (X,Z): $\Pi_{it}^{LS} = (X-c)q^{imp} + q^{exp}(p^{exp} - c)$, $\Pi_{it}^{PI} = 0$

XVI. (Z,B): $\Pi_{it}^{LS} = (Z-c)q^{imp} + q^{exp}(p^{exp} - c)$, $\Pi_{it}^{PI} = 0$

XVII. (Z, X): $\Pi_{it}^{LS} = (Z-c)q^{LS} + (q^{exp} + q^{T})(p^{exp} - c)$, $\Pi_{it}^{PI} = q^{T}(X - p^{exp} - k)$

XVIII. (Z,Z): $\Pi_{it}^{LS} = (Z-c)q^{LS} + (q^{exp} + q^{T})(p^{exp} - c)$, $\Pi_{it}^{PI} = 0$

Compared to the analysis in the absence of price spread sharing, the parallel trader makes no profit in this case when his price is the same as the price of the manufacturer. This leads to a new equilibrium, (XVII), at which the price of the

parallel trader is X, which is lower than Z, which is the price of the manufacturer. So at the equilibrium, $(P_{it}^{LS}, P_{it}^{PI})$ = (Z, X). Profits for the parallel trader are

$$\Pi_{it}^{PI} = q^{T}(X - p^{\exp} - k) \tag{9}$$

and profits for the manufacturer are

$$\Pi_{it}^{LS} = (Z - c)q^{LS} + (q^{\exp} + q^{T})(p^{\exp} - c) \tag{10}$$

Another case in which the parallel trader could have a positive profit would be if both the parallel trader and the manufacturer price their products between B and Z, with $P_{it}^{PI} < P_{it}^{LS}$. Both occur profits in this case, but this strategy is strictly dominated by outcome XVII, where $(P_{it}^{LS}, P_{it}^{PI})$ = (Z, X)

6.4.3.2 Co-payments

Another policy measure which in principle favours parallel imports over locally sourced products is the presence of patient co-payments, particularly co-insurance (rather than a flat co-payment)[9]. Co-insurance helps fight moral hazard and encourages generic dispensing. Co-insurance also encourages the dispensing of parallel traded medicines. Patients benefit from the price difference as they pay a smaller co-payment. In this case, the game is exactly the same as in the previous case, as there is an exogenous factor pressing for lower parallel trade prices compared to the locally sourced prices. The outcome is again $(P_{it}^{LS}, P_{it}^{PI})$ = (Z, X). Co-insurance type co-payments are present in Sweden and in Germany since the beginning of 2004.

[9] When the patient is burdened by a flat fee per product, the out-of –pocket payment remains the same regardless of the price. In the case of co-insurance, the out-of-pocket payment is a function of the price.

6.4.3.3 Clawbacks

Discounts are generally granted to pharmacies on behalf of the parallel traders. Generic products are also subject to discounting (Kanavos, Costa-Font, Seely 2008) and, as in the case of parallel trade, these are not officially announced and their extent is not known. Health insurers assume a reasonable discount that pharmacists may be benefitting from and impose clawbacks in order to benefit from the discounts that pharmacists receive from parallel traders, as clawbacks are typically lower than the overall discounts received. Following this policy, pharmacists have a strong incentive to dispense parallel traded products because they maximise their rent from discounts. By dispensing even more parallel traded products or by achieving even higher discounts they may even manage to make a profit. Clawbacks are in place in the United Kingdom and the Netherlands. This does not necessarily lead to official prices of parallel traded products being lower than locally sourced ones though. Clawbacks will lead to higher unofficial discounts for pharmacists rather than to lower prices. The equilibrium in the absence of any policies was upward convergence between the price of the locally sourced and the parallel traded product. This equilibrium is not affected by clawbacks alone. When implemented together with other policies though, clawbacks will push the price of the parallel traded product upwards towards, if this would have been lowered to a level lower than that of the locally sourced product due to another policy.

6.4.3.4 Quotas

Finally, quotas directly promote the dispensing of parallel imported medicines. This measure is present in Germany. In particular, pharmacies have to reach a certain percentage of parallel traded products as a proportion of their total

sales. This creates demand from pharmacists for parallel traded products; otherwise they will be burdened by financial penalties. The parallel traders observe this demand, so they understand that they do not have to dispense at a lower price to be able to sell the products they imported, as quotas make pharmacists seek parallel traded products anyway. Thus quotas lead to upward price convergence. Once the quota is reached though, this incentive on behalf of the pharmacists disappears. Therefore, quotas work for only part of the parallel traded products which are dispensed. After the quota is reached, the market becomes similar to a market without quotas for the remaining products. If the quota is not high enough and is easily reached, it may actually have no effect on parallel trade. Quotas do not have any effect on the initial equilibrium without policy interventions, but when implemented together with other policies which push prices of parallel traded products downwards, quotas will revert part or the whole price reduction which would take place in the presence of only the other policies.

6.4.3.5 Conclusion

In conclusion, in the absence of any policy interventions, the outcome of a game between the manufacturer and the parallel trader is that both set their prices at the price of the locally sourced product prior to the presence of parallel trade. This, however, may change in the presence of policy interventions. Cost sharing and sharing savings with pharmacists lead to infinite equilibria, while quotas and clawbacks lead to upward price convergence. The price of the locally sourced product remains stable at its initial level in all cases though, in the presence or not of policies targeting parallel trade.

6.4.4 Generic Entry and Parallel Trade

Patent expiry brings more players in pharmaceutical markets. Generic competitors enter the market at a price which is a fraction of the originator's price. Empirical evidence has showed that originator producers do not compete against generics in terms of price. Frank and Salkever (1993 and 1997) used data from the United States to show that prices of originators do not decrease post patent expiry, and may actually increase (generics paradox). The authors point out that a necessary condition for such price increases is that entry leads to a decline in the own-price elasticity of reduced-form brand-name demand. Grabowski and Vernon (1992) found that pioneering firms did not attempt to deter entry through their pricing strategies. Rather, in most cases, the firms continued to increase their prices at the same rate as prior to entry. Rizzo and Zeckhauser (2005) also found that producers of brand-name products do not decrease prices after generic market entry. Caves, Whinston and Hurwitz (1991) conclude that generic entry only leads to a slow-down in the increase of originator medicine prices. Therefore, the originator price is not expected to decrease post patent expiry. But the parallel imported originator product may follow a different strategy.

After a product goes off patent, the higher branded price is not covered by health insurance any longer. The price which is covered is that of a cheaper generic. As a result, the originator medicine only keeps a small fraction of the total market (Kanavos, Costa-Font, Seeley 2008). In order to get its product reimbursed by health insurance, the parallel trader may decrease the price of his product, choosing to compete against generics in importing countries, depending on generic prices. This can happen if the price of the generic in the import country is higher than the price of the originator in the export country plus any transportation costs. Such a strategy

may allow the parallel trader to secure a significant market share in the off patent market. Therefore, it is reasonable to expect that under certain circumstances generic entry may push prices of parallel imported medicines down.

At the same time, prices of locally sourced products remain unaffected. In the absence of parallel trade, this happens because post patent expiry the originator keeps only a small part of the market. These consumers are the most brand loyal ones, hence they are insensitive to changes in prices, meaning that the absolute value of price elasticity of these particular consumers is lower than 1. Thus, a 1% decrease in the price of the originator product will lead to an increase in consumption by less than 1%, leading to a decrease in total revenue. Contrary, an increase in the price will lead to an increase in total revenue. Besides, engaging in a price war with generic producers will only push the price of the product further down, as generic producers can carry on decreasing their prices down to very low levels.

In the presence of parallel trade and generic competitors, the producer of the originator product will again sustain his price at high levels. A price war against the parallel trader will make the producer worse off, as analyzed in section 6.4.1. The fact that generic producers are also present only makes the possibility of a further price reduction as a result of a price war more likely. Therefore, we do not expect generic entry in the presence of parallel trade to lead to a decrease in the price of the originator product, but it may well affect the parallel trader, leading to a decrease in prices of parallel traded products.

6.4.5 The effect of Pharmaceutical Parallel Trade on Social Welfare

The advocates of parallel trade suggest that this practice leads to savings for health insurance and helps cut medicine spending. This could possibly be the case in

the short run in some countries via direct savings from dispensing parallel imported products, when they happen to be priced at lower levels than the locally sourced product. Nevertheless, the long term effects of parallel trade should not be ignored. The agents who suffer from this practice are the manufacturers. For them, parallel trade is equivalent to covering demand in the importing country at the lower prices of the exporting country.

In the absence of parallel trade, the originator producer's profits are the sum of profits in the importing and exporting country:

$$\pi_{it}^{LS} = \left(p_{it}^{LS} q_{it}^{LS} - cq_{it}^{LS}\right) + \left(p_{it}^{\exp} q_{it}^{\exp} - cq_{it}^{\exp}\right) =$$

$$= \left(p_{it}^{LS} - c\right) q_{it}^{LS} + \left(p_{it}^{\exp} - c_{it}\right) q_{it}^{\exp} \qquad (11)$$

Where c_{it} is the unit cost of production, which can be assumed to be the same in both countries, as they are produced by the same company, in the same plant and with the similar transportation costs in order to reach both markets.

In the presence of parallel trade, the originator producer will sell fewer units of the medicine in the local market, as these units will be purchased abroad by a parallel trader and imported into the local market. Thus, assuming that total demand remains constant in each market, the producer's sales will increase in the exporting market as much as the drop in sales in the importing market. Total sales in both markets together for the originator producer will remain the same, but the parallel imported products are purchased by the parallel trader at a lower price abroad. Profits for the originator medicine manufacturer in the presence of parallel trade are:

$$\pi_{it}^{LS} = \left(p_{it}^{LS}\left(q_{it}^{LS} - q_{it}^{PI}\right) - c\left(q_{it}^{LS} - q_{it}^{PI}\right)\right) + \left(p_{it}^{\exp} q_{it}^{PI} - c_{it} q_{it}^{PI}\right) + \left(p_{it}^{\exp} q_{it}^{\exp} - cq_{it}^{\exp}\right) \quad (12)$$

The difference between profits in the absence and in the presence of parallel trade is:

$$\Delta\pi_{it}^{LS} = \left(p_{it}^{LS} - p_{it}^{\exp}\right)q_{it}^{PI} \qquad (13)$$

Parallel trade causes a drop in the manufacturer's profits by the difference in price times the sales of parallel trade.

Parallel traders (or the supply chain in general) benefit from parallel trade by their profits:

$$\pi_{it}^{PI} = \left(p_{it}^{PI} - (p_{it}^{\exp} + tc_{it}^{PI})\right)q_{it}^{PI} \qquad (14)$$

Concerning consumers, if the prices are the same as the locally sourced product, they do not benefit from lower prices. In the case where the parallel traded product is priced at a lower level than the locally sourced product, the price is still higher than the exporting price, so a large proportion of the difference ends up as the parallel traders' profit.

Reduced manufacturer profitability due to parallel trade though may lead to lower levels of future R&D. This leads to lower future profits of the firm, say - $E\left(\Delta\pi_{i,t+n}^{LS}\right)$ and fewer new medicines in the future, which might impact health compared to what would occur in the absence of parallel trade ($E(\Delta h)$).

The total benefits of parallel trade are:

$$\left(p_{it}^{PI} - (p_{it}^{\exp} + tc_{it}^{PI})\right)q_{it}^{PI} \qquad (15)$$

The total welfare losses due to parallel trade are:

$$\left(p_{it}^{LS} - p_{it}^{\exp}\right)q_{it}^{PI} + E\left(\Delta\pi_{i,t+n}^{LS}\right) + E(\Delta h) \qquad (16)$$

As $\left(p_{it}^{LS} - p_{it}^{\exp}\right)q_{it}^{PI} > \left(p_{it}^{PI} - (p_{it}^{\exp} + tc_{it}^{PI})\right)q_{it}^{PI}$, it is clear that social welfare decreases due to parallel trade. The manufacturer observes parallel trade today and estimates returns of future medicines subject to parallel trade practice. Therefore a lower return is expected, potentially leading to less future innovation.

6.4.6 Conclusion

We have theoretically analyzed the impact of parallel trade on competition in the pharmaceutical market and how prices of parallel traded products evolve. We showed that in the absence of particular policies, parallel trade does not affect the prices of locally sourced products. The presence of such policies though may change the outcome. Some policies may lead to the price of the parallel traded product to be lower than that of the locally sourced product. Such policies are sharing savings with the pharmacist and co-payments. Policies which lead to upward price convergence are clawbacks and quotas. Of course, combinations of such policies make things more complicated and the outcomes depend on the intensity of these policies and the market agents' reaction. The price of the locally sourced product remains stable at its initial level in all cases though, in the presence or not of policies targeting parallel trade. The next step is to test these findings empirically, in the main parallel importing countries, which are Germany, the Netherlands, Sweden and the United Kingdom.

6.5 Price Differences between Locally Sourced and Parallel Imported Medicines

After having in theory analysed the effects of parallel trade on prices and competition, we now observe empirical data to see how parallel traded medicines are priced compared to locally sourced products. This section focuses only on the price spread rather than the effect on locally sourced medicine prices. The next section which involves econometric analysis will focus on whether prices of locally sourced products are affected by parallel trade.

