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Generic Competition and Price Regulation in the European Union Pharmaceutical Market:

The Case of Cardiovascular Medicines

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
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Date of Approval:
April 4, 2014

Keywords: European pharmaceutical industry, price competition, pricing and reimbursement regulation, hedonic regression, panel data

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Acknowledgments

I am truly thankful to my dissertation committee, Bradley P. Kamp, Ph.D., Gabriel Picone, Ph.D., Andrei Barbos, Ph.D., and Aysegul Timur, Ph.D., for their valuable comments, tremendous help, patience and advice. I could not have finished this dissertation without their support. Especially I would like to thank my dissertation committee chairs, Bradley P. Kamp, Ph.D., and Gabriel Picone, Ph.D., for their belief in me and leadership that helped me accomplish this goal.

I gratefully acknowledge support from Aysegul Timur, Ph.D., for providing me the data used in this dissertation and for her unlimited assistance in understanding the data set. Without her support, I would not have been able to utilize the data.

I am also thankful to my graduate director, Michael Loewy, Ph.D., for encouraging and helping me during my Ph.D. study in the Department of Economics starting from the very first day of this journey to the end.

Lastly, I appreciate the helpful comments, suggestions, and continuing support from my colleagues, Karen Langbehn, Zheni Stefanova, Robyn Kibler, and Youssef Fassi Fehri, in my research.

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Abstract

The purpose of this dissertation is to examine the extent of competition between generic products and therapeutic substitutes under different regulatory regimes in the European Union (EU) pharmaceutical industry. In particular, this study investigates generic competition among the five largest European pharmaceutical markets; the United Kingdom, Germany, France, Italy and Spain, with comprehensive IMS data for 10 years (1994-2003), in order to estimate the effect of generic entry on drug prices at the product level. This analysis finds that generic entry has a negative effect on prices in countries with free pricing originator market, whereas in EU countries with strict price and reimbursement regulation, generic competition is ineffective and/or counterproductive. Fewer generics and less competitive late entrants are consistent with incentives in regulated environments: low regulated prices for originator products discourage generic entry following patent expiration. These findings suggest that regulation of both manufacturers' prices and retail pharmacy prices undermines price competition in the off-patent sector, and that budgetary savings from generic price competition are not realized in countries with strict regulatory systems.

Chapter 1

Introduction

1.1 The History of the European Union

The European Union (EU) refers to 28 member countries, which collectively form a political and economic community throughout Europe. European countries started forming the EU in the late 1940s, shortly after the end of World War II. In 1950, Belgium, France, Germany, Italy, Luxembourg, and the Netherlands (the EU's "founding members") drafted an initial treaty representing the interests and goals of this political and economic partnership. In 1957, the Treaty of Rome was signed. The treaty allowed for additional countries to join. Now, nearly 57 years since the initial inception of the EU in 1957, the EU has expanded to 28 member countries (geography.about.com, The European Union: History and Overview).

In 1987, the Single European Act (SEA), a revision to the Treaty of Rome that further solidified European integration and expanded the community's power (particularly for R&D, the environment, and foreign policy) created a "single market" for trade (EUR-Lex, 2014). Two years later, in 1989 – given the dismantling of the Berlin Wall – the EU's economic power became even stronger. For instance, during the 1990s, the single market phenomenon gave EU member countries the opportunity to trade easily within the Union, which meant that production was more efficiently allocated and as a result, increased. Perhaps most importantly, though, was the signing of a new amendment in 1992, the Treaty of Maastricht, which introduced the idea of European citizenship and launched the Economic and Monetary Union (EMU) (http://europa.eu,

Treaty of Maastricht on European Union). The Treaty of Maastricht defined five goals that were vital for providing support and structure to the European Economic Union:

1) to strengthen the democratic governance of participating nations

2) to improve the efficiency of the nations' economies

3) to establish economic and financial unification

4) to develop the "Community social dimension"

5) to establish a security policy for involved nations

While the notion of a single currency within Europe was being discussed among leadership within the European Economic Community even in 1969, the Treaty of Maastricht made this agenda an even more eminent topic. Thirty years after this initial conversation, on January 1, 1999 the euro was launched by 11 of the 15 member states of the EU. The "Eurozone," which initially consisted of 11 member states (1998) that agreed to adopt the euro as their common currency, has since grown to 18 countries, with Latvia representing the most recent addition, having adopted the euro on January 1, 2014 (http://europa.eu, The History of the European Union). The remaining EU member states (except for Denmark and the UK) are legally bound to adopt the euro when convergence criteria are met; however, only a few countries have set firm target dates for accession (Kuchler, 2006). For example, Sweden has circumvented the requirement to adopt the euro because it does not meet the membership criteria (i.e., two years' membership in ERM II, which Sweden has chosen not to join) (Government Offices of Sweden, EMU and the Euro).

There are many benefits to adopting a single European currency: for instance, the euro provides efficiency because of a single market that easily facilitates the travel of goods among EU countries, therefore eliminating exchange rate problems, providing price transparency,

creating a single financial market, securing price stability and low interest rates, and providing a currency used internationally and protected against from potential shocks by the large amount of internal trade that occurs within the Eurozone (European Commission, 2010). Since its launch, the single currency euro, which is controlled by the European Central Bank (ECB), has become the second largest reserve currency in the world (DB Research, 2007).

1.2 Regulating Pharmaceuticals in Europe

Healthcare expenditures in Europe, as in most of the developed world, continue to rise. For example, both Germany and France spent over 10% of GDP on health care in 2009 (Eurostat/Eurpoean Commission). Governmental regulation plays a major role in this industry. Governments regulate pharmaceutical markets to protect public health; secure patient access to safe and effective medicines; improve the quality of care; and control pharmaceutical expenditures. More specifically, a government's involvement in the pharmaceutical sector pertains to analyses of both the supply-side and the demand-side of the market (Mossialos et al., 2004).

It is important to maintain a productive and transparent relationship between the pharmaceutical industry and the government because this is often an important determinant of the government's approach to managing pharmaceuticals at the national level and, in this case, at the level of the EU. For instance, even though most aspects of market authorization are uniform across EU member states, there are still aspects of the regulation of the pharmaceutical industry that vary significantly among EU countries. These variations are direct responses to the ways in which health and industrial policy objectives are formulated and operated at national levels (Mossialos et al., 2004). Pricing and reimbursement policies represent two of the most significant

differences among EU countries' approaches to pharmaceutical regulation. For instance, some countries negotiate pharmaceutical prices via direct control, while others regulate prices indirectly (e.g., through profit controls or maximum reimbursement prices). Despite these differences, in general, most countries prioritize similar objectives, although some countries are more willing to trade-off slightly higher pharmaceutical prices if they see a valuable return from pharmaceutical companies in terms of R&D. When all of these factors are considered, it's apparent that the relationship between government and industry has a significant impact on the market structure for pharmaceuticals in the EU.

The European Commission is responsible for regulating the pharmaceutical market in three areas (Mossialos et al., 2004):

1. national prices, profit, reimbursement, rational use and advertising
2. free movement and competition issues
3. market access through harmonization and eventual centralized authorization procedures through the European Agency for the Evaluation of Medicinal Products (EMEA).