Tables 6.2, 6.3, 6.4 and 6.5 show the price spread between locally sourced products and parallel traded products in Germany, the Netherlands, Sweden and the United Kingdom in 2003, 2004, 2005 and 2006. Products which face generic competition are indicated with an asterisk. The Tables show that products which face generic entry demonstrate higher price differences between locally sourced and parallel trader products. This shows that, as explained in a previous section, the parallel trader may choose to compete against generics in an off- patent market.

The country with the lowest price spread is the United Kingdom (Table 6.5). Most medicines have a zero percent price spread. An exception is Captopril, which faces generic competition. But this is clearly an outlier, as parallel traded captopril accounts for less than 1% of the UK market. Parallel traded Omeprazole, Simvastatin and Ramipril, which all face generic competition, also have lower prices than the corresponding locally sourced medicines. All other products however have exactly the same price. The fact that in the vast majority of cases in the United Kingdom the price of the parallel imported medicine is the same as that of the locally sourced, reflects the absence of policies which would lead to lower parallel trade prices. Co-payments are flat in the UK, and there is no sharing of savings with

pharmacists. Clawbacks are present, but this only leads to pharmacies dispensing more parallel traded products, rather than cheaper products.

The country with the higher price spread is the Netherlands (Table 6.3). There is no single parallel imported product with the same price as the respective locally sourced product. This reflects the savings-sharing policy which is present in the Netherlands. Pharmacists have a strong incentive to demand lower prices from the parallel traders, which are passed on to the retail market. However, the highest price differences occur for off-patent products. Sweden is a similar case. Patient co-payments are relative to prices in this country, so there is downward pressure on the parallel traded medicines. Again, the largest price differences occur for off-patent products. Some price differences are very large, but most cases are products with small market share of parallel imports. Finally, Germany has some products with zero price spread and others with large price differences. Products with zero spread are patent protected, while price differences are present for off-patent products. Before these are reached parallel traders have no incentive to sell at lower prices. But patient co-payments are also present. These two policy measures have opposite effects on prices of parallel traded products, hence the large volatility in the price spread.

Table 6.2 Price spread between Locally Sourced and Parallel Imported Medicines – Germany (percent), 2003-2006

	2003	2004	2005	2006
Lansoprazole	4.27	6.25	6.84	21.18*
Omeprazole	9.42*	39.59*	32.82*	35.38*
Pantoprazole	4.20	7.82	5.67	2.12
Atorvastatin	N/A	N/A	N/A	N/A
Pravastatin	6.57	6.57*	0.00*	N/A
Simvastatin	19.77*	41.85*	36.80*	40.96*
Captopril	21.78*	38.98*	40.72*	21.78*
Enalapril	16.05*	25.15*	35.42*	16.05*
Quinapril	0.00	0.00	N/A	0.00
Ramipril	3.69	0.00*	0.00*	28.07*
Losartan	N/A	N/A	N/A	N/A
Valsartan	7.59	3.00	0.00	N/A
Citalopram	5.07*	10.97*	14.44*	24.99*
Clozapine	N/A	N/A	N/A	N/A
Olanzapine	3.34	5.15	5.00	2.48
Paroxetine	4.79	8.94	16.23	12.30
Risperidone	10.03	12.90	7.42	12.11
Sertraline	3.45	2.07	9.38	13.46*

Asterisk indicates generic presence.
Source: The authors from IMS

Table 6.3 Price spread between Locally sourced and Parallel Imported Medicines – Netherlands (percent), 2003-2006

	2003	2004	2005	2006
Lansoprazole	12.51	9.44	11.74	40.34*
Omeprazole	20.64*	N/A	N/A	N/A
Pantoprazole	18.74	9.67	12.08	15.13
Atorvastatin	16.01	12.69	12.66	9.71
Pravastatin	7.33	26.17*	17.24*	33.43*
Simvastatin	11.84*	22.58*	30.24*	49.61*
Captopril	14.81*	N/A	N/A	N/A
Enalapril	14.00*	N/A	N/A	N/A
Quinapril	17.20	14.57	5.13	8.59
Ramipril	12.74	13.20*	6.95*	12.79*
Losartan	11.99	12.65	9.80	11.59
Valsartan	9.01	N/A	N/A	N/A
Citalopram	7.38*	3.38*	N/A	10.76*
Clozapine	N/A	N/A	N/A	43.04
Olanzapine	7.78	7.59	7.60	7.57
Paroxetine	6.15	N/A	N/A	N/A
Risperidone	9.26	7.84	7.50	9.57
Sertraline	13.49	12.74	11.80	3.95*

Asterisk indicates generic presence.
Source: The authors from IMS

Table 6.4 Price spread between Locally sourced and Parallel Imported Medicines – Sweden (percent), 2003-2006

	2003	2004	2005	2006
Lansoprazole	N/A	N/A	N/A	N/A
Omeprazole	7.74*	8.95*	6.80*	23.92*
Pantoprazole	N/A	N/A	N/A	N/A
Atorvastatin	6.28	9.55	2.87	5.21
Pravastatin	5.83	9.83*	2.88*	11.84*
Simvastatin	30.06*	85.86*	87.90*	90.39*
Captopril	N/A	N/A	N/A	N/A
Enalapril	13.13*	N/A	N/A	N/A
Quinapril	N/A	N/A	N/A	10.28
Ramipril	16.25	0.00*	0.00*	65.82*
Losartan	N/A	1.12	1.12	N/A
Valsartan	6.00	6.73	2.27	2.27
Citalopram	7.83	7.14	78.42	80.40
Clozapine	19.57*	31.56*	34.97*	18.63*
Olanzapine	12.24	10.42	3.38	8.35
Paroxetine	N/A	N/A	N/A	N/A
Risperidone	14.97	10.32	2.89	0.36
Sertraline	10.00	9.41	31.66	66.70*

Asterisk indicates generic presence.
Source: The authors from IMS

Table 6.5 Price spread between Locally sourced and Parallel Imported Medicines - United Kingdom (percent), 2003-2006

	2003	2004	2005	2006
Lansoprazole	0.00	0.00	0.00	0.00*
Omeprazole	7.86*	15.29*	10.15*	0.00*
Pantoprazole	0.00	0.00	0.00	0.00
Atorvastatin	0.00	0.00	0.00	0.00
Pravastatin	0.00*	0.00*	9.00*	0.00*
Simvastatin	4.55*	10.45*	20.71*	18.00*
Captopril	46.48*	45.85*	48.61*	31.60*
Enalapril	0.00*	0.00*	0.00*	0.00*
Quinapril	0.00	0.00	4.69	0.00
Ramipril	0.00	9.34*	16.67*	15.33*
Losartan	0.00	0.00	0.00	0.00
Valsartan	0.00	0.00	0.00	0.00
Citalopram	0.00*	0.00*	0.00*	0.00*
Clozapine	N/A	N/A	N/A	0.00
Olanzapine	0.00	0.00	0.00	0.00
Paroxetine	8.40	0.36	0.00	0.00
Risperidone	0.00	0.00	0.00	0.00
Sertraline	0.00	0.00	0.00	4.10*

Asterisk indicates generic presence.
Source: The authors from IMS

6.6 The Econometric Model

6.6.1 Data

In conducting this analysis, data from the Intercontinental Medical Statistics (IMS) pharmaceutical sales database were used. IMS also records volume and prices of parallel imports. Price data on parallel trade were acquired from countries. IMS collects and reports market data on pharmaceutical sales, prices and market shares of all products and product presentations in many countries. The data have been validated and their accuracy ranges between 98%-99% (IMS, 2002). Collected and reported data are based on actual invoiced sales of pharmaceutical products.

Data were obtained for the 2003-2006 period. The focus of the analysis was the retail (pharmacy) market in four countries (notably Germany, Sweden, The Netherlands and the United Kingdom), which have been known to encourage parallel imports and their price level for prescription pharmaceuticals is above the European average. Therefore, the potential for parallel trade from lower-priced countries is in principle significant. Of the entire retail market, a segment comprising six therapeutic (product) categories was selected. The product categories were proton pump inhibitors (PPI), HMG CoA reductase inhibitors (statins), ACE I inhibitors, ACE II inhibitors, SSRIs, and atypical anti-psychotics. These categories were chosen because they provide a large number of high-volume and high-price products[10], many of which are patent protected and, therefore, potentially more susceptible to PT.

For each product and product formulation within these product categories, data was obtained on market shares, prices, sales, and volumes (in terms of packs) sold. All pecuniary (price and sales) figures were expressed in Euros (€). It was possible to distinguish between market shares of volumes, sales, and prices of locally-sourced and parallel imported versions of the same product.

A very important aspect of the selected data and period is that this period covers both in-patent and off-patent medicines. This allows controlling for factors such as generic entry. Prior to generic entry the manufacturer of the branded product is a monopolist in the market. Patent expiry though allows new players to enter the market. These are generic competitors, which are not subjected to R&D costs as the branded manufacturer is. They enter the market immediately after patent expiry and swiftly take up the vast majority of the market, due to policies promoting generic

[10] These categories include very widely prescribed life-saving and very effective products for severe chronic conditions, such as (peptic and duodenal) ulcer, depression, hypertension, angina, prevention of heart disease, hyperlipidemia, and schizophrenia.

prescribing and dispensing in Europe. This aspect of competition should not be ignored, as it may influence the behaviour of the originator firm. Including both products which are in- patent (and hence do not face generic competition) and medicines which do face generic competitors, allows controlling for this very important factor. Further, the sample also includes some medicines which in some countries over certain periods do not face parallel trade competitors. This also allows for observing the differences in pricing behaviour in the presence or not of parallel traders in the market of a particular product.

6.6.2 The Empirical Model

The game theoretic approach showed how prices of locally sourced and parallel traded products are set as a result of parallel trade, in the presence or not of relevant policies. The descriptive section showed that in United Kingdom the price spread is usually zero, suggesting that there is price convergence. But we do not know yet whether this price convergence is upward or downward. Upward convergence would show that parallel trade does not lead to any savings in the United Kingdom. Similarly, in the Netherlands and Sweden there is a significant price gap, which means that direct savings may occur by dispensing parallel traded products. But if the price of the locally sourced product also decreases as a result of parallel trade, this would mean that indirect savings also occur, making parallel trade a significant contributor to cost containment. In Germany, some medicines have zero price spread, while others have a positive price spread.

For all previously mentioned cases, in order to determine whether there is downward or upward convergence, hence positive or zero savings (United Kingdom and some molecules in Germany) respectively, or whether parallel trade leads to

indirect savings apart from direct savings (the Netherlands, Sweden and some molecules in Germany) we use econometric methods. Indirect savings would occur if the parallel traded product triggers a response from the manufacturer in terms of lowering the product's price. In this case savings would also occur by dispensing the locally sourced product.

According to economic theory, the price of the product depends on the presence of other competitors. The price of the locally sourced product may be influenced by the presence of generics in the market. Thus a cut in parallel trade prices may be the result of generic entry rather than the presence of parallel traded products. The hypothesis is that parallel traded products do not affect the price of the locally sourced product, but as a competitor, they can enter the equation describing the type of market. The price of a locally sourced product is:

$$P_{it}^{LS} = P_{it}^{LS}(G, PI) \qquad (17)$$

where G represents competition from generics and PI competition from parallel traders.

Using equation (16) we create the empirical model. Instrumental variable panel data regressions are run, using prices of the locally sourced products as the dependent variable. The equations which will be empirically estimated are (18), (19), (20) and (21):

$$P_{i,t}^{LS} = \alpha_i + \beta_0 + \beta_1 mspt_{i,t} + \beta_2 generics_{i,t} + \beta_3 statins_{i,t} + \beta_4 acei_{i,t}$$

$$+ \beta_5 ppi_{i,t} + \beta_6 aceii_{i,t} + \beta_7 atyp_{i,t} + \beta_8 exr_{i,t} + \sum_{k=9}^{11} \beta_k time_{i,y} + \varepsilon_{i,t} \qquad (18)$$

$$P_{i,t}^{LS} = \alpha_i + \beta_0 + \beta_1 pt_{i,t} + \beta_2 generics_{i,t} + \beta_3 statins_{i,t} + \beta_4 acei_{i,t}$$

$$+ \beta_5 ppi_{i,t} + \beta_6 aceii + \beta_7 atyp + \beta_8 exr + \sum_{k=9}^{11} \beta_k time_{i,y} + u_{i,t} \qquad (19)$$

$$P_{i,t}^{PT} = \alpha_i + \beta_0 + \beta_1 mspt_{i,t} + \beta_2 generics_{i,t} + \beta_3 statins_{i,t} + \beta_4 acei_{i,t}$$

$$+ \beta_5 ppi_{i,t} + \beta_6 aceii_{i,t} + \beta_7 atyp_{i,t} + \beta_8 exr_{i,t} + \sum_{k=9}^{11} \beta_k time_{i,y} + \mu_{i,t} \qquad (20)$$

$$P_{i,t}^{LS} - P_{i,t}^{PT} = \alpha_i + \beta_0 + \beta_1 mspt_{i,t} + \beta_2 generics_{i,t} + \beta_3 statins_{i,t} + \beta_4 acei_{i,t}$$

$$+ \beta_5 ppi_{i,t} + \beta_6 aceii_{i,t} + \beta_7 atyp_{i,t} + \beta_8 exr_{i,t} + \sum_{k=9}^{11} \beta_k time_{i,y} + v_{i,t} \qquad (21)$$

where i indicates the specific product in the specific country and t indicates time. P^{LS} is the price of the locally sourced product, measured in logs. *mspt* is the market share of each parallel traded product, as a proportion of each particular product (capturing parallel trade market penetration). *pt* is a dummy variable indicating the presence or not of parallel traders in the market of a particular medicine. *generics* is a 0-1 dummy variable which indicates the presence of generics in the market of each particular molecule. *statins*, *acei*, *ppi*, *aceii*, *atyp* and *ssri* are dummy variables for each therapeutic class. They are used to control for differences in demand across therapeutic classes. *ssri* is not included in the regression as this would lead to a singular matrix. *exr* is the exchange rate, measured in logs. Finally, we also use time dummies to control for time effects.

In equation (21), the dependent variable is the log of the ratio of prices. According to the properties of logarithms though, $\log\left(x/y\right) = \log x - \log y$. In other

words, the log of a ratio of numbers is equal to the difference of the logs of these numbers. Hence we can write the dependent variable as $P_{i,t}^{LS} - P_{i,t}^{PT}$ where $P_{i,t}^{LS}$ is the log of the price of the locally sourced product and $P_{i,t}^{PT}$ is the price of the parallel imported product. Policies targeting parallel trade which influence prices (*share* and *copay*) are excluded from the empirical model due to colinearity problems. Policies influencing volume of parallel trade are used as instruments, as explained later. Summary statistics are in Table 6.6.

Table 6.6 Summary Statistics

Variable	Observations	Mean	Std. Dev.
P^{LS}	287	4.403	1.228
P^{PT}	225	4.309	1.244
mspt	287	15.289	16.833
generics	288	0.389	0.488
copay	288	0.438	0.497
quota	288	0.250	0.434
clawback	288	0.500	0.501
share	288	0.250	0.434
acei	288	0.222	0.416
ppi	288	0.167	0.373
aceii	288	0.111	0.315
atyp	288	0.167	0.373
exr	288	-0.555	0.963
dist	288	19.294	3.247

Due to endogeneity between prices and parallel trade penetration, we use instrumental variables to estimate equations (18), (19) (20) and (21). The instruments used are *ldist* and *policy*. *ldist* is the average Euclidian distance of latitude and longitude between each importing and exporting country capitals measured in logs. Parallel traders are subject to transportation costs. These costs may be significant and extend beyond the price difference between the importing and the exporting country, making parallel trade not profitable. A smaller

geographical distance between importing and exporting countries may be important in making parallel trade profitable, thus changing the state from zero parallel trade originating from a particular exporting country to a positive volume of parallel trade from that country.

Policies encouraging parallel trade penetration are also used as instruments. The inclusion of two different policy dummies , namely *quota* and *clawback* causes some collinearity problems. Therefore, we used a new variable, *policy*, which is the sum of the other two policy dummies: *quota* and *clawback*. *copay* indicates the presence of patient co-payments; *quota* indicates the presence of quotas for parallel traded products for pharmacists; *clawback* indicates clawback mechanisms for pharmacists. *share* and *copay* are not included because they may affect prices directly, rather than through the market share. Using *policy* instead of *quota* and *clawback* addresses collinearity problems.

We use Panel Data analysis in order to estimate the model. Panel data is used because it can give "more informative data, more variability, less collinearity among variables, more degrees of freedom and more efficiency" (Gujarati 2003). Thus, having a different intercept for each country may allow us to have a better and more efficient model. The constant term, β_i is different for each product in each country and is determined using either fixed or random effects.

We assume heterogeneity between countries due to the fact that different policies apply. According to this assumption, the constant term that is different for each country captures the effects of those variables that are peculiar to the *i*-th individual and that are constant over time. The error term is assumed to be independent and identically distributed over individuals and time, with mean zero and variance σ_ε^2. Alternatively, the random effects approach assumes that the

intercepts of the individuals are different but that they can be treated as drawings from a distribution with mean μ and variance σ_α^2. The essential assumption here is that these drawings are independent of the explanatory variables. (Verbeek 2005). The panel identifier in this model is the pharmaceutical product per country. In this way we can distinguish, both, between countries and between medicines. This is useful because there can be different demand structures not only from country to country but also from medicine to medicine within the same country.

Equation (18) examines the effects of parallel trade penetration (*mspt*) on prices of locally sourced medicines. Equation (19) examines the effects of the presence of parallel traded products (*pt*) on the market. A negative and statistically significant coefficient for *mspt* or *pt* would suggest that parallel trade leads to lower prices for locally sourced products. This would provide evidence that parallel trade would trigger competition and would also lead to indirect savings, apart from direct savings. If the coefficient is negative or statistically insignificant, it would indicate that parallel trade does not affect prices of locally sourced products. Equation (20) examines the effect of parallel trade penetration on prices of parallel imported medicines. Finally, equation (21) examines the determinants of the ratio of locally sourced and parallel imported medicine prices.

6.6.3 Empirical Results

6.6.3.1 Aggregate Level Results

Estimation results of the instrumental variable panel data analysis of equations (18) and (19) are in Table 6.7. Equations (18) and (19) show the effects of parallel trade penetration and parallel trade presence respectively on prices of locally

sourced products. The estimation results of the fixed effects model of equation (18) demonstrate a positive and statistically insignificant coefficient of *mspt*, which shows that prices of locally sourced products are not influenced by parallel trade penetration. The coefficient of the variable representing generic entry is also statistically insignificant, showing that prices do not respond to generic entry either (this is known in the literature as the "generics paradox", as discussed previosuly).

Results are similar for the random effects model. The coefficient of *mspt* is positive and statistically insignificant, and the coefficient of *generics* is once again insignificant. Coefficients of some therapeutic class dummies are statistically significant, indicating cross class price variability.

The Hausman Test suggests that we follow the random effects approach: The chi-squared statistic is 0.14, which indicates that the difference between the consistent fixed effects and the random effects estimator is statistically insignificant. Therefore, it is safe to use random effects, which are a more efficient estimator compared to fixed effects, as according to the Hausman test they give consistent results. Nevertheless, both approaches suggest that parallel trade penetration does not affect prices of locally sourced medicines.

Table 6.7 Instrumental Variables Panel Data Estimation

Dependent Variable: $P_{i,t}^{LS}$

	FE	RE	FE	RE
mspt	0.070	0.001		
	(0.186)	(0.014)		
pt			-1.681	-0.476
			(2.709)	(1.127)
generics	0.202	-0.114	-0.043	-0.091
	(0.856)	(0.107)	(0.170)	(0.098)
statins		0.706***		0.732**
		(0.261)		(0.346)
acei		-0.532**		-0.601*
		(0.268)		(0.350)
ppi		0.277		0.243
		(0.265)		(0.347)
aceii		-0.995***		-1.057***
		(0.299)		(0.407)
atyp		1.676***		1.670***
		(0.268)		(0.342)
ln_exr	28.292	-0.411***	-5.112	-0.375***
	(75.858)	(0.079)	(10.719)	(0.135)
time1	-0.038	-0.053	-0.178	-0.089
	(0.122)	(0.060)	(0.213)	(0.096)
time2	-0.119	-0.160***	-0.351	-0.208*
	(0.162)	(0.062)	(0.320)	(0.124)
time3	-0.255	-0.144*	-0.315	-0.186
	(0.328)	(0.074)	(0.291)	(0.117)
constant	12.117	-2.906***	-3.872	-2.451**
	(39.132)	(0.312)	(4.493)	(1.071)
Observations	287	287	287	287
R^2 within	0.210	0.214	0.212	0.057
R^2 between	0.067	0.406	0.047	0.310
R^2 overall	0.065	0.403	0.046	0.304
Wald χ^2	4208.23	166.84	11300.42	112.09
Hausman χ^2	0.14		0.24	

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively.
Standard Errors in Parenthesis

Findings from the estimation results of equation (19) point towards the same direction. In both the fixed effects and the random effects models, the coefficient of *pt* (which indicates presence of parallel trade for a particular molecule in a particular country) is negative but statistically insignificant. The same holds for the coefficient of *generics*.

The Hausman test again suggests that it is safe to follow the random effects approach. Results for fixed effects and random effects are very similar, so which approach is followed does not change the findings.

The coefficients of *mspt* or *pt* are not negative and statistically significant (Table 6.7) in any of the country specific regressions. This indicates that parallel trade does not spark competition in any of these markets and price convergence is not downward, if any.

The estimation results of equation (20) are shown in Table 6.8. In the fixed effects approach, the coefficient of *mspt* is positive and statistically insignificant, indicating no effects of parallel trade penetration on prices of parallel traded medicines. The effect of generic presence also appears to be insignificant. In the random effects model, again, the coefficient of the variable representing parallel trade penetration is statistically insignificant, although negative this time. The coefficient of *generics* is statistically significant at the α=10% level, indicating a negative effect of generic entry on prices of parallel traded products. The coefficients of *statins*, *ppi*, *aceii* and *atyp* are statistically significant, showing some cross therapeutic class price variability.

In this case the Hausman test (2.85) suggests that it is safe to rely on the random effects approach, which is more efficient than the fixed effects approach. The number of observations is smaller than in the estimation of equations (18) and

(19) because only observations which include the presence of parallel traded products are included.

Table 6.8 Instrumental Variables Panel Data Estimation

Dependent Variable: $P_{i,t}^{PT}$

	FE	RE
mspt	0.043	-0.002
	(0.102)	(0.017)
generics	0.053	-0.222*
	(0.557)	(0.134)
statins		0.694**
		(0.287)
acei		-0.148
		(0.295)
ppi		0.701**
		(0.297)
aceii		-0.904***
		(0.339)
atyp		2.122***
		(0.298)
ln_exr	42.043	-0.526***
	(65.782)	(0.109)
time1	-0.090	-0.058
	(0.104)	(0.074)
time2	-0.183	-0.209**
	(0.114)	(0.086)
time3	-0.289	-0.218**
	(0.287)	(0.107)
constant	15.882	-3.042***
	(27.724)	(0.378)
Observations	225	225
Rsq within		0.244
Rsq between	0.115	0.473
Rsq overall	0.134	0.604
Wald chi sq	4843.48	173.13
Hausman chi sq	2.85	

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively. Standard Errors in Parenthesis

Table 6.9 shows the estimation results of equation (21). In the fixed effects model, the coefficient of *mspt* is positive and statistically significant, which suggests that the relative prices of the locally sourced products and parallel traded products do not change as parallel trade penetration increases. The impact of generic entry on relative prices is insignificant.

In the random effects approach, the coefficient of *mspt* is again insignificant, but negative this time. What does change, compared to the fixed effects approach, is that the coefficient of *generics* is statistically significant.

Table 6.9 Instrumental Variables Panel Data Estimation

Dependent Variable: $P_{i,t}^{LS} - P_{i,t}^{PT}$

	FE	RE
mspt	0.018	-0.002
	(0.053)	(0.006)
generics	0.150	0.121**
	(0.289)	(0.060)
statins		0.047
		(0.097)
acei		0.001
		(0.103)
ppi		-0.080
		(0.100)
aceii		-0.086
		(0.117)
atyp		-0.018
		(0.105)
ln_exr	-1.632	-0.083**
	(34.189)	(0.037)
time1	0.034	0.023
	(0.054)	(0.045)
time2	0.047	0.093*
	(0.059)	(0.049)
time3	0.033	0.112**
	(0.149)	(0.055)
constant	-1.032	0.061
	(14.409)	(0.136)
Observations	225	225
Rsq within		0.038
Rsq between	0.068	0.195
Rsq overall	0.061	0.156
Wald chi sq	81.05	28.17
Hausman chi sq	13.99	

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively. Standard Errors in Parenthesis

6.6.3.2 Country Specific Results

We now estimate the same static models at country level. Due to the small number of observations, using panel data would create problems with regards to the

asymptotic properties (Verbeek 2005). The total number of observations is 287. The number of observations per country is limited to 72, with the exception of Germany, where there is one missing observation. Per time unit though, there are only 18 observations (for 18 medicines). This is lower than 30, which would be the absolute minimum number of observations per time period included in the panel. Thus we estimate the country-specific models using instrumental variable regressions. The same instruments are used as in the panel data approach, notably *policy* and *ldist*. The equations estimated per country are as follows (the equation corresponding to equation (19) is not included due to not enough variation for dummy variable *pt* at the country specific level):

$$P^{LS} = \beta_0 + \beta_1 mspt + \beta_2 generics + \beta_3 statins + \beta_4 acei + \beta_5 ppi + \beta_6 aceii + \beta_7 atyp + \beta_8 exr + \sum_{k=9}^{11} \beta_k time + \varepsilon \quad (22)$$

$$P^{PT} = \beta_0 + \beta_1 mspt + \beta_2 generics + \beta_3 statins + \beta_4 acei + \beta_5 ppi + \beta_6 aceii + \beta_7 atyp + \beta_8 exr + \sum_{k=9}^{11} \beta_k time + \mu \quad (23)$$

$$P^{LS} - P^{LS} = \beta_0 + \beta_1 mspt + \beta_2 generics + \beta_3 statins + \beta_4 acei + \beta_5 ppi + \beta_6 aceii + \beta_7 atyp + \beta_8 exr + \sum_{k=9}^{11} \beta_k time + \nu \quad (24)$$

The country specific estimation results of equation (22), which shows the determinants of locally sourced product prices, are in Table 6.10. Parallel trade penetration has no statistically significant effect on locally sourced prices in Sweden

and the United Kingdom, but in Germany and the Netherlands, an increase in the market share of parallel trade appears to have a positive effect on prices of locally sourced medicines. This finding suggests that in these particular countries not only does parallel trade not lead to lower prices, but actually it may encourage price increases. Generic entry has a statistically insignificant effect in all three countries, suggesting that generic competition does not affect originator locally sourced medicine prices in any of the four countries.