Currently, there are a variety of approaches used to regulate pharmaceuticals in Europe, which means that public policy objectives that seek to control costs while improving efficiency, quality of care, and equity are significantly affected. Comparing international approaches is useful for explaining how and why these different policies are being implemented and their effectiveness and efficiency across countries. Additionally, contextual information about the social, economic, medical, health care, and political environments of these particular countries is important for a deeper understanding about how these policies are developed and implemented in practice. A policy adopted in one country, therefore, may not be appropriate for another country due to the countries' different health and industrial policy objectives.

In an effort to provide guidance for negotiating various health/industrial policy trade-offs, a framework of general principles for "best practice" has been developed for policy makers' reference. These best practices consist of the following directives:

- the objective of the policy must be clear from the outset, and consideration must be given to its possible impact on all of the evaluative dimensions (i.e., efficiency, equity, quality, and cost)
- price control (alone) cannot improve efficiency; to control total expenditures, demand-side applications are very important for improving efficiency, equity, and quality
- newly innovated drugs and variations in product mixtures affect drug expenditures; therefore, one of the biggest challenges to policy makers is to consider how to define "valuable innovation" so that drug expenditure reflects the value of drugs' benefits to society (Mossialos et al., 2004).

1.3 The Off-Patent Pharmaceutical Market in Europe

Many irregularities exist within pharmaceutical markets, some of which are insurance and third party payers, information asymmetry, and agency relationships. As a result, price competition is said to be weak because of the impact of all of these market imperfections. This ultimately means that for the pharmaceutical market in the EU, prices may not respond to the entry of new products to the market as is normally predicted. Additionally, this atypical pattern may also lead to low levels of elasticity of demand (Vandoros et al., 2012). Because of the irregularity that exists within this sector, market regulations are used to offset these market failures and to provide more efficient resource allocation.

It is important to understand the dynamics of this market because knowing these dynamics

can better inform how governmental regulations are imposed; thus contributing to or preventing the growth of this unique market. When an original drug's patent expires, generic drugs can enter the market and compete to capture the market share from the originators. Generic equivalents are considered to be very effective substitutes for original drugs, and are therefore expected to capture a significant share from the market originators; however, despite these expectations and the proven equivalence of generics with original drugs' potency, some patients still prefer branded to generic products. This preference can be explained through a variety of reasons: for instance, some patients may simply believe that branded products are better than generics, or in other cases, their physicians may suggest that they purchase branded products over generics (Vandoros et al., 2012). Although this sort of brand loyalty may provide some motivation for the consumer to continue purchasing the original drug, there is evidence from the EU that this situation does not substantially limit off-patent competition after a patent's expiration. In general, because of financial incentives, physicians, pharmacists and patients most often make decisions in favor of using generics; thus increasing product selection due to price sensitivity (Kanavos et al., 2007). The characteristics of the off-patent pharmaceutical market create the potential for price competition, which can be encouraged by pricing and reimbursement regulations.

The market for generic drugs has received more serious attention in EU countries over the past few years, primarily due to new policies that promote the use of off-patent drugs. These subsequently result in the penetration of generic medicines into the market. Germany is the most highly developed generic market in Europe because; it is also the largest pharmaceutical market in Western Europe. In contrast, generic markets in the UK, France, Italy, and Spain are not as developed as Germany. To categorize the generic markets in EU countries as highly or less developed, it is important to look at differences in:

- the extent of generic entry and the penetration of branded generics
- price differences between original brands and generics
- price regulation of on-patent and off-patent drugs
- the extent of product selection based on price (Mrazek et al., 2004)

In the EU, the status of off-patent pharmaceutical markets is determined largely by policy developments and regulations. In 1998, a Mutual Recognition Procedure (MRP) – which is used when a company wants to market the same product in more than one EU country – provided market authorization for generic medicines to compete with the on-patent market (Ghalamkarpour, 2009). As mentioned briefly above, national health care systems are extremely influential in affecting the penetration of generic medicines in pharmaceutical markets. Of the EU countries that have a greater penetration of generics in their pharmaceutical markets, most all have adopted policies supporting their use (e.g., generic substitution, reference pricing, financial incentives targeting physicians, pharmacists or patients); however, in other EU countries, widespread concerns about the safety and quality of generics have negatively influenced their use, resulting in a substantially less robust penetration of generics into these markets (Mrazek et al., 2004).

Markets in EU countries are different from other countries' markets primarily because of how pricing regulations are structured within the off-patent pharmaceutical sector. Of these various regulations, the reference pricing system is one of the most important and common strategies for managing generic drug prices. This type of pricing system classifies drugs into groups that are considered to be close substitutes for the originals, and sets a single reference price for each group as the maximum reimbursement allowed for all drugs in that group (Vandoros et al., 2012). The reference pricing system has been successful in encouraging product

prices to converge to a specific level; there are very few instances in which decreases below the reference price occur (Mrazek et al., 2004).

Determining the most appropriate regulatory interventions for each country depends on the objectives of the country's policy makers, national health care systems, the involvement of health care professionals, and the availability of supply. These are very important implications that ought to be discussed further by policy makers, the industry, health professionals and the public, as generics continue to play an even more significant role in pharmaceutical policies in the EU (Vogler, 2012).

1.4 Contributions

Patents and the lack of good substitutes for new drugs provide substantial monopoly power, which encourage national governments in the EU to develop price control policies (Danzon and Chao, 2000a). When patents expire, generic substitutes introduce price competition into the market. Ultimately, the extent to which generics capture the market share from branded original drugs depends upon a particular government's regulatory policies.

This dissertation is unique and necessary because it examines the extent of competition between generic products and therapeutic substitutes under different regulatory regimes within the pharmaceutical industry in the EU. In particular, the study described within this paper investigates the effect of generic competition on drug prices at the product level among the five largest European countries – the UK, Germany, France, Italy and Spain – given an analysis of comprehensive Intercontinental Medical Statistics (IMS) data over the span of 10 years (1994-2003). This analysis finds that generic competition has a significant negative effect on price for Germany, whereas for the countries with strict price regulation (the United Kingdom, France,

Italy, and Spain), the number of generic competitors has either no effect or a positive effect on prices. As Danzon and Chao (2000a) points out, this is consistent with evidence that in countries with strict regulation, generic competitors are predominantly either licensed co- marketers or new versions of old molecules that manufacturers introduce in order to obtain a price increase. On the other hand, in countries with relatively free pricing regime, successive generics enter at lower prices, and prices at the product levels are negatively related to the number of generics.

This dissertation is structured as follows: Section two provides a background of the EU pharmaceutical market; section three is a literature review describing the nature of off-patent market competition; section four outlines the research strategy implemented in this study; section five presents empirical results; and finally, section six provides concluding remarks and suggestions for future research related to this topic.

Chapter 2

A Background of the Pharmaceutical Industry in the European Union

The purpose of this chapter is to carefully examine the pharmaceutical industry in the EU, and specifically, to focus on explaining how this market's characteristics differ from other markets (e.g., the United States). The ultimate goal is to identify the implications of pricing and reimbursement regulations.