Table 6.10 Instrumental Variable Estimation

Dependent Variable: $P_{i,t}^{LS}$	Germany	Netherlands	Sweden	UK
mspt	0.041**	0.102**	0.055	-0.039
	(0.018	(0.048)	(0.025)	(0.034)
generics	-0.150	0.323	-0.680	0.177
	(0.339	(0.385)	(0.476)	(0.352)
statins	1.310**	0.209	-0.081	1.279***
	(0.501	(0.604)	(0.641)	(0.468)
acei	0.457	0.491	-2.178***	0.335
	(0.432	(0.457)	(0.732)	(0.580)
ppi	1.498***	1.520***	-1.792***	1.318***
	(0.418)	(0.482)	(0.642)	(0.454)
aceii			-1.793**	
			(0.697)	
atyp	1.755***	2.464***		2.205***
	(0.416)	(0.500)		(0.465)
time1	0.019	0.231	-0.290	-0.062
	(0.365)	(0.448)	(0.585)	(0.415)
time2	-0.184	0.325	-0.649	-0.113
	(0.357)	(0.493)	(0.623)	(0.413)
time3	-0.215	-0.045	-0.437	-0.067
	(0.366)	(0.442)	(0.609)	(0.423)
constant	-4.013***	-4.689***	-1.207*	-2.931***
	(0.475)	(0.640)	(0.623)	(0.938)
Observations	71	72	72	72
Rsq	0.441	0.131	0.298	
Adjusted Rsq	0.359	0.004	0.197	
F- statistic	4.45	3.09	6.91	0.01

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively.
Standard errors in parenthesis

Equation (23) shows the effects on prices of parallel imported products. Results are shown in Table 6.11. Prices of parallel traded products do not increase as their market penetration increases. The coefficient of *mspt* is statistically insignificant in the results of all four country regressions. Generic entry apparently has a negative and statistically significant effect on prices of parallel traded products in Sweden. Results of the regressions for Germany, the Netherlands and the United Kingdom suggest that generic entry does not affect prices.

Table 6.11 Instrumental Variable Estimation

Dependent Variable: P^{PT}	Germany	Netherlands	Sweden	UK
mspt	0.047*	0.051	-0.006	-0.040
	(0.024)	(0.032)	(0.028)	(0.027)
generics	-0.146	0.253	-1.313**	0.064
	(0.376)	(0.335)	(0.623)	(0.282)
statins	1.070	0.698	0.908	1.246***
	(0.679)	(0.422)	(0.585)	(0.377)
acei	0.528	0.981**	-0.915	0.041
	(0.552)	(0.424)	(0.819)	(0.467)
ppi	1.639***	1.402***		1.311***
	(0.520)	(0.461)		(0.365)
aceii			-0.918	
			(0.815)	
atyp	2.789***	3.326***	1.600**	3.293***
	(0.580)	(0.479)	(0.750)	(0.431)
time1	0.058	0.095	0.230	-0.081
	(0.418)	(0.365)	(0.617)	(0.344)
time2	-0.261	0.147	-0.007	-0.178
	(0.408)	(0.407)	(0.714)	(0.342)
time3	-0.339	-0.377	-0.047	-0.404
	(0.431)	(0.371)	(0.766)	(0.342)
constant	-4.274***	-4.372***	-1.189	-2.776***
	(0.713)	(0.525)	(0.776)	(0.762)
Observations	57	53	46	69
Rsq	0.479	0.501	0.525	0.388
Adjusted Rsq	0.379	0.396	0.406	0.294
F- statistic	7.73	5.91	4.04	7.52

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively. Standard errors in parenthesis

Equation (24) shows the impact of parallel trade and generic competition on the ratio of prices of the locally sourced product and the corresponding parallel traded product (Table 6.12). Of course, observations include only time periods and products at which parallel trade is present, otherwise there would be no particular ratio of locally sourced and parallel traded medicine prices. In none of the country -

specific regressions was the coefficient of *mspt* statistically significant. This finding suggests that parallel trade market penetration does not affect relative prices of locally sourced and parallel imported medicines. This is also an indication that parallel trade does not trigger competition.

Table 6.12 Instrumental Variable Estimation

	Germany	Netherlands	Sweden	UK
Dependent Variable: $P^{LS} - P^{PT}$				
mspt	3.94E-04	-0.001	-0.025	0.002
	(0.004)	(0.005)	(0.017)	(0.005)
generics	0.142**	-0.016	0.345	0.150
	(0.061)	(0.050)	(0.384)	(0.058)
statins	0.062	0.017	0.437	0.022
	(0.110)	(0.063)	(0.360)	(0.077)
acei	0.004	0.025	-0.436	0.288***
	(0.089)	(0.064)	(0.505)	(0.095)
ppi	-0.026	0.012		0.001
	(0.084)	(0.069)		(0.074)
aceii			0.143	
			(0.503)	
atyp	0.030	0.026	0.416	0.005
	(0.094)	(0.072)	(0.462)	(0.088)
time1	-0.004	0.015	0.255	0.013
	(0.068)	(0.055)	(0.381)	(0.070)
time2	0.037	0.019	0.553	0.096
	(0.066)	(0.061)	(0.440)	(0.070)
time3	0.043	-0.031	0.726	0.097
	(0.070)	(0.056)	(0.472)	(0.070)
constant	0.023	0.118	0.241	-0.135
	(0.115)	(0.079)	(0.479)	(0.155)
Observations	57	53	46	69
Rsq	0.234	0.019		0.391
Adjusted Rsq	0.087	0.019		0.298
F- statistic	1.45	0.16	1.03	4.61

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively.
Standard errors in parenthesis

The country specific regressions do provide some insight the effects of parallel trade in each particular country. Nevertheless, the country specific

regressions are subject to limitations compared to the general regressions including all countries, originating from the fact that ordinary least squares are used instead of panel data, and the relatively small number of observations.

6.6.3.3 The Dynamic Model

In order to capture the dynamic effects of parallel trade, we include a lag in the dependent variable. When using panel data, the unobserved panel-level effects are correlated with the lagged dependent variable, making the estimators inconsistent. This can be addressed by estimating a dynamic panel data model using the first-differenced GMM estimator (Arellano and Bond, 1991). However, this estimator may also not perform well if the autoregressive parameters are too large, which is proved to be the case in our model. Therefore, we use the Blundell Bond estimator (1998) which addresses this problem. Another indication of the appropriateness of the Blundell Bond estimator is whether the first lagged dependent variable has a coefficient very close to one.

One lag of the dependent variable is used (P_{t-1}) given the yearly nature of the data and the fact that coefficients can be interpreted as elasticities. This estimation procedure relies on an assumption concerning the initial conditions and provides a framework that enables us to deal explicitly with potential endogeneity in explanatory variables using a set of appropriate instruments. Using panel data in estimating common relationships across countries is particularly appropriate because it allows for the identification of country-specific effects that control for missing or unobserved variables. Unit root tests were performed using simple OLS regressions on their lagged values, which is consistent under the null hypothesis.

Accordingly, the dynamic model can be expressed as follows:

$$P_{i,t}^{LS} = \alpha_i + \beta_0 + \beta_1 P_{i,t-1}^{LS} + \beta_2 mspt_{i,t} + \beta_3 generics_{i,t} + \beta_4 statins_{i,t} + \beta_5 acei_{i,t} + \beta_6 ppi_{i,t} + \beta_7 aceii_{i,t} + \beta_8 atyp_{i,t} + \beta_9 exr_{i,t} + \varepsilon_{i,t} \quad (25)$$

$$P_{i,t}^{LS} = \alpha_i + \beta_0 + \beta_1 P_{i,t-1}^{LS} + \beta_2 pt_{i,t} + \beta_3 generics_{i,t} + \beta_4 statins_{i,t} + \beta_5 acei_{i,t} + \beta_6 ppi_{i,t} + \beta_7 aceii_{i,t} + \beta_8 atyp_{i,t} + \beta_9 exr_{i,t} + u_{i,t} \quad (26)$$

$$P_{i,t}^{PT} = \alpha_i + \beta_0 + \beta_1 P_{i,t-1}^{PT} + \beta_2 mspt_{i,t} + \beta_3 generics_{i,t} + \beta_4 statins_{i,t} + \beta_5 acei_{i,t} + \beta_6 ppi_{i,t} + \beta_7 aceii_{i,t} + \beta_8 atyp_{i,t} + \beta_9 exr_{i,t} + \mu_{i,t} \quad (27)$$

$$P_{i,t}^{LS} - P_{i,t}^{PT} = \alpha_i + \beta_0 + \beta_1 \left(P_{i,t-1}^{LS} - P_{i,t-1}^{PT}\right) + \beta_2 mspt_{i,t} + \beta_3 generics_{i,t} + \beta_4 statins_{i,t} + \beta_5 acei_{i,t} + \beta_6 ppi_{i,t} + \beta_7 aceii_{i,t} + \beta_8 atyp_{i,t} + \beta_9 exr_{i,t} + v_{i,t} \quad (28)$$

Note that as in the static model, the log of the ratio of prices which is the dependent variable, can be written as the difference of the logs of the prices, according to the properties of logarithms. Hence, the dependent variable is $P_{i,t}^{LS} - P_{i,t}^{PT}$.

By adding a lag, we would obtain an inconsistent "within" estimator as both our dependent and our lagged dependent variable are correlated with the country-specific effect. Therefore, we take the first differences of equations (25), (26), (27) and (28), to obtain equations (29), (30), (31) and (32) respectively:

$$P_{i,t}^{LS} - P_{i,t-1}^{LS} = \gamma_1\left(P_{i,t-1}^{LS} - P_{i,t-2}^{LS}\right) + \gamma_2\left(mspt_{i,t} - mspt_{i,t-1}\right) + \gamma_3\left(generics_{i,t} - generics_{i,t-1}\right) + \\ + \gamma_4\left(statins_{i,t} - statins_{i,t-1}\right) + \gamma_5\left(acei_{i,t} - acei_{i,t-1}\right) + \gamma_6\left(ppi_{i,t} - ppi_{i,t-1}\right) + \\ + \gamma_7\left(aceii_{i,t} - aceii_{i,t-1}\right) + \gamma_8\left(atyp_{i,t} - atyp_{i,t-1}\right) + \gamma_9\left(exr_{i,t} - exr_{i,t-1}\right) + \varepsilon_{i,t} - \varepsilon_{i,t-1} \quad (29)$$

$$P_{i,t}^{LS} - P_{i,t-1}^{LS} = \gamma_1\left(P_{i,t-1}^{LS} - P_{i,t-2}^{LS}\right) + \gamma_2\left(pt_{i,t} - pt_{i,t-1}\right) + \gamma_3\left(generics_{i,t} - generics_{i,t-1}\right) + \\ + \gamma_4\left(statins_{i,t} - statins_{i,t-1}\right) + \gamma_5\left(acei_{i,t} - acei_{i,t-1}\right) + \gamma_6\left(ppi_{i,t} - ppi_{i,t-1}\right) + \\ + \gamma_7\left(aceii_{i,t} - aceii_{i,t-1}\right) + \gamma_8\left(atyp_{i,t} - atyp_{i,t-1}\right) + \gamma_9\left(exr_{i,t} - exr_{i,t-1}\right) + u_{i,t} - u_{i,t-1} \quad (30)$$

$$P_{i,t}^{PT} - P_{i,t-1}^{PT} = \gamma_1\left(P_{i,t-1}^{PT} - P_{i,t-2}^{PT}\right) + \gamma_2\left(mspt_{i,t} - mspt_{i,t-1}\right) + \gamma_3\left(generics_{i,t} - generics_{i,t-1}\right) + \\ + \gamma_4\left(statins_{i,t} - statins_{i,t-1}\right) + \gamma_5\left(acei_{i,t} - acei_{i,t-1}\right) + \gamma_6\left(ppi_{i,t} - ppi_{i,t-1}\right) + \\ + \gamma_7\left(aceii_{i,t} - aceii_{i,t-1}\right) + \gamma_8\left(atyp_{i,t} - atyp_{i,t-1}\right) + \gamma_9\left(exr_{i,t} - exr_{i,t-1}\right) + \mu_{i,t} - \mu_{i,t-1} \quad (31)$$

$$\left(P_{i,t}^{LS} - P_{i,t}^{PT}\right) - \left(P_{i,t-1}^{LS} - P_{i,t-1}^{PT}\right) = \gamma_1\left(\left(P_{i,t-1}^{LS} - P_{i,t-1}^{PT}\right) - \left(P_{i,t-2}^{LS} - P_{i,t-2}^{PT}\right)\right) + \gamma_2\left(mspt_{i,t} - mspt_{i,t-1}\right) + \\ \gamma_3\left(generics_{i,t} - generics_{i,t-1}\right) + \gamma_4\left(statins_{i,t} - statins_{i,t-1}\right) + \gamma_5\left(acei_{i,t} - acei_{i,t-1}\right) + \\ \gamma_6\left(ppi_{i,t} - ppi_{i,t-1}\right) + \gamma_7\left(aceii_{i,t} - aceii_{i,t-1}\right) + \gamma_8\left(atyp_{i,t} - atyp_{i,t-1}\right) + \\ \gamma_9\left(exr_{i,t} - exr_{i,t-1}\right) + v_{i,t} - v_{i,t-1} \quad (32)$$

By estimating equations (29), (30), (31) and (32), we would not obtain a consistent estimator because $P^{j}_{i,t-1}$ and $\varepsilon_{i,t-1}$ are correlated (where *j* refers to originator or parallel imported prices). Thus we will use $P^{j}_{i,t-1}$ - $P^{j}_{i,t-2}$ as an instrumental variable by making use of $P^{j}_{i,t-2}$. The latter is correlated with the former, but is not correlated with the lagged error term. The effect of generic entry is insignificant.

Estimation results of equations (29) and (30), both with the price of locally sourced medicines as dependent variable, are in Table 6.13. For equation (29), with parallel trade penetration as an explanatory variable, the first lag of the dependent variable does not have a statistically significant coefficient. The same holds for *mspt*. Thus, similarly to the static model estimation results, there is no evidence that

parallel trade penetration affects prices of locally sourced medicines. Regarding results of equation (29), the lagged variable does have a statistically significant effect. The coefficient of *pt* is insignificant, indicating, once again, that prices of locally sourced medicines are not affected by the presence of parallel trade. The effect of generic entry is insignificant.

Table 6.13 Blundell-Bond Dynamic Panel Data Estimation

Dependent Variable: $P_{i,t}^{LS}$

L1.	-1.546	-1.252**
	(0.971)	(0.668)
mspt	-0.022	
	(0.020)	
pt		-0.016
		(0.567)
generics	-0.009	0.088
	(0.201)	(0.147)
statins	11.337	1.930
	(16.514)	(12.984)
acei	-83.859	-12.081***
	(95.105)	(4.646)
ppi		-3.309
		(3.429)
aceii	-132.300	
	(165.883)	
atyp	-76.944	-15.232
	(87.610)	(12.212)
ln_exr	-7.561	-1.907
	(9.950)	(6.238)
time1	0.331**	0.332**
	(0.169)	(0.143)
time2	0.124	0.137
	(0.109)	(0.087)
constant	33.266	-1.578
	(44.193)	(1.176)
Observations	215	215
Wald chi sq	81.70	292.90

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively. Standard Errors in Parenthesis

Equation (31) is a dynamic model exploring price determinants of parallel traded products (results are in Table 6.14). The lagged variable is insignificant, and so is the coefficient of the variable indicating the market share of parallel trade. Therefore, the results of the dynamic model are in accordance with the findings of the static models which suggest that prices of parallel traded products do not change as parallel trade market penetration takes place. Also, generic entry does not appear to affect the price of parallel traded products, as the coefficient of *generics* is negative but insignificant.

Table 6.14 Blundell-Bond Dynamic Panel Data Estimation

Dependent Variable: $P_{i,t}^{PT}$

L1.	-0.012
	(0.638)
mspt	-0.009
	(0.013)
generics	-0.328
	(0.145)
statins	13.246
	(9.469)
ppi	-50.525
	(37.177)
aceii	47.766
	(31.333)
atyp	-14.024
	(9.741)
ln_exr	10.209
	(6.940)
time1	0.099
	(0.070)
time3	0.038
	(0.088)
constant	6.373
	(6.676)
Observations	158
Wald chi sq	203.92

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively. Standard Errors in Parenthesis

Table 6.15 shows the estimation results of the dynamic model with the ratio of locally sourced and parallel traded prices as dependent variable (equation (32)). According to the results, parallel trade market penetration has no effect on the relative prices of locally sourced and parallel imported medicines. Generic entry also has no effect on relative prices.

Table 6.15 Blundell-Bond Dynamic Panel Data Estimation

Dependent Variable: $P_{i,t}^{LS} - P_{i,t}^{PT}$

L1.	0.164
	(0.446)
mspt	0.008
	(0.005)
generics	0.298
	(0.123)
statins	5.651
	(9.551)
acei	13.587
	(28.118)
ppi	7.135
	(21.865)
atyp	16.135
	(35.104)
ln_exr	-2.759
	(6.145)
time1	-0.023
	(0.047)
time3	-0.051
	(0.059)
constant	-9.016
	(19.626)
Observations	158
Wald chi sq	211.81

*,**,*** refer to statistical significance at 10%, 5% and 1% level respectively. Standard Errors in Parenthesis

The empirical analysis included static and dynamic models in order to study whether parallel trade market penetration (or presence) affects prices of locally sourced products, parallel imported products or the ratio of prices. We do not find any empirical evidence from any model that prices of locally sourced products decrease following parallel trade product entry or market penetration. This suggests that parallel trade does not trigger competition with originator locally sourced medicines. Results also suggest that prices of parallel imported products do not increase as parallel trade market share increases. Finally, the ratio of prices remains unaffected by parallel trade penetration. Results are robust and similar in all specifications. These findings suggest that parallel trade does not trigger competition in branded medicine markets. Some weak evidence does exist though, that prices of parallel imported products may be pushed downwards as a result of generic entry, which indicates that in off-patent markets parallel traders may choose to compete against generic providers.

6.7 Discussion and Policy Implications

The game theoretic approach suggests that parallel trade does not trigger competition, so the locally sourced products do not demonstrate a price decrease as a result of parallel trade. Normally, prices of parallel traded products are also priced at the same level as the locally sourced product. However, in the presence of particular policies (sharing the price difference with pharmacists and patient co-insurance), prices of parallel traded product may deviate downwards. Descriptive statistics show that in the absence of policies favouring parallel trade, the locally sourced and the parallel traded product are priced at the same level, with some exceptions in the presence of generic competitors. The previously mentioned policies, however, do

lead to a price spread between the two products. The econometrics analysis confirms that prices of locally sourced products do not decline due to parallel trade, and that in general there is upward price convergence. Similar results are found from the employment of a dynamic model. With regards to country specific results, there is no evidence from any of the four study countries that locally sourced prices decline due to parallel trade.

Findings are different than what Ganslandt and Maskus (2004) found in their study. The authors had suggested that prices of locally sourced products in Sweden decrease as a response to competition from parallel trade. Linnosmaa et al (2003) suggested that savings from parallel trade are low in Finland because parallel trade has not intensified competition, which is an indirect implication from our findings. This is also what Kanavos and Kowal (2008) and Kanavos and Costa-Font (2005) suggest in their studies.

This study has shown that policies favouring parallel trade do not help achieve savings for health insurance when parallel traded products are priced at the same level as locally sourced products. Policies which lead to lower parallel traded products may indeed lead to some direct savings when dispensing parallel traded products, but there is no evidence from this study that savings occur when locally sourced products are dispensed, because their price does not change as a response to parallel trade. Also, in some cases although the parallel traded product is cheaper than the locally sourced one, generic products are present which could address the cost containment concerns at least as well as a parallel traded product. Regulators should be cautious when taking measures which encourage parallel trade, as in the long run the effects of parallel trade may be adverse.

We have showed theoretically that parallel trade may decrease investment in R&D and social welfare in general. The manufacture is the agent who actually invests in R&D in order to develop the molecule. The parallel trader simply buys the product in one market and sells it in another, making a profit from arbitrage. Even when the parallel imported product is priced at lower levels than the locally sourced product, gains still occur for the parallel trader. These profits are also lower profits for the manufacturer. The manufacturer loses the price difference between the importing and the exporting country. As the manufacturer's profits are invested in R&D, parallel trade means lower funds available for R&D and fewer innovative medicines in the future. Therefore, although parallel trade may lead to some savings in some countries with a positive price spread between the locally sourced product and the parallel traded product, in the long run the overall impact of parallel trade on social welfare may be negative.

The European situation has some relevance for the US policy environment, in light of the Dorgan – Snowe Bill (Pharmaceutical Market Access and Medicine Safety Act), that was introduced to Congress in January 2007. Key components of the Dorgan-Snowe Bill put forward at that time included a selection of permitted countries from where to import prescription medicines, the precise identification of the medicines that would qualify for importation, requirements for the registration of importers and exporters, labelling requirements, tracking and tracing requirements, and trader fees (capped at 2.5% of the price of the medicines imported annually) payable to the US government, among others.

Although this legislation has not been passed by the previous Congress, it is likely that similar legislative acts may be debated in the future. The relevance of the findings in this study are compelling for such debates. This analysis has showed that

parallel trade has not lead to downward price convergence in the pharmaceutical market and that competition is not enhanced due to parallel trade. Therefore, US policy makers should not expect that lifting barriers for parallel trade in the United States would lead to lower pharmaceutical prices or help contain health costs. Some savings would occur directly by dispensing parallel traded medicines, but this would not trigger competition or lead to lower prices for locally sourced products, which actually represent the largest part of the market. Importantly, prescription medicine re-importation in the US would in reality involve the importation of other countries' medicine price controls into the United States, and hence a weakening of intellectual property rights within the US.

6.8 Conclusions

We have studied the competition aspect of parallel trade both theoretically and empirically. The game theoretic approach shows that the manufacturer has no incentive to deviate from his initial price when parallel traded products appear in the market. The pricing strategy of the parallel trader should also be that of following the price of the locally sourced product and setting the price at that level. Things may change in the presence of particular policies though. When insurers share the price difference between locally sourced and parallel traded products with pharmacists, there is a strong incentive on behalf of the pharmacists to demand prices for parallel traded products which are lower than those of locally sourced products, as this directly generates profits for them. Co-payments create pressure on parallel traders to set prices at a lower level than locally sourced products and the co-paying consumers benefit from this price spread. Quotas lead to an incentive for pharmacists to demand parallel traded products at any price up to the level of that of

the locally sourced product as they are penalized if the do not reach the quota. But if the quota is not high enough and is reached easily, it may actually have no effect. Finally, clawbacks lead to demand of parallel products on behalf of the pharmacists. This leads to higher unofficial discounts for pharmacists rather than to lower prices.

Empirical data on prices of locally sourced and parallel traded products show different price spreads (if any) in different countries. In the United Kingdom in almost all cases the parallel traded products are priced at the same level as the locally sourced product. This is probably the result of the absence of relevant regulation, which leads to the initial Nash Equilibrium which was discussed in the game theoretic section of the study. In the Netherlands, price spreads are positive in all cases, reflecting the effect of sharing the price spread with the pharmacists on prices. In Sweden, in almost all cases the price spread is positive. This could be due to the presence of patient co-payments as a proportion of the price of the medicine. In Germany, some parallel imported medicines are priced at the same level as the locally sourced ones, while others are priced at lower levels. This could be the result of the presence of both quotas (which work for only a part of the market) and co-payments which are larger, the higher the price of the product.

The econometric analysis shows that the prices of locally sourced products are not affected by parallel trade presence or penetration and that any downward movement of the prices are a result of genericization rather than due to parallel trade. In other words, parallel trade does not spark competition between the parallel imported medicine and the locally sourced one.

The data on price spreads in combination with the results of the econometric analysis lead to the conclusion that parallel trade does not trigger competition in the pharmaceutical market and prices of locally sourced products do not decline due to

parallel trade, thus no savings occur for health insurance by dispensing locally sourced products due to parallel trade penetration. Thus parallel trade does not lead to indirect saving. Savings only occur directly by the dispensing of parallel imported product, only if they are priced at a lower level than the locally sourced product. This means that in the United Kingdom, with a few exceptions, there are no savings, (either direct or indirect) for health insurance due to parallel trade. In the Netherlands, Sweden and Germany some savings occur due to the price spread, but these occur only when parallel imported medicines which are cheaper than locally sourced medicines are dispensed.