2.1 Identifying Characteristics of Pharmaceutical Markets

The pharmaceutical industry is responsible for manufacturing, processing, researching, and producing medicinal drug products that provide treatments and remedies for a variety of medical conditions. Oftentimes, a close relationship exists between the product market and the "therapeutic class," which is a system for classifying medical drugs by their functions. The European Commission's Competition Directorate has adopted the practice of defining the relevant product market according to the therapeutic classes identified in the Anatomical Therapeutic Classification (ATC) system, which is recognized and used by the World Health Organization (WHO) (OECD, 2002).

The pharmaceutical market is a high-technology, knowledge-intensive industry. In terms of market structure, this market consists of two main groups: the large firms (i.e., patent holders) that expend the biggest portion of Research and Development (R&D) investments, and the

smaller-sized firms, which operate in the off-patent market (OECD, 2002). Among other factors, this market is heavily influenced by regulatory policies, which have been developed with the intention of providing three vital benefits:

1) improving innovation with intensive research and development

2) auditing the quality of drugs for public health

3) managing the costs of pharmaceutical expenditures

Growth in the industry, from patents issued for newly developed pharmaceuticals, is a vital component in the achievement of these goals. In this industry, companies' investments in R&D ventures are often extremely costly and risky; therefore, R&D expenses are most often financed with funds obtained through intellectual property rights, especially patents. In 1998, the EU adopted what is called a "mutual recognition procedure," which is an agreement that EU member states will recognize the national marketing authorizations of one another. This policy granted marketing authorization for all of the EU countries and allowed for the free movement of medicinal products throughout the EU (OECD, 2002).

The pharmaceutical market is distinguished from other markets primarily because both its demand and supply side have characteristics not found in typical "well-behaved" markets. On the demand side, there are physicians acting as agents for consumers. Physicians are considered "imperfect agents" for consumers, since they are not responsible for the financial obligation of purchasing drugs. Another important characteristic of the demand side is the fact that consumers often are reimbursed some if not all of the purchase price. These reimbursement policies differ across countries as well as across drugs in the same country. Reimbursement policies increase demand while at the same time, cause demand to be less elastic. This is important in the EU, as member countries typically provide generous insurance coverage.

Maintaining competition within the pharmaceutical industry depends on the number of producers and the nature of demand for products on the market. The pharmaceutical industry is understood to be a market with a high degree of effective competition because it includes such a large number of rival producers, and because these rivals then compete among one another by responding to the price-sensitive demand for drugs. In outlying cases where competition is not primarily focused on price, it is typically shifted to R&D or to marketing.

2.2 Pricing and Reimbursement Regulations in the EU Pharmaceutical Market

The pharmaceutical industry is heavily regulated. Every moment of the life of a pharmaceutical product, from its initial conception to earning marketing approval, commercialization, patent expiration and generic competition, is subject to extremely strict regulation. Regulatory controls on production and government insurance on the consumption side result in both supply and demand being affected by government policies. Thorough analysis requires investigating both supply and demand. For instance, on the supply side, there is a high cost – and thus risk – associated with R&D activities. For this reason, Intellectual Property Rights, which protect newly innovated drugs from competition with a substantial reward, are designed to encourage R&D by providing drug companies with the opportunity to recoup the substantial investments that have been made in R&D for the development of new medications. Alternatively, on the demand side, health insurance systems affect the quality and the quantity of drug consumption. This ultimately means that the interaction of the supply side with the demand side allows for an understanding of the specific type of unique competition that exists within particular markets (OECD, 2001).

2.2.1 The Regulation of Drug Supply

Patents have significant power in motivating continued investments in research and innovation in the pharmaceutical industry because without the protection provided by patents, pharmaceutical companies would be unlikely to risk investing in the R&D of new drugs (OECD, 2001). The value of patent protection depends on the length of the period of exclusivity. For instance, currently in the EU, the effective life of a patent is less than 20 years. However, due to increasing concerns about the consequences of a potential decrease in the effective life term, a "supplementary protection certificate," which extends patent life up to five additional years, was adopted in 1993 in all European countries (OECD, 2001).

A patent is a reward for companies investing in R&D. Patent protection not only confers exclusive rights to the production, sale, and use of newly developed drugs, but due to the entry barrier it creates, prices can also be set and remain well above marginal cost. The total economic value of a patent depends on the individual drug's market characteristics, such as pricing and reimbursement policies, availability of therapeutic substitutes and ability to price discriminate (OECD, 2001). Although patents are generally accepted as necessary for encouraging continued investments in developing new products, they also may be responsible for creating market distortions, such as the higher price of a pharmaceutical as compared with the cost of alternative products, forcing patients to incur higher costs for treatment.

Lastly, patents make innovations public information, which means that they provide access to new knowledge for other entrepreneurs' use in the development of new technologies, and eventually, for competitors. Although a patent is often the primary motivating factor in the development of pharmaceutical products, a patent's expiration marks the beginning of a new cycle of competition: the entry of generics into the market.

When a patent expires, the patent-holder loses monopoly power in the production and distribution of the patented molecule. Drugs that have an equivalent composition as the originally patented drugs, named generics, may then enter the market.

However, despite the resulting increase in competition because of the introduction of generics into the market, regulatory controls have substantial impacts on the effects of this competition on prices. Additional factors such as brand loyalty and consumers' price insensitivity may limit the extent of generic competition. Numerous case studies provide evidence that original drug prices often increase following the entry of a generic drug (at a lower price) (OECD, 2001). In response to this scenario, national health care systems in Europe have developed pricing regulations for post-patent drug markets. Countries within the EU use formalized pricing regulations to control generic prices, which support generic uptake following the patent's expiration. The most commonly used regulatory policies are reference pricing and price caps (Vandoros, 2013). Reference pricing is the most popular regulatory policy used in off-patent markets within EU countries. Under reference pricing, prices among similar products (or prices for the same product in other EU countries) are compared and grouped together accordingly, in order to determine a maximum reimbursement price. European countries that use reference pricing in off-patent markets include Germany, France, Italy and Spain. Another policy, used in the UK, is price capping. Under price capping, generic prices are set at a maximum percentage of branded prices (Vandoros, 2013).

Another technique used to promote the use of generic medicines is to provide incentives to pharmacists. Given that pharmacists are responsible for dispensing prescriptions to their clients, it is assumed that they can also play an important role in promoting consumers' use of generic medicines. However, because generics are promoted through generic substitution, when generic

substitution is allowed, physicians and patients can usually reserve the right to refuse substitution (Mrazek et al., 2004). Therefore, policymakers sometimes offer financial incentives that motivate pharmacists to dispense less expensive generic drugs to their patients; this incentive occurs across the EU countries. Additionally, pharmacists' decisions to select the lowest-cost generic equivalents are also encouraged through the use of higher margins on generic products (Mrazek et al., 2004).

In the generic pharmaceutical market, market interventions are necessary for correcting demand-side imperfections. If these interventions do not occur, the market may not achieve a high-volume use of generics, despite a lower price as compared with the price of the original product. However, determining whether or not a given country should apply any of these specific approaches depends almost entirely on the contexts of its policy makers' objectives, health care systems, and health care professionals.