7. Conclusions and Policy Implications

Pharmaceutical markets do not have the same dynamics as regular markets. Regulation, third- party payers and patents make market dynamics unique. Existing industrial organization models and empirical evidence from other markets do not always apply to this special type of market. This thesis has considered three important aspects of competition in pharmaceutical markets in order to fill in gaps in the literature.

First, previous research had not examined the impact of generic entry on originator prices in markets subject to some form of regulation. Second, the impact of generic entry on a possible switch in consumption between different molecules of the same therapeutic class was unknown. Third, parallel trade had not been studied from a holistic approach. Although a previous study had suggested that parallel trade does not lead to decreases in prices of locally sourced products (Kanavos and Vandoros 2010), the behaviour of rational agents involved in the pharmaceutical market and why a particular equilibrium is reached had not been explained previously, and no study provided a combination of empirical and theoretical models to explain market dynamics in the presence of parallel trade.

7.1 Summary of the Dissertation's Contribution

7.1.1 Generic entry and the effect on originator prices

The first aspect of competition studied in this thesis is the impact of generic entry on the prices of branded products which go off patent. Patent expiry, triggering generic entry, transforms a monopolistic market into a market with a number of competitors. Economic theory suggests that the introduction of competition in a

market leads to a decrease in prices among all competitors, unless there are differentiation issues impacting price. Previous research had pointed out that in unregulated pharmaceutical markets prices of originators increase rather than decrease post patent expiry. This thesis examined whether the so-called "generics paradox" holds in markets subjected to some form of regulation. The econometric analysis showed that even in markets subjected to forms of regulation, prices of branded products increase rather than decrease post patent expiry. This finding suggests that there is little price competition between the originator and generic products of the same molecule. Consumers who continue to purchase the originator product post generic entry are the most brand loyal ones; hence their price elasticity is low. The originator producer is willing to give up a further part of his market share by increasing his price. As these consumers are irresponsive to price, the total revenue of the originator producer will increase. The generics paradox indicates that savings occur post patent expiry only through the dispensing of generic products. Dispensing originator products does not lead to any savings due to a lack of price competition in the market.

7.1.2 Competition within therapeutic class

The second aspect this thesis examined is competition between drugs in the same therapeutic class. The thesis investigated whether there is a switch in consumption from a molecule which goes off patent towards molecules from the same therapeutic category which are still patent protected in the case of a therapeutic class comprising products that are considered to be close substitutes. Conceptually, it is shown that a monetary unit invested in advertising or promoting an in- patent product has greater returns than a monetary unit invested in advertising or promoting

an off- patent product. Consequently, it is more efficient for the manufacturer to relax promotion efforts for the off-patent originator drugs and focus on other products, usually from other therapeutic categories, which are patent protected and generate higher profits. This causes a shift towards molecules within the same therapeutic class which are still patent protected, whose manufacturers advertise more intensively than the off- patent drug. Promotion of the originator product has a spillover effect on generic drugs of the same molecule. Post patent expiry generics gain a large market share of the molecule, and volume of the off –patent originator product will decrease, as well as the total market share of the molecule (originator and generic). Hence this analysis examined the effect of patent expiry on total volume of the molecule, including both originator and generic volume.

The econometric analysis showed that post patent expiry there is a gradual decrease in the relative volume of the off- patent molecule over time compared to the volume of the in- patent drugs of the same therapeutic class. This part of the thesis showed that there is within-class competition present in pharmaceutical markets and a switch from off-patent products to in-patent products of the same therapeutic class. As the in- patent molecules do not have generic alternatives, this switching in consumption leads to increased health costs for health insurers.

7.1.3 The impact of parallel trade on medicine prices

The third and final aspect of competition examined in this thesis was the impact of parallel trade on pharmaceutical prices. The analysis explored whether manufacturers of locally sourced products compete in price against parallel traded products. Governments in importing countries often regard parallel trade as a cost containment mechanism and have adopted policies promoting the dispensing of

parallel traded products. Parallel trade could help reduce costs if either the parallel traded products are cheaper than the locally sourced ones, or if they trigger competition, forcing locally sourced products to lower their prices as a response to the presence of parallel trade. The game theoretic approach showed that in the absence of regulation promoting parallel trade, the Nash Equilibrium is that the parallel trader sets prices of the imported product at the same level as the locally sourced product and the manufacturer does not lower his price as a response to parallel trade. The outcome of this game is upward price convergence. In the absence of policies promoting parallel trade, no savings occur for health insurance, but the profits of the innovative pharmaceutical manufacturers decline. In the presence of particular policies promoting parallel trade, prices of imported products may be set at a lower level than the locally sourced products, but the manufacturer does not engage in a price war, leaving his price unchanged. Other policies do not provide any incentive for the parallel trader to set a price lower than that of the locally sourced product.

Descriptive analysis showed that prices converge in the absence of policies promoting parallel trade and a price gap occurs in the presence of some of those policies. The price gap is significant for off- patent drugs, possibly because the parallel traders choose to compete against generic products. The econometric results showed that there is upward price convergence towards the price of the locally sourced originator drug. This study showed that parallel trade is not a source of competition in pharmaceutical markets, and although the product is homogenous, in aggregate terms there is no price competition between the manufacturer and the parallel trader. In some cases though, in which the product is subject to generic entry, there may be price competition between the parallel trader and generic

manufacturers rather than with the locally sourced originator brand. The findings suggest that policy makers should be cautious when encouraging parallel trade, as savings to health insurance do not always occur.

7.1.4 Overall summary

Overall, this thesis has shown how competition affects in- patent products in different regulation, geographical and competition contexts. It appears that there is no price competition between originators and their generic alternatives, or between locally sourced products and parallel traded ones. Quantity competition though seems to be present between drugs of the same therapeutic class and there is a within-class switch in consumption post patent expiry.

7.2 Impact on Stakeholders

All three studies have important implications for pharmaceutical market stakeholders. This section discusses the impact of the findings of each study on health insurance and policy makers, the pharmaceutical industry, generic producers, parallel traders and patients.

7.2.1 Health Insurance and Payers

Health and pharmaceutical care costs are rising and as cost containment and efficiency in prescribing remain a challenge for policy makers, it is very important for them to understand pharmaceutical market dynamics. The three studies in this thesis have analyzed very important aspects concerning the reactions of the pharmaceutical industry to different market environments and policy situations.

Different cases require different action on behalf of policy makers, in order to achieve the goal of cost containment, without lowering treatment quality.

The generics paradox study suggests that generic entry does not trigger price competition between the originator drug and the generic versions. Originator prices increase (depending on the intensity of regulation) or remain constant post patent expiry. Thus there are no savings from generic entry by dispensing originator products, as competition does not necessarily lead to a decrease in originator prices. There are several reasons why this may happen. Primarily, post patent expiry, a large part of consumers switch to generic products. The part who continue to consume the branded product are the ones with lower price elasticity. If demand is inelastic, the originator producer can increase profits by increasing the price. The percentage decrease in consumers will be lower than the percentage increase in price, and the total revenue will be larger than before increasing the price. This is closely linked with brand loyalty, as more brand loyal consumers demonstrate lower price elasticity levels. Another reason for an increase in originator prices is competition at the presentation level. Not all producers market the same presentations, so at presentations with fewer competitors prices can be higher than in other with higher levels of competition. Fixed or low co-payments, linked to the originator product may be another predictor of the generics paradox, implying patient moral hazard. In order to achieve savings from patent expiry, generic products have to be dispensed instead of the originator drug. Generics are cheaper and their price drops gradually as their market share increases and further entry intensifies. Therefore, genericization has to be swift post patent expiry and policies helping generic market penetration have to be implemented and vigorously enforced. Policies can target different aspects of the drug decision-making process. Physician prescribing can be

targeted, through the implementation of compulsory generic or molecule prescribing (rather than brand name prescribing) and enforcement through the use of IT systems on a real-time basis. Physician budgets can also encourage generic prescribing, provided they do not create disincentives to cost-saving or indirectly lead to multi-tier systems. Pharmacy-level policies are also hugely important and complement physician-level policies. In particular, substitution policies allow pharmacists to substitute a prescribed branded product with its generic alternative. Flat fee per prescription eliminates the incentive to dispense more expensive drugs, as opposed to progressive margins, while regressive margins for pharmacists in principle provide an incentive to dispense cheaper generic products rather than branded ones, depending on the design of the regressive margin scheme and the price difference between the alternative products. Finally, patient information is vital in the effort to contain costs. Patients must be informed that generic products are of the same quality as branded drugs, in other words quality of care is just as good, therefore, they should not hesitate to trust a generic drug instead of the corresponding branded one. Reference pricing in principle encourages generic dispensing, as when patients wish to purchase a branded product or a highly priced generic they will have to pay the difference out of pocket.

Policies targeting generic prices can help reduce costs further. Reference pricing and price caps are popular policy measures in many European Union countries, but their effectiveness over time may be questionable in terms of helping reduce prices further and faster. Recently, tendering for out-patient drugs has been implemented in Germany and the Netherlands. This may be a further step towards cost containment, although there is a possibility that tendering systems may drive out competition in the long run, leading to relatively higher prices in the future.

The second study (switching post patent expiry) shows that in some cases there is a switch in consumption from a molecule that goes off- patent towards other molecules in the same therapeutic class that are still in- patent. Evidence from ACE Inhibitors shows that after captopril (the first ACE inhibitor) went off- patent, the ratio of total captopril volume (including the originator and generics) over the volume of all other in-patent ACE inhibitors declined. Simply, consumption was largely switched from the off- patent product (captopril) to other ACE Inhibitors which were still in- patent. Similar findings hold for the second and third ACE inhibitor that faced generic entry (enalapril and lisinopril respectively). There is evidence of a diversion of consumption from an off- patent molecule to in-patent molecules. This also suggests that there is substitutability among ACE I alternatives, which is also supported by the clinical literature. The effects on health insurance expenditure on pharmaceuticals can be significant. In off-patent markets, the implementation of appropriate generic policies, results in large savings for payers. When in-patent originator drugs though are prescribed, a cheaper generic alternative is not available, so health insurance has to reimburse the expensive originator. These findings are alarming for health insurance, but appropriate policies can help face these problems. A solution is to make the off- patent drug first line treatment. This will make physicians prescribe the off- patent drug first, and only prescribe other drugs of the same class if necessary but it does not imply solid evidence on substitutability among alternatives within the therapeutic or product class. This has to be combined with other policies promoting generic penetration. Such policies should target physician prescribing and pharmacy dispensing.

Another measure that can help address this switch in consumption is setting a reference price at the class level (instead of the molecule level). This reference price

could be set at the average price of the cheaper generics of the off- patent molecule. There is evidence that this is happening in classes such as ACE inhibitors which different molecules are considered to be close substitutes. Both the Netherlands and in Germany are pursuing such policies to a degree, but they are, of course, contestable because of the extent to which they can be generalised across other therapeutic categories which may comprise drugs that are not close substitutes. Dispensing in- patent products of the same class will be subject to a co-payment on behalf of the patients. The manufacturers of the in- patent products will also have the option to lower their price at the reference price level and be covered by health insurance, but this is highly unlikely to happen, as shown in the generics paradox study (study 1), since originator products do not compete on price with generics.

Study 3 suggests that parallel trade does not trigger competition between locally sourced and parallel traded products. The prices of locally sourced products remain unaffected by parallel trade, while parallel traders price their products at the same level as the locally sourced drug in most cases, at least for in-patent drugs. Overall, there appears to be an upward rather than downward price convergence. This means that parallel trade does not lead to indirect savings by triggering price competition, as the price of the locally sourced product remains unchanged. Savings may occur from the parallel traded products in some countries and for particular drugs. Often this concerns off-patent drugs, so savings do not really occur, as cheap generic alternatives can be dispensed instead. Further, parallel trade can be perceived as a threat to R&D and the development of future drugs, as manufacturers of innovative originator products lose part of their profits. Parallel trade for them is equivalent to selling their product in the high price market at the prices of the low price market. This threat to innovation become more concerning when taking into

account the decreasing number of new drugs introduced on the market, due to tighter regulation and the relatively high cost of developing new medicines which target only a relatively small group of patients (Taylor 2003). Parallel trade can make this problem even more severe.

Clearly, some policies do encourage parallel trade. These include sharing savings with pharmacists, implementing quotas, co-payments and clawbacks. The first two measures are implemented explicitly to encourage parallel trade. The latter two are implemented in order to encourage generic dispensing, as well as provide an incentive to dispense parallel traded products. When health insurance shares part of the savings with pharmacists or when co-payments are present, there is an incentive for parallel traders to price the imported product at a price which is lower than that of the locally sourced product. The size of the price difference depends on the bargaining power of all sides involved, namely the pharmacist, the wholesaler and the patients' elasticity of demand. Quotas and clawbacks do not provide any incentive for the parallel trader to price the product at a lower level than the locally sourced drug. In the absence of policies promoting parallel trade price converge upwards occurs for in-patent products. Thus, some savings can occur for health insurance when potential savings are shared with pharmacists or when co-payments are present, but these savings are small compared to total pharmaceutical expenditure (Kanavos and Kowal, 2008). Policy makers should be skeptical when it comes to encouraging parallel trade as it may lead to some savings in some countries and under certain circumstances, but are unlikely to engage en masse on a rule of thumb.