2.2.2 The Regulation of Drug Demand

Health insurance is another important factor affecting the demand for pharmaceuticals. For example, if all consumers in the market were fully insured, the consumers would not substitute across drugs of different perceived quality based on price differences. In this case, drug companies would be willing to increase their investments in perceived quality of these drugs as they could obtain a higher profit margin. The branded drugs would have an advantage and generics would find it hard to capture market share. However, consumers do not write the prescriptions. So even with insurance, originators still have a high incentive for influencing physicians' prescribing behavior.

This hypothetical full insurance is not available in most countries. The entire price of the drug is not always reimbursed. There are various reimbursement policies operating within EU countries. The most commonly employed reimbursement policies in the EU are copayments and positive listing. Certain pharmaceuticals are partly or completely excluded from health insurance coverage. A "copayment" refers to the out of pocket cost to the consumers. Patient co-payments are levied according to four mechanisms: a fixed fee (per item, per prescription, or according to pack size); a percentage of the value of the prescribed drug; a deductible up to a certain limit; and a combination of the above, usually a fixed fee or a deductible plus a percentage of the value of the drug. The total cost of treating the disease affects the demand for pharmaceuticals, in general, while a change in the marginal cost of a drug provides an incentive to substitute lower-priced forms of the same molecule.

Another commonly used reimbursement policy is a "positive list," which is the explicit listing of pharmaceutical products by the health care funder, indicating whether or not a specific product may be adopted for reimbursement (OECD, 2001). The main objective of this reimbursement regulation is to provide detailed information about the availability of effective and less expensive pharmaceutical products.

Physicians play an influential role in consumers' decision-making processes about pharmaceuticals because they usually face incentives from regulatory policies to promote particular drugs. Furthermore, on an even higher level, drug companies and health insurers have great incentives to influence physicians' prescribing decisions through direct "command and control,'' or through the use of financial incentives which seek to align the incentives of the physician with the insurer (OECD, 2001). Of these two approaches, the "command and control" approach is by far the most common. Widely employed forms of controls on physicians include

guidelines on prescribing practices and some type of limits on the quantity of drugs that can be prescribed per day or per episode. For example, physicians may be required to substitute among drugs within a particular therapeutic class, to try low-cost therapies first, or to seek advance approval before prescribing certain drugs. One drawback of the command and control intervention is that doctors may not necessarily choose the best alternatives for their patients, in terms of costs and benefits analyses (OECD, 2001). In order to respond to this issue, some regulatory controls provide financial incentives to physicians in order to maintain a high level of cost-effectiveness in their prescribing behavior. As OECD (2001) defines, "GP fundholder" programme in the U.K. is one of the leading examples of such financial incentives. Under this scheme, the health provider receives a fixed payment per year, and is able to exercise discretion over how these funds are used in the purchase of health outcomes. In this scheme competition between suppliers is an essential element. In the absence of competition, the health care supplier would have a strong incentive to restrict access to health services and would have little incentive to maintain a high level of care. In the GP fundholder scheme, the local doctor (the General Practitioner) receives a fixed sum each year according to the number of people in his/her care. The GP fundholder is responsible for allocating these funds in such a way as to purchase the maximum amount of health care possible and is able to retain any savings resulting from more efficient use of pharmaceuticals. Under this programme, GPs have quite strong incentives to choose the best mix of pharmaceutical inputs. By 1994 about one-third of all UK GPs were involved in a fundholder scheme (OECD, 2001).

In the generics market, there are no barriers to entry or economies of scale prohibiting the production of the same drugs by different competitors, making it a highly competitive market.

But government health services do have monopsony power. By employing price control mechanisms, competition can be introduced into drug production (OECD, 2001).

In the 1990s, one of the priorities of the EU health care system was controlling pharmaceutical expenditures. Numerous market factors affect pharmaceutical expenditures such as newly innovated and more expensive drugs, adjustments in the product mix, and changes in how diseases are treated. In order to more effectively control pharmaceutical expenditures, EU countries have employed regulatory policies designed to generate lower costs while improving efficiency.

As noted above, the pharmaceutical market has notable imperfections in the supply and demand sides of the market, which cause market failures (such as a high level of drug expenditures). In order to reduce pharmaceutical expenditures, EU governments employ price controls on the supply side of the market. Price regulations vary among EU countries, reflecting distinct pricing strategies that result from national goals. One of the most important system of pricing regulations is direct price controls. Examples of direct price controls include negotiated prices, maximum fixed price, international price comparisons, and price cuts or freezes (Mrazek et al. 2004). An indirect price regulation is a different method of regulation achieved through profit controls and reimbursement limits (OECD, 2001).

An important part of this dissertation examines pharmaceutical price regulations within the EU and their impacts on the market structure, particularly the competitive effects of generic entry on the pharmaceutical market. Existing literature in this field provides empirical results, which compare drug prices between countries having different supply and demand-side policies. Due to differences in methodology, it is difficult to generalize conclusions from these studies. Studies that have examined the relationship between the price level and regulatory regimes have

provided contradictory results. For instance, the U.S. General Accounting Office (1994) showed that pricing policies in France, Germany, and the UK were causing drug price increases that were lower than the overall inflation rate during the 1980s and 1990s (Mrazek et. al, 2004). Garattini et al. (1994), Jonsson (1994), and Rovira et al. (2001) provided evidence that countries with strict pricing and reimbursement regulations (e.g., the United Kingdom, France, Italy, and Spain) have lower prices than countries with less strict regulatory structures (e.g., Germany). On the other hand, Reekie (1998) and Danzon and Chao (2000a) examined both on-patent and off-patent pharmaceutical markets and provided evidence that less-regulated markets (such as Germany) have lower prices as compared to strictly regulated markets. The differences in these empirical results can be explained by heterogeneity in the methodologies used, the products considered, the study periods chosen, and the methods of estimation. Three common regulatory methods are detailed below.

In direct price controls, fixed maximum pharmaceutical prices are set. The level of maximum price depends on certain contextual factors (such as prescribing behavior, budget limits, and the volume of the country's pharmaceutical industry) and therefore varies across different EU countries. All EU countries (except for Germany and the UK) use direct price controls for on-patent drugs. In Germany, newly patented drugs can be freely priced at launch, and in the UK, prices for newly patented drugs are regulated through profit controls. Since 2003, this type of free pricing regime has also been used in France, but only for innovative drugs.

An indirect method of regulation, employed in the UK, is profit controls. Under the UK's policy, drug companies are allowed to make a profit of up to 21 percent return on capital invested. If a company exceeds a 21 percent rate of return, it can retain up to 40 percent over the originally permitted return if it has not received a price increase for any product in the same year.

If profit exceeds the margin of tolerance, the company must cut its prices and repay the excess profit to the Department of Health (Mrazek et. al, 2004).

The other commonly employed regulation is reference pricing. Reference pricing sets fixed reimbursement limits for products assigned to the same group. Patients are responsible for paying any excess of the price of the prescribed drug over the reference price. Imposing this additional cost to patients is expected to be effective in increasing consumers' awareness of the prescribed drug's price and in encouraging them to choose a drug listed at the reference price (Mrazek et al., 2004).

Various studies show that reference pricing has proven effective in reducing price differences among drugs defined as "therapeutic substitutes." EU countries use reference pricing for products defined in the same category, with similar therapeutic values. When no generic equivalents exist, these classifications often become controversial. In Germany, France, Italy, and Spain, a reference pricing regulation is applied only to off-patent drugs (Vandoros et al., 2012).

A wide literature shows how a downward price convergence occurs as a result of the implementation of a reference pricing policy. For example, Pavcnik (2002) shows evidence of price decreases in the German pharmaceutical market following patients' choices to switch to drugs at the reference price. As a result, German pharmaceutical companies eventually responded by reducing their prices. In other cases, Donatini et al. (2001) and Nink et al. (2001) show that reference pricing causes some savings in pharmaceuticals, but only for the short-term (Italy and Germany). For instance, Nink et al. (2001) explain their finding that some German doctors prescribe products that were not included in the reference pricing system and they do not spend time to discuss co-payments with their patients.

Both direct and indirect price controls are effective in slowing price increases and/or lowering drug prices; however, the impact of these price controls on drug expenditures depends on growth within the mix of products on the market (which includes more expensive drugs). On the demand side of the market, consumers' cost awareness about alternative treatments is an important factor in promoting competition primarily because this awareness generates competition for lower prices. Additionally, financial incentives for health care providers, pharmacists and patients also play an important role in patients' cost awareness of generic drugs.

2.3 Summary of Features of the EU Pharmaceutical Industry

Pharmaceutical pricing and reimbursement systems are often very complex, as they are customized to respond to the specific economic and health care needs of a country. Furthermore, in the EU, health care systems continuously adjust as Member States review their health care systems (searching for strategies to increase the efficiency of pharmaceutical services) or strive to keep their pharmaceutical budget within specific limits. These efforts often cause a reaction from other players in the market, such as pharmaceutical manufacturers, wholesalers, doctors, pharmacists or patients. Some examples of these reactions include changes in pricing and reimbursement regulations within the market or in patients' consumption patterns.

Collectively, these developments provide comprehensive and up-to-date information, which is useful for monitoring price competition in both on-patent and off-patent pharmaceutical markets. Therefore, it is important to understand comprehensive and detailed information about pharmaceutical systems within the individual EU Member States because doing so elicits information about similar cost drivers and policy measures, which can make maintaining the

existing monitoring and enforcement of in-patent and off-patent market competition rules more efficient.

The purpose of this dissertation is to examine the extent of generic competition in European countries, given an understanding of these countries' different pharmaceutical price regulations and health care structures. This study is focused on generic price competition within the pharmaceutical industries of the five largest European markets: the United Kingdom, Germany, France, Italy and Spain. Both within and across these countries, different interventions are being applied to in-patent and off-patent markets (See Table 8). For example, in Germany, markets for on-patent drugs are largely unregulated and prices are set relatively freely; however, once generics enter the market, the German government uses reference pricing to set reimbursement rates. In the UK, originator medicine prices are free from direct regulatory intervention, but are subject to a rate of return regulation. Additionally, once generics enter the market, the UK's government uses price caps. France, Italy, and Spain, on the other hand, use direct price controls for originator drugs and reference pricing system for generic drugs.

It is especially important to gather available information and to acquire more specific knowledge about how the pharmaceutical systems in the Member States of the EU function (European Commission, 2006) because doing so allows for:

1. achieving increased transparency within this industry and exposing the particularities of competition rules
2. identifying the relevant players in the pharmaceutical market of each Member State
3. investigating regulatory measures as well as demand side and supply-side strategies adopted with regard to cost-containing effects in the pharmaceutical market
4. providing information for EU policy-makers pertaining to mechanisms on pricing,

reimbursement and dispensing of pharmaceuticals

5. providing an in-depth, comprehensive description of the in-patent and off-patent competition in EU Member States.

Chapter 3

Literature Review

The purpose of this chapter is to provide a comprehensive overview of the existing literature on generic price competition in the EU pharmaceutical market. This information is critical for justifying where this study's topic originates. It is important to note that although this information is extremely pertinent to this topic, it is not necessarily useful for drawing generalized conclusions primarily because of the studies' methodological differences, the range of products considered, the extent to which generics were included or not included in the study's sample, the length of time in which data was collected for analysis, and the method used to calculate price indices (Danzon, 1998; Kanavos and Mossialos, 1999). Drawing universal conclusions from this data is additionally complicated when considering the identification of causal effects because of the many secondary factors that influence drug prices (Kanavos et al., 2007), for instance:

- differences in health system structure and financing
- pharmaceutical subsidies
- cost-containment policies
- product mix
- production costs

Price competition has been an important topic in various empirical studies of the pharmaceutical industry. However, studies that focus on price competition offer conflicting results about how regulation impacts drug prices. For instance, Jonsson (1994) and Kanavos et al. (2013) suggest that countries with strict price regulations have lower prices than countries with less strict price regulations. On the other hand, the studies of Grabowski & Vernon (1996), Rizzo & Zeckhauser (2005) and Caves et al. (1991) cite empirical evidence showing that prices do not decrease after generics enter the market; they argue that generic entry only leads to a slower rate at which drug prices (ultimately) increase. Danzon and Chao (2000a) cite empirical evidence identifying how, in less-regulated markets, competition has kept prices low. Therefore, as stated above, it is not possible to draw accurate, universal conclusions from these studies due to differences among the methodological choices of the researchers, as well as 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).

A similar situation exists after patent expiry, when competition from generics initiates price fluctuation in the market (Magazzini et al., 2004). Anis et al. (2003) conclude that in cases where less regulation is imposed, substantially more competition exists. Their study ultimately concludes that pricing regulations failed to achieve the goal of lowering prices and in fact, in this case, pricing regulations resulted in the opposite occurrence. Hudson's study (2000), which also examines the relationship between patent expiry and the diffusion of generics, finds that both generic entry and the lag time between patent expiry and generic entry can be traced to the size of the market at the time of the patent's expiration. These findings also provide evidence supporting the argument that the rate at which the original brand loses revenue is proportional to both the size of the market and the price of the original brand prior to generic entry. In the US,

the impact of generic entry on original brand sales is found to be much bigger, as compared with statistics from the UK, Japan and Germany. This finding is most likely a reflection of the larger size of the U.S. pharmaceutical market and the consequence of its regulatory environment.

Hudson (2000) also argues that more successfully marketed drugs initially attract generic competition but tend to lose sales after patent expiry. Conversely, less successful drugs aren't as adversely affected by generic competition. Thus, a patent's value to a particular company ought to be computed by taking into account not only the period of patent protection, but also the period after the patent's expiration. Since patent expiry does not always induce the entry of generics to the market, and because there is sometimes a lag time of several years between patent expiry and generic entry, firms' revenues will not disappear immediately, but will gradually decrease over a period of time. Thus, it can be reasonably argued that a patent's value extends beyond the actual moment of its expiration.

The results of these studies suggest that generic competition has less of an effect on prices in tightly regulated markets for three specific reasons. First, pricing and reimbursement regulations keep the prices of branded drugs lower, and this reduces the motivation for generics to enter the market. Second, strict regulatory system reduces opportunities for generic competition because major market players – patients and physicians - have less incentive for substituting generic drugs for original branded products; thus, demand elasticity is lower in this context. Third, producers sometimes exploit pricing regulations via co-marketing generics with generic suppliers or developing new products with only minor changes from the originals, and then negotiating higher prices (Pammolli et al., 2002).