7.2.2 Originator Pharmaceuticals

As these studies examine branded pharmaceutical markets, there are important implications for the research-based pharmaceutical industry.

The study on the generics paradox (study 1) has shown that the producer of the originator drug, has the incentive to increase prices post generic entry. This is a special case of competition, as the introduction of direct competitors leads to higher prices, although economic theory suggests that more competition leads to lower prices. The answer to this paradox lies in the presence of brand loyal patients, or brand loyal physicians, who generate demand on behalf of patients. As generics steadily increase their market share and take up most of the market, the patients who insist on purchasing the branded version of the particular drug are the most brand loyal ones. Lack of alternatives may also be the case. These patients are the least respondent to increases in price, thus demand is inelastic for these patients. As a result, when the branded product's price increases, relatively few patients switch to a generic alternative and total revenue increases for the branded producer. Our findings are based on prior actual behaviour of drug manufacturers, so manufacturers are aware of the price elasticity of brand loyal consumers and take advantage of it.

Study 2 suggests that there is a switch in consumption from drugs which face generic entry towards drugs of the same therapeutic class that are still in- patent. This finding is more alarming for generic manufacturers rather than for the innovative pharmaceutical industry. This switching effect is most likely due to a drop in advertising and promoting efforts on behalf of the producer of the product which went off patent, as post patent expiry they lose most of the market to generic producers, and would rather focus on other drugs which the company produces. This

is a good chance for other pharmaceutical companies to step in and try to attract part of the off patent molecule's market share.

The game theoretical approach of study 3 suggests that the best strategy for the manufacturer of the branded products is not to compete in terms of price with the parallel trader. The parallel trader has the flexibility to reduce his price down to the level of the price in the exporting country, which is the price at which he buys the product, plus the per- unit transportation cost. This is his break- even point. The parallel trader will respond to any decreases in the manufacturer's price with a decrease in price on his behalf, until the price reaches his break- even point. If the price decreases further he will have to leave the market. For the manufacturer, getting involved in a price war will make prices eventually decrease down to the break- even point of the parallel trader. Taking into account the relatively small market share of the parallel trader, this strategy will most likely lead to a decrease in total revenue for the manufacturer. Further, competing against a parallel trader will make parallel trade a cost-containment mechanism for health insurance and policy makers will take more aggressive measures in order to encourage this. In any case, the game theoretic approach shows that the manufacturer is better off "ignoring" the parallel trader rather than competing against him in terms of price.

7.2.3 Generic manufacturers

The generics paradox study shows that generic manufacturers do not face price competition from the producer of the originator product. The originator's price increases post patent expiry, in an effort to maximize profits from the brand loyal consumers, which are least responsive to price changes. This leads to an even larger market share for generic producers. This is a positive fact for generic producers, as

they enjoy larger revenue in total, without having to lower the price further. The fact that there are many generic producers though forces them to compete against each other for market share. The presence of regulation can provide an equilibrium point for the producers' price. A reference price can act as a point at which generic prices converge, without any explicit collusion between companies. The same can happen with price caps. In any case, generics have to compete against one another and can ignore the pricing strategy that the originator producer follows, as he may not choose to compete against generics. Competition between generics can be fierce though, and given the large number of producers and the low unit cost of production, it can lead to very low prices.

Findings from study 2 (switching post patent expiry) are alarming for generic producers. This study suggests that there is a switch in consumption from the product that goes off patent towards other in-patent products from the same therapeutic class. This leads to a drop in total volume of the product that goes off patent, or an increase which is disproportionate compared to the increase in the volume of in-patent drugs of the same class. The implications for generic producers are very important: as generics gain a large part of the market post patent expiry, this switch towards in patent drugs is a great threat to their presence on the market over the longer term and may lead to exit due to insufficient market share.

Findings of study 3 are on parallel trade of originator drugs so in general there are no direct implications for generic producers although this study does provide some information which can be of interest to generics. It appears that prices of parallel traded products that are off patent are significantly lower than the locally sourced product. This does not appear to happen to prices of in-patent drugs, which converge upwards towards the locally sourced price. This can be an indication that

parallel traders compete against generic drugs and set lower prices in order to possibly attract part of their market share. Further research has to be conducted on this complex issue before reaching conclusions, but if this indeed holds, it is a threat to generic producers.

7.2.4 Parallel traders

Study 3 has direct implications for the behaviour of parallel traders. The game theoretic approach shows that the best strategy for the parallel trader is to set the same price as that of the locally sourced originator product. Any downward deviation could trigger a price war that will make the parallel trader worse off and may force him out of the market. Even if the originator manufacturer does not lower its price in response to the parallel trader's lower price, a price lower than that of the locally sourced originator product will lead to lower profits, given the fact that quantities imported by parallel traders are in the majority of cases limited (as quantities in the exporting markets are limited) and that they manage to sell all quantities they import. Besides, parallel trade generates profit through arbitrage involving little risk, and parallel traders have no incentive to jeopardize their returns by engaging in a price war with originator manufacturers. Thus, the game theoretic approach shows that the optimal pricing strategy for the parallel traders is setting the price at (or close to) the locally sourced drug's level.

7.2.5 Patients

Patient care is not only about affordability and availability of safe and efficacious medicines, but also about costs, as they indirectly pay health costs via

their contributions or taxes and directly pay copayments. Patients paying contributions in practice care little about the costs of their personal treatment for a specific condition as overall spending on this is low, unless copayments are high and structured in a particular way to encourage one type of drug vs another (e.g. brand vs. generic). Patients do care about total health expenditure levles though, as higher expenditure could mean higher taxation (for tax-based systems) or higher contributions (for insurance-based systems). Alternatively, the quality or quantity of health services may decrease. Consequently, patients are concerned about health costs rising, either directly or indirectly due to the threat of increased taxation or contributions or lower quality services. Therefore the implications discussed in the section concerning health insurance and policy makers also apply to patients.

The generics paradox analyzed in study 1 highlights the importance of patient information, particularly within the context of doctor - patient relationship, but also, increasingly, in the context of pharmacist - patient interaction. Patients must be aware of their alternative choices. Currently, patients have access to much more information than they had in the past, so they can participate in decision making along with their physician, but are also subject to misleading information from various sources. In an environment where direct to consumer advertising for medicines is not allowed, it is very important for decision makers to provide reliable, validated and comprehensive information on diseases and treatments. This will not only make patients feel more confident, less confused and allow them to discuss treatments with their physicians, but also help contain costs through wider generic prescribing, acceptance and use.

7.3 Limitations

The three studies in this thesis are not without limitations. The IMS data used for the empirical analysis of all three studies is 98% accurate, according to IMS itself (IMS 2002). This is a high rate of reliability, but it is still not 100% accurate, and findings are subject to this limitation. In general though, the IMS database is the only and most commonly used database for the analysis of pharmaceutical market dynamics, from an intertemporal and comparative perspective.

Another limitation is that some explanatory variables were excluded from the econometric models due to multicollinearity. Multicollinearity does not bias coefficients of other non-collinear explanatory variables, or the direction of changes of the explanatory variables suffering from multicollinearity. However, it can influence the coefficients of the collinear coefficients, thus making the interpretation of the magnitude of changes impossible. Dummy variables are often subject to multicollinearity, and as our models included a significant number of such variables, the model specification had to be determined with great caution. Therefore, in order to avoid multicollinearity problems, some variables were not included in the empirical models. Nevertheless, this exclusion is not thought to have affected the conclusions and policy recommendations of the three studies.

Endogeneity problems in econometric estimations were addressed with the use of instrumental variables. All instruments were tested to determine if they are suitable for each case, and were proved to be strong and appropriate. However, no instrument can be absolutely perfect, due to the endogenous and the (at least weak) interactive nature of almost any variable surrounding economic agents and markets.

In addition, the impact of important variables used in conceptual frameworks in studies 1 and 2 could not be tested empirically because of the fact that advertising data on particular drugs is not available and brand loyalty is difficult to quantify.

Study 2 (switching effects post patent expiry) provides empirical evidence from only one therapeutic class (ACE inhibitors). Findings concern this particular class and any generalizations to other classes should be subject to interchangeability across molecules of the same class.

Finally, the empirical analysis in study 3 does not use discounts provided by parallel traders in the empirical analysis, because such discounts are unofficial and undeclared, and therefore, cannot be captured. As these discounts are not publicly available, it is not possible to pursue empirical research taking the actual discount levels into account. Nevertheless, the model used reflects the effects of parallel trade on public prices which are reimbursed by health insurers and, therefore, the findings are reliable.

7.4 Further Research

This thesis has studied three very important topics related to market dynamics in pharmaceutical markets and in different regulatory and geographical contexts. Additional research can bring these issues further.

With regards to study 1 (the generics paradox revisited), future research could use data from heavily regulated markets in order to determine if the generics paradox holds in even more rigid regulatory environments. Data from France, Spain, Italy or elsewhere would provide further insight into this phenomenon, as the countries included in the generics paradox study in this thesis have elements of flexible pricing.

Future research on switching within therapeutic class could consider a wider range of therapeutic classes, in order to examine whether this finding holds for other drugs, possibly with lower levels of substitutability. Research can also be conducted with regards to possible consumption switching across different therapeutic classes (e.g. from ACE I to ACE II inhibitors, or from SSRIs to SNRIs). Also, taking discounts into account (although practically very difficult) would be useful for an in-depth analysis of incentives and games between parallel traders and pharmacists.

Another limitation is the use of instrumental variables, which are used to address endogeneity problems. Instruments used have been tested and appear to be good instruments, but the choice of a perfect instrumental variable is always challenging.

Finally, research on parallel trade could include a more detailed model with data on generic prices and study competition across molecules when all options are available (originator, parallel traded and generic) in a prescription market. Considering all aspects of the market and focusing on parallel trade of off- patent drugs would provide valuable insight into this controversial topic.

This PhD thesis has analysed three very important aspects of pharmaceutical markets. Using theory and empirical evidence it has studied in depth how market players react in three different situations and how prices and market shares evolve. Findings provide valuable policy implications and set a framework for further research in the field. In an environment of rising health costs, it is very important that policy makers consider the findings of such studies when implementing pharmaceutical policies. In any case, understanding market dynamics and

determinants of competition can help shape the direction and intensity of supply and demand-side policies.

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Appendix

Pricing and Reimbursement in Outpatient Prescription Drug Markets.

The Appendix provides an overview of the main pharmaceutical policies in the seven countries studied in this thesis (Denmark, France, Germany, Netherlands, Norway, Sweden and the United Kingdom). This is based mostly on information from the PPRI country profiles (2007 and 2008) by ÖBIG, Kanavos and Gemmill (2005) and Espin and Rovira (2007).

Table A.1 Overview of Pharmaceutical Policy Measures in Seven European Countries, 2007

	DK	FR	GER	NL	NO	SE	UK
Reference pricing	X	X	X	X			
therapeutic clustering			X	X			
Mandatory generic substitution	X		X			X	
Optional generic substitution		X		X	X	X	
Generic price controls		X			X	X	X
Regressive pharmacy markups	X	X			X	X	
Profit controls							X
clawbacks			X	X			X
Tax-funded health system	X				X	X	X
Contribution funded health system		X	X	X	X		
Use of CEA	X			X	X	X	X

A.1 Denmark

In principle, prices of pharmaceuticals are free in Denmark. However, products reimbursed by health insurance are subject to regulatory interventions. International reference pricing applies for originator in-patent medicines.

Reference pricing was implemented in Denmark in 1993. Drugs are grouped at the molecule level and the price of the cheapest is determined as the reference price, which is the price that health insurance reimburses. If the physician explicitly prescribes a product whose price exceeds the reference price, the price difference must be covered by the patient.

On the demand side, wholesale margins are negotiated between wholesalers and pharmaceutical manufacturers, as they are not regulated. Pharmacy mark-ups were regulated and were determined by a formula, depending on the price of each product. This was a function of the price of the product, a fixed fee and a conscription percentage. This involved indirect profit controls for pharmacies, which were negotiated every two years and led to the determination of the formula based on which their margins were calculated. However, this system changed in 2007 in order to eliminate any incentives that pharmacists had to dispense more expensive products. According to the new formula used, pharmacists gain 8.8% of the pharmacy purchase price plus a fixed fee. Pharmacists are allowed to receive discounts by the wholesalers. VAT for pharmaceuticals is at the standard 25% level, which is much higher than other European countries. There are no claw-backs in Denmark.

Prescription guidelines are set for physicians, but are usually not obligatory. Physicians prescribe by pharmaceutical product rather than by chemical compound. However, generic substitution is obligatory at the pharmacy since 1997 (substitution

was introduced in 1991 but was initially not mandatory). Substitution is mandatory at the chemical substance level (ATC level 5), meaning that a branded product can be substituted by its generic, or a generic product can be substituted by another cheaper generic. Physicians can ask for a product not to be substituted without providing a reason for it. Patients can also deny substitution. In both cases though, patients have to pay the difference between the price of the product and the cheaper alternative out-of-pocket. If the price difference between the prescribed product and its generic alternative is negligible, substitution is not mandatory.