Conversely, in less-regulated regimes, innovators of effective drugs can profit from higher prices, which subsequently attract the entry of generics. In response to this competition, the

original brand producer sometimes tries to differentiate its product (e.g., advertising or applying market segmentation strategies). Within these less-regulated regimes, the pre-entry prices of pioneer brands can be maintained (or, in some cases, extended) upon patent expiry because of strong brand loyalty toward original brands (Caves, Whinston & Hurwitz, 1991; Grabowski & Vernon, 1992). Alternatively, off-patent pioneer products sometimes become Over-The-Counter drugs (OTCs) and are paid for out-of-pocket by the consumer. Almost immediately upon the entry of off-patent pioneer products into the OTC market, competition among generics becomes substantial and soon after, prices fall; reducing market shares of the branded drug. In countries where the pharmaceutical market is managed by less-regulated regimes, markets generate a sharp distinction between innovators and imitators (Pammolli et al. 2002).

In contrast, Garattini (1994) and Rovira (2001) have found that countries with strict price regulation policies have lower overall prices than countries with less strict regulations. On the other hand, Reekie (1998) claims that competition yields low prices in markets with less strict regulation (e.g, Germany). And, empirical study from Canadian pharmaceutical markets shows that the effect of generic competition to keep prices low was very moderate or nonexistent (Jones et al., 2001).

Despite consumers' benefits from lower market prices as a result of stricter price regulation policies, one of the consequences of this type of price regulation is what is referred to as a "ratchet effect" (Bergman & Rudholm, 2003). This effect occurs when prices signal low marginal costs.

Price competition sometimes leads generic products to exit, or partially withdrawal from the product market. In this case, it would be expected that new generic competitors would attempt to capture market share while the originator primarily keeps capturing the small market

share of the brand loyal market (Kanavos et al., 2007). However, generic firms have incentives to maximize their market shares in response to use the existing regulatory measures (such as reference pricing) to their advantage in order to maximize market shares and rents (Aronson et al., 2001; Kanavos et al., 2007).

Brekke et al. (2007) have studied the impact of regulatory regimes on generic price competition and pharmaceutical pricing using a unique policy experiment in Norway, where Reference Pricing (RP) replaced price cap regulation in 2003 for a sample of generic products. In this case, they found that RP leads to lower relative prices because of strong brand-name price reductions. They also found that RP increases generic competition, resulting in lower brand-name market shares.

In a similar study, Dalen et al. (2006) examined the impact of index price regulation on both demand and market power. Their results suggest that the index price helped to increase market shares of generic drugs. Puig's (2010) study examined the impact of European pharmaceutical price regulation on generic price competition and found that RP systems cause a reduction in the consumer price of all pharmaceuticals subject to this system, to a varying degree in different countries and different periods of time. Beyond the price reduction forced by pricing regulation alone, the entry of new generic competitors is useful for lowering the real transaction price of purchases made by pharmacies (dynamic price competition at the ex-factory level).

Podnar et al.'s (2007) research addresses how a sector of the Slovenian pharmaceutical market was influenced by reference pricing. On the basis of their descriptive analysis, they argue that the RP system caused an increase in the share of generic drugs. Similarly, Adriaen et al. (2008) examined the pricing strategies of generic medicines following patent expiry in Belgium and concluded that pricing strategies are influenced by regulatory aspects, such as:

- successive reductions in reference prices and prescription status of medicines
- market incentives in the form of price competition between generic medicines and competition between originator and generic medicines by medication class
- market power held by the manufacturer of the originator medicine

Therefore, they argue that there is no single pricing strategy that authorities can use to predict the pricing behavior of generic medicines following patent expiry or to foresee the development of the generic medicines market. Furthermore, Kanavos et al., (2007) finds that cost savings to health insurance is not realized because of the ineffective generic policies and because generic drug prices are high and depend on originator drug prices. They also find that reference pricing attracts generic entry and reduces generic prices marginally.

In terms of the pharmaceutical market in the EU, Perry (2006) suggests that while it is necessary to ensure that pricing systems encourage price competition and more affordable quality healthcare for patients, it is equally important that pricing systems are managed with the objective of guaranteeing the long-term sustainability of the EU-based generic medicine industry so that it can compete effectively in EU and global markets. Consequently, it is governments' responsibility to address the generics challenge head on. Some suggest that they ought to accomplish this by implementing pro-generics policy measures, particularly in the area of pricing and reimbursement, while better informing doctors, pharmacists and patients about the benefits of generic medicines.

Augurzky et al. (2009) provide information on ex-factory generic prices, reference prices, manufacturers, type of prescription drug, and market entries and exits. Their results show that there is no full price adjustment: a 1%-change in reference prices leads to a 0.3%-change in market prices. Furthermore, the introduction of a RP reduces the market prices of the affected

products by approximately 7%. Kanavos et al., (2007) has argued that reimbursed generic prices may be too high, and as a result, a significant proportion of the reimbursed price accrues to the distribution chain in a fashion that resembles an indirect subsidy. This ultimately means that it is possible for a single purchaser (such as the NHS) to purchase generic drugs more cheaply than it expects to and, consequently, realize further cost savings (which could be allocated elsewhere in the service).

The theoretical discussion presented above concludes that there may be limitations in generic penetration, which may, in turn, hinder the benefits of generic competition. In fact, there may be barriers to entry in generic markets resulting from (Kanavos et al., 2007):

- regulatory or discounting practices
- strategic pricing by first entrants, implying that there may be first mover advantages in the market for generics (Hollis, 2002)
- interaction between stakeholders, such as providers, physicians and pharmacists and their incentive structures

Empirical studies in literature does not provide a clear explanation for the nature of generic competition, the impact of regulation and the extent to which countries differ in their price sensitivity to drugs. Overall, pharmaceutical markets respond to significant imperfections both from the demand side and supply side, which leads to significant differences among markets. One way to pursue further research on this topic is to examine the influence of generic competition among different markets (Kanavos et al., 2007). Therefore, in response to the need for additional scholarship in this area, this dissertation focuses on how drug prices change over time as a consequence of generic competition, taking into consideration different regulatory regimes across the countries examined.

The results of this analysis suggest that the relationships between the dynamics of drug prices and generic competition are, at the very least, complex and differentiated across countries. This study explores ways of analyzing these differences by utilizing a different empirical strategy: a fully interacted model and an extremely comprehensive data set that traces the market for cardiovascular medicines in the five biggest European countries. More specifically, this dissertation examines the effects of generic competition on individual product prices at the retail level and finds that generic competition has a negative effect on price for relatively less strictly regulated markets, whereas for countries with strict price regulation policies, the number of generic competitors has either no effect or a positive effect on prices. These results are consistent with evidence that in countries with strict regulatory policies, generic competitors are predominantly either licensed co-marketers or new versions of old molecules that manufacturers introduce in order to obtain a price increase (Danzon and Chao, 2000a). In contrast, in countries with free pricing, successive generics enter the market at lower prices, and therefore, prices at the product level are inversely related to the number of generics available. These findings suggest that regulations undermine generic competition and that the cost savings from post-patent competition are not realized in countries with strict pricing and reimbursement policies.

Chapter 4

Research Methodology

This chapter explains the conceptual framework, data and methods employed in this study. The first section describes the research questions of this analysis. The second section summarizes the data used. Finally, the third section explains the methodologies, variables and the empirical models estimated.

4.1 Conceptual Framework

Drug pricing, including generics, is a major responsibility of the national health services of nearly every country. Policies toward drug pricing differ across various nations. As such, competition amongst generics and on patent drugs also differs. This study aims to examine the extent of competition between generic products and therapeutic substitutes under different regulatory regimes. In particular, this analysis focuses on the effect of generic entry on prices in the five largest European pharmaceutical markets. Cardiovascular drugs are the focus of the study. Ten years of comprehensive IMS data at both the molecule and individual product level are employed.

4.2 Data

This study analyzes retail prices of drugs used to treat cardiovascular disease (CVD), the

third-leading cause of death in OECD countries. Importantly, the effectiveness of CVD drug therapies is short-term, so patients must continually receive treatment to maintain its health benefits. As detailed in Table 10, similar to Dickson and Jacobzone (2003) and Timur (2006), the study sample consists of drugs from eight CVD therapeutic categories, which cover both newer and older innovations that form the core of pharmacotherapy for CVD.

Data used in this study were obtained from IMS Health, an international pharmaceutical consulting company that collects sales and price data from various countries. Data are collected at the level within the pharmaceutical market supply and distribution chain that provides reliable information. The IMS Health measure for all dosage forms and strengths is the IMS standard unit (SU). The SU is a single dose e.g., one tablet or capsule, five liquid milliliters (i.e. one teaspoon), or one ampoule or vial of an injected product (IMS 2005). Prices are measured at the ex-manufacturer level and converted from local currencies to euros by IMS Health using constant exchange rates. A country's SU price for a molecule is its volume-weighted average price per dose over all presentations, including generic, licensed, OTC, and parallel imported products (Danzon and Furukawa 2003; Timur, 2006). Products are categorized by the Anatomic Therapeutic Category (ATC) system, which is developed and maintained by European Pharmaceutical Marketing Research Association, EphMrA (EPHMRA 2004). Products are categorized in the sales, medical and promotional audits according to the EphMrA/PBIRG Anatomical Classification System, the main principle of which is that there is only one Anatomical Classification code allocated to a product/pack. This allows each product to be classified consistently in all countries (EphMrA, 2004; Timur, 2006).

The IMS data used here are on all drug sales through retail pharmacies for 10 years between 1994 and 2003. The study restricts the sample to single-molecule ‘‘global’’ products,

that is, products that contain a single active ingredient (molecule) and are available in all five countries. A given molecule may have multiple products (defined by molecule, manufacturer, and IMS product name)—for example, originator brand, licensees, parallel imports, and generics—and each product may have multiple packs, defined by strength, presentation forms, and pack sizes. Although the sample of molecules is uniform across countries, the number of products per molecule, manufacturers, and packs differ across countries. The main unit of analysis here is the product, aggregated over packs for each product.

The sample includes the five largest pharmaceutical markets in the European Union: Germany, the United Kingdom (UK), Italy, Spain, and France. These countries are also the leading pharmaceutical markets in the world after the US and Japan. The study sample contains 259 molecules with a total of 3347 products. The study further restricts the sample to molecules that are available in all five countries as described above. Germany is specified as the baseline country because it contains the most products, is the largest market in the EU, and it is the relatively least regulated market in the EU.

4.3 Variable Definitions

Price. For each pack, IMS reports the price per standard unit. This study defines the average price per standard unit for each product as the volume-weighted average over all forms and packs of the product. For the regression analysis the paper uses the log transformation of price and of all explanatory variables where proportional effects are expected.

Quality. This study controls for several ‘‘quality’’ characteristics that impact the product’s efficacy and its price. ***Molecule Age***, measured as (log) months from the last observation month to the launch date of the first product in the molecule in that specific country. Molecule Age is an

inverse indicator of therapeutic effectiveness, assuming that more recent compounds are generally more effective. Molecule Age is the same for all products in a molecule but is country specific. ***Strength*** is the mean grams of active ingredient per standard unit, averaged over all packs within the product. One can expect a positive relationship between strength and price. ***Form Code*** is the number of different product formulations for each molecule and product, and is intended to reflect choice and convenience available to patients. Forms include different types of tablets, capsules, ampoules, powders, drops, syrups, syringes, and liquids, along with different strengths and pack sizes. The coefficient is expected to be positive, assuming that manufacturers launch new forms only where the expected increase in price is sufficient to cover the fixed costs of developing a new form.

Competition. Measures of competition distinguish between generic and therapeutic substitutes. ***Generic Competitors*** is the number of generically equivalent products in the molecule, including originator, licensed, and parallel imported products, as well as post patent generic imitators. The expected effect of generic imitators on price is negative in markets where manufacturer prices are unregulated. ***Therapeutic Substitute Molecules*** is the number of molecules within the same three-digit therapeutic category ATC3. These drugs are competitors that are chemically distinct but used to treat the same indication, thus reflecting increased availability of substitutes and should thereby be negatively related with price. ***Generic Entry Lag*** is the (log) number of years between the product's own launch date and the launch date of the first product in the molecule (plus one). This ranges from one for the originator product to large positive values for late entrants. The expected sign is negative, under the hypothesis that the originator product has a first-mover advantage relative to later generic producers of the same molecule, which offer little or no therapeutic advantage. ***Therapeutic Substitute Molecule Entry***

Lag is (log) years from the launch of this molecule to the launch of the first molecule in the therapeutic category. The sign could be negative or positive, depending on whether first-mover advantage of the pioneer molecule in a class dominates or is dominated by superior efficacy of later molecules. ***Pack Size*** is the number of SUs averaged over all packs in a molecule. This market variable is converted to standard units according to IMS (2005) guidelines. Price is expected to be inversely related to pack size in countries with competitive retail pharmacy, where manufacturers, particularly generics, compete by offering volume discounts to pharmacists on large packs.

4.4 Methodology

This study investigates the effect of generic entry on pharmaceutical prices by employing two different research strategies. The first section explains the nature of the quasi-hedonic regressions model and the second section describes the fully interacted model in detail.

4.4.1 Quasi-hedonic Price Regressions

This analysis first uses hedonic price regressions to address cross-country differences in product specifications. Products serving the same purpose might have different attributes in different countries. In the sample of this study, the forms, strength levels, and pack sizes are the quality and market characteristics of drugs that vary across countries.