Patients pay a flat fee of DKK10 per pack dispensed. They are also subject to a 100% to 15% co-payment on each dispensed product, depending on the annual expenditure per person. Co-payments for children under the age of 18 range from 50% to 15%. Chronically ill patients pay lower co-payments and have an upper limit of annual out-of-pocket payment. Terminally ill patients do not pay any co-payment. Drugs for inpatient use are free for all patients.

A.2 France

France is a tightly regulated country regarding pharmaceutical policies. Legislation surrounding pricing and reimbursement of pharmaceuticals is closely monitored and regulated by various policies. Generic and originator prices are subject to policies in an effort to contain costs. While negotiations with the authorities and international referencing are used for the price setting of originator products, in the case of generics both reference pricing and price capping are implemented, making France one of the most tightly regulated countries in western Europe. Apart from the supply side, policy measures also apply on the demand side in order to provide a holistic approach to const containment and efficient use of medicines.

Prices of originator drugs are set after negotiations between manufacturers and the authorities. The price of the originator that the manufacturer applies for must be close to the price levels in other European countries (Germany, Italy, Spain and the United Kingdom). Any changes in prices in these countries must lead to a change in prices in France. Internal reference pricing is used, as price comparisons are made across drugs. Generic prices are set at 50% of the corresponding originator price, and are also subject to implicit reference pricing.

From the demand side, regressive wholesale margins apply in France. These margins are regulated and decrease as the price of the product increases. Pharmacists receive a flat fee per pharmaceutical product, which burdens patients. Further, they receive a mark-up, which is regressive. Arrangements have been made so that pharmacists receive the same amount, regardless of whether they dispense an originator product or its generic alternative. Pharmacists may receive discounts,

which are regulated and are negotiated with the supplier. The discount cannot exceed 10.74% for generics supplied by wholesalers and 15% for generics supplied directly by the producer.

Patients pay a flat fee of €0.50 out-of-pocket per pack dispensed. Annual out-of-pocket expenditure is capped at €50. Also co-payments as a percentage of the price of the product occur in some cases. On average, 76% of pharmaceutical expenditure is reimbursed. Patients under 16 years of age and chronically ill patients are exempted from co-payments. Also, claw-backs were introduced in France in 1999 in an effort by health insurance to gain part of the discounts offered to pharmacists by wholesalers.

Physicians are encouraged, but not obliged, to prescribe by International Non-proprietary Name (INN). However, an increase in pharmaceutical expenditure may indirectly prevent physician fees from rising, so physicians have an indirect incentive to promote generic prescription rather than originators. Generic substitution by pharmacists has been allowed since 1999, but is not obligatory. However, there are indirect incentives for pharmacists to substitute branded products with generics, as if the recommended rate of substitution is not reached, new rates will be introduced, leading to losses for pharmacists.

Finally, the VAT standard rate is 19.6%. However, for pharmaceuticals eligible for reimbursement the VAT rate is 2.1% and 5.5% for other pharmaceuticals.

A.3 Germany

Germany follows a framework of a relatively free market for pharmaceuticals, but this is combined with regulatory measures (such as reference pricing) which apply mostly to off-patent markets. This combination of free pricing and regulation make Germany a special and interesting case.

From the supply side, branded in-patent products are freely priced. Internal or external reference pricing for patent protected markets and profit controls do not apply in Germany. Reference Pricing is used in Germany for the reimbursement of off-patent molecules. Reference price is the highest price level at which a product can be reimbursed. Any upward difference in the price has to be paid out-of-pocket by the patient. Reference prices are reviewed annually. The reference price is usually determined at the therapeutic class level (although it used to be determined at the molecule level). In particular, drugs are grouped into three groups. The first group includes all drugs of the same chemical substance (such as branded products and their generic bio-equivalents). The second group includes different molecules which are therapeutically and pharmacologically comparable, for instance me-too drugs and generics. The third group includes drugs of different chemical substances which are considered therapeutically comparable. In-patent products are subject to the reference price, unless they are considered as having contributed to therapeutic improvement. In order for a product to be reimbursed, its price must not exceed that of the most expensive product in the lowest third of the reference group. Pricing is free for in - patent products. Patients under 18 years of age do not pay out of pocket for prescription pharmaceutical products. Adults are reimbursed at the 100% of the

price of the drug, but are subject to co-payments. For drugs costing less than 5 Euros there is no co-payment. Products prices between 5 and 50 Euros are subject to a 5 Euro flat co-payment fee. Drugs priced between 50 and 100 Euros are subject to a 10% co-payment, while drugs whose price exceeds 100 Euros are subject to a flat 10 Euro co-payment. The VAT rate for outpatient prescription drugs was increased from 16% to 19% in January 2007.

On the demand side, generic substitution is mandatory for pharmacists, which have to dispense generic drugs instead of branded products, unless otherwise explicitly stated in the prescription by the physician. Although pharmacist mark-ups were regressive, this practice changed in 2004. Ever since, pharmacists receive a flat fee per prescription, plus a fixed rate of 3% of the wholesaler's price. Also, the wholesalers' margin has decreased from 7.3% in 1996 to 4% in 2004. Profit controls, external reference pricing and cost-plus pricing are not present in Germany.

A.4 Netherlands

The Netherlands, alongside France, has a tightly regulated framework for the pricing and reimbursement of pharmaceutical products. This includes therapeutic clustering for the purpose of reference pricing. The recent implementation of tenders in outpatient markets also suggests that efforts to decrease off-patent medicine prices has been augmented.

For originator products, price caps, reviewed biannually, apply in the Netherlands. Reference pricing in the Netherlands takes place at the therapeutic class level. This means that when determining a reference price, it is not only an originator but also its generic alternatives which are included in the basket. Actually, other molecules of the same therapeutic class are also subject to the same reference price.

Generic policies are also tight and do not rely on competition. By law, generic prices had to be at least 40% lower than the corresponding originator price. A further reduction took place in 2008, making generic prices at least 50% lower than originator prices. This reflects the presence of price freezes and price cuts. Recent developments include the implementation of tenders for the provision of medicines in out-patient market by some of the main insurers. However this is limited to certain molecules.

On the demand side, physicians are encouraged to prescribe generic medicines. Some health insurance funds offer financial incentives to prescribe efficiently. If a product is prescribed by INN, pharmacists can (but are not obliged to) dispense the cheapest generic. However, if the physician has prescribed by brand

name, the pharmacists must dispense that particular product. Pharmacists gain one third of the price difference between the originator and the generic product, which is a financial incentive for them to dispense generic drugs. Pharmacists are paid based on a fixed tariff on each prescription. Claw-backs for pharmacies were introduced in 1998. The level of the claw-back increased gradually from 2% in 1998 to 6.82% in 2002, with a maximum of €6.80 per prescription.

Patients are not subject to any co-payments in the Netherlands. Patients only pay out-of-pocket if the product dispensed is more expensive than the reference price, if this applies.

A.5 Norway

Internal reference pricing was abolished in Norway in 2001. This was replaced by a price-capping system. All pharmaceutical products sold are subject to a maximum price, regardless of whether they are reimbursed by health insurance or not. Maximum prices are set according to an international reference pricing system. The price is set at the average of the three lowest prices of a group of European countries (Austria, Belgium, Denmark, Finland, Germany, the Netherlands, Ireland, Sweden, UK). New pharmaceuticals undergo pharmacoeconomic evaluation before reimbursement is approved. This is not connected to market authorisation. Products whose chemical substance has already been approved (e.g. generics) do not have to go through the same procedure for reimbursement approval, provided that they are not more expensive.

Generics are priced according to a stepped price model. Generic prices are gradually reduced over time. Initially, generics must enter the market at a price which is at least 30% lower than the originator's price. Six months later, the price must be at least 55% lower than that of the originator. Finally, a year after generic entry, generic entry must be at least 65% lower than originator prices.

Patients have to pay out-of-pocket co-payments for pharmaceuticals purchased from pharmacies. The co-payment is 36%. Drugs for the treatment of serious contagious diseases are exempted from co-payments and are reimbursed 100%. No other fixed co-payments exist. Patients also have to pay any difference between the reimbursement price and the price of the product, if they choose to

purchase a product whose price exceeds the reimbursement price, unless the physician explicitly states in the prescription that the product should not be substitutes for medical reasons. The maximum out-of-pocket expenditure per person is NOK 1,740 per year. There is also a maximum co-payment per prescription, which is NOK 510.

Wholesaler mark-ups are not regulated, but on average they are between 5% and 7% for branded products, and much higher for generics. Pharmacy margin is 8% for up to NOK200 and 5% for above this threshold, by law. Discounts are not forbidden. VAT for pharmaceuticals in Norway is 25%, which is equal to the standard VAT rate and alongside Denmark is the highest for prescription medicines in the study countries.

Generic or INN prescribing is not compulsory in Norway. Patients can choose to purchase the more expensive product (instead of a generic alternative), but they have to pay the price difference out-of-pocket. Pharmacists are obliged to inform patients of the existence of a cheaper product of the same chemical substance. Pharmacists also have a financial incentive to promote generics, as many pharmacies are owned by wholesalers, which have a larger margin for generics rather than originators.

A.6 Sweden

Sweden has been moving towards a relatively free pricing model for prescription medicines. Having abolished reference pricing in 2002 and moving towards a different approach of pricing and reimbursement of pharmaceuticals, the target for Swedish policy makers is to encourage a more competitive and less regulated type of market.

On the supply side, pricing of originator products is free in Sweden. However, cost-effectiveness of a product is taken into account by the medical products agency when reaching a decision about its reimbursement.

Reference pricing for reimbursement of generic products was implemented in 1993 and abolished in 2002. Until then, the reference price was used to set the reimbursement price of off-patent drugs. Generic competition is encouraged in Sweden by automatically accepting prices of drugs that do not exceed highest of the present price of a particular drug group. Prices are reviewed monthly and competitors do not know the price suggested by other competitors. This results in price cuts.

On the demand side, pharmacies are a state monopoly. Depending on the price of the product dispensed, the pharmacist's margin on prescription drugs is a percentage of the wholesaler price plus a fixed margin. There are three bands, depending on the price, and the percentage decreases with price, while the fixed margin increases with price. Prescription drugs are not subject to VAT and claw-backs are not present in Sweden.

Physician prescribing is done using the brand name rather with the INN. However, since 2002, generic substitution at the pharmacy level is mandatory.

Pharmacists are obliged to substitute a product with the cheapest alternative. What drugs are considered as alternatives is determined by the Medical Products Agency. Physicians can object substitution, in which case the prescribed brand is dispensed. The patient can also choose not to have his drug substituted by the pharmacist, provided that he pays the price difference out-of-pocket.

Out of pocket patient co-payment rates are regressive, depending on total yearly expenditure. The co-payment rate starts at 100% and decreases gradually down to 0%. Co-payments are capped at SEK 1,800 out of pocket per patient per year. All children under 18 years of age are pooled together and are treated as one beneficiary when calculating co-payments.

A.7 United Kingdom

The United Kingdom follows free-market approach in many aspects of the pharmaceutical market. It is actually the least regulated market in the European Union with regards to pharmaceutical pricing. Measures such as reference pricing and generic price controls which are very common in other European countries are not implemented in the United Kingdom.

On the supply side, in-patent drugs are freely priced in the United Kingdom, but are subject to rate-of-return regulation, which in practice are "profit controls". This is known as the Pharmaceutical Price Regulation Scheme (PPRS). Returns of the investment in a developing a drug cannot exceed a certain percentage. In particular, the 2005 PPRS scheme has a target of 21% of return on capital. Firms with profits exceeding the agreed margin have to reduce their prices or pay back part of their profits to the Department of Health. Recommendations with regards to the use of drugs are made to the NHS by the National Institute for Health and Clinical Excellence (NICE). NICE assesses the cost effectiveness of drugs and creates guidelines, but also rules in favour or against the use of particular molecules by the NHS, based on their cost per QALY.

Generic drugs are also freely priced, but a maximum price scheme was introduced in 2000, which sets upper limits to generics' prices.

On the demand side, pharmacist and wholesaler margins are not regulated in the United Kingdom, so they are not used as a disincentive for the dispense of more expensive products, as in other European countries in which regressive margins apply. Prescription drugs dispensed from pharmacies have a zero-rate VAT, while

OTC drugs are subject to VAT at the rate of 17.5%. Drugs prescribed in hospitals are also subject to 17.5% VAT. Claw-backs are deducted from pharmacy reimbursement levels. The size of the claw-back depends on the pharmacy size. On average claw-backs are around 10%.

Prescription of medicines is recommended to be done by INN (rather that by brand name). Pharmacists are obliged to dispense a branded product if this is explicitly mentioned on a prescription. Physician prescribing is monitored and primary care prescribers have a certain budget for prescribing purposes.

Patients are not burdened by percentage co-payments. Alternatively, they have to pay a standard prescription fee per item dispensed. Patients can be exempted from the obligation of prescription fees, depending on the disease the medication is supposed to treat, their age, their income and the method of delivery.