This study examines the price models through quasi-hedonic regressions for three reasons (Danzon and Chao, 2000a; Timur et al. 2010). First, while the standard hedonic model assumes that price determinants differ randomly across products, pharmaceutical prices are expected to differ systematically across countries, reflecting differences in health care regimes. Because

some price variation across countries is explained by factors other than observed product characteristics and that change very little over time, the models include country-specific intercepts. Second, hedonic price regressions estimate the marginal contribution of each characteristic to the value of a product. However, pharmaceutical market imperfections drive a wedge between price and marginal value. These include deviations between patient and physician preferences, moral hazard from insurance coverage, and monopsony power of national health systems on the demand side, along with patent restrictions providing monopoly power to producers and marketing restrictions through drug approval and testing requirements on the supply side. Third, drug prices also vary across countries because of time-varying differences in regulatory and reimbursement environments. To address this, our model specifies market competition measures, which would not appear in a pure hedonic regression, as additional explanatory variables. This study uses the same model for all countries, but tests for cross-national differences in parameters.

As defined in Danzon and Chao (2000a) and Timur et al. (2010), this model uses log transformations of product prices and characteristics,

$$\ln P_{k,j,t} = \alpha + \sum_{c=1}^{8} \beta_c \ln X_{c,k,j,t} + \sum_{t=1}^{9} \varphi_t d_t + \sum_{j=1}^{4} \phi_j d_j + \sum_{t=1}^{9} \sum_{j=1}^{4} \lambda_{j,t} d_j d_t + \sum_{k=1}^{K} \delta_k d_k + u_{k,j,t} \quad (1)$$

All the product quality and competition (market) characteristics appear on the right hand side of Equation 1. Accordingly *k*, *j*, and *t* represent an individual product, country and year respectively. *P* measures the average price per standard unit for each product that is the volume-weighted average over all forms and packs of the product. X_c indicates a vector of quality and competition characteristics of products. β_c captures the different impact of the imperfectly competitive market for pharmaceuticals in different countries and thus measures the country-specific differences between the baseline country Germany and other countries. The model also

includes d variables that are indicators for country j, year t and product k. $\lambda_{j,t}$ is the parameter that estimates the average price difference in time t between the baseline country Germany and country j, which is omitted from the country indicator vector, across products. This price gap is net of variation induced by differences across quality and competition characteristics, products, time and countries (Timur et al. 2010). And, finally u is the regression error in the quasi-hedonic regressions model.

This analysis estimates quasi-hedonic price regressions model by employing panel data methods, where the product-specific intercepts are treated as fixed effects. The fixed effects model refers to the possibility that each unit of observation, market, quality, and time period, would have unique parameters. Following this, in this model, there are market, quality, and time specific "fixed" effects. This analysis combines data from pooling methodology. It is important to note that drug prices also reflect intrinsic value that is not observable. If these are time-invariant and product-specific, then the fixed effects model is efficient (Wooldridge, 2001). On the other hand, this study also estimates a random effects model (by holding ATC3 indicators constant for market and regulatory factors) for time-invariant characteristics because they are not identified in the fixed effects model. The two time-invariant competition variables, generic entry lag and therapeutic substitute molecule entry lag, are included as an explanatory factor in the random effects model.

In the panel data model, δ_k is called a ''random effect'' when it is treated as a random variable, and a ''fixed effect'' when it is treated as a parameter to be estimated for each cross section observation (Wooldridge, 2001). The term fixed effect means that one is allowing for arbitrary correlation between the unobserved effect δ_k and the observed explanatory variables $X_{k,j,t}$. Accordingly, δ_k is called an "individual fixed effect." In the quasi-hedonic price regressions

model, the zero conditional mean assumption - where the mean of the error terms given a specific value of the independent variable is zero $E(u_{k,j,t} \mid X_{k,j,t}, \delta_k) = 0$ is the necessary condition for consistent fixed effects and random effects estimations. Additionally, the observed explanatory variables and the unobserved effect have to yield zero correlation between them, because the random effects model implicitly places δ_k in the error term, therefore the assumption of $Cov(X_{k,j,t}, \delta_k) = 0$ is very crucial for consistent estimations (Wooldridge, 2001). In this analysis, the whole point of using panel data is to allow for δ_k to be arbitrarily correlated with $X_{k,j,t}$. A fixed effects analysis achieves this purpose explicitly, and yields arbitrary correlation between the observed explanatory variables and the unobserved effect, $X_{k,j,t}$ and δ_k respectively. Therefore, the fixed effects model gives more robust estimation than the random effects model does (Wooldridge, 2001). The advantage of the random effects model is consistent estimations of time-invariant variables (generic entry lag and therapeutic substitute molecule entry lag), which cannot be estimated in the fixed effects model, because it is not possible to distinguish the effects of time-invariant observables and unobservables (Wooldridge 2001). Finally, this study uses the Hausman (1978) test to compare the results between the random effects and fixed effects analyses, and concludes in favor of fixed effects model.

Tables 3 and 4 report the product level and molecule level results of fixed and random effects estimation of Equation 1 respectively. All variables are specified in log form, thus each coefficient is interpreted as the elasticity of price with respect to the quality or market characteristic. The regressors have the expected signs in the analysis.

4.4.2 Fully Interacted Model

The fully interacted model expands the quasi-hedonic price regressions model (Equation

1) to estimate the effect of quality and competition (market) characteristics on price across different countries between 1994 and 2003. Mean values of the quality and competition (market) characteristics, parameter values and fixed country effects represent heterogeneity across different countries and over time, therefore this model measures price differences between the baseline country Germany and all other countries by considering all these discrepancies for consistent estimations.

In the fully interacted model, quality and competition (market) characteristics have different effects across different countries and over time. The regression includes controls for product characteristics that vary over time within a drug. Thus, the model controls for drug quality and market characteristics that varies across drugs. The new model in Equation 2 includes interactions between product characteristics and country fixed effects; product characteristics and year fixed effects; and finally interactions between product characteristics, country fixed effects and year fixed effects. This model includes product fixed effects to control for unobserved drug heterogeneity, and year fixed effects to control for price inflation and for all other unmeasured time effects. Rather than estimate separate regressions for each country, the study pools the data for all five countries and estimates a fully interacted model as follows:

$$\begin{aligned}\ln P_{k,j,t} &= \alpha_0 + \sum_{c=1}^{9} \beta_c \ln X_{c,k,j,t} + \sum_{j=1}^{4} \phi_j d_j + \sum_{t=1}^{9} \varphi_t d_t + \sum_{t=1}^{9}\sum_{j=1}^{4} \lambda_{j,t} d_j d_t \\ &+ \sum_{c=1}^{9}\sum_{j=1}^{4} \rho_{c,j} d_j \ln X_{c,k,j,t} + \sum_{c=1}^{9}\sum_{t=1}^{9} \gamma_{c,t} d_t \ln X_{c,k,j,t} \\ &+ \sum_{c=1}^{9}\sum_{t=1}^{9}\sum_{j=1}^{4} \theta_{c,j,t} d_j d_t \ln X_{k,j,t} + \sum_{k=1}^{K} \delta_k d_k + u_{k,j,t} \qquad (2)\end{aligned}$$

The new model has the same definitions of variables and parameters as in Equation 1, and additionally uses new coefficients ρ, γ, and θ for the new interactions between the product characteristics and the country and year indicators. As in Equation 1, β_c measures the country-

specific differential between parameter effects for Germany and other countries j. Net implicit prices for product characteristics are β for Germany in 1994, $(\beta + \gamma_t)$ for Germany in year t =1995 - 2003, $(\beta + \rho_j)$ for other countries j in 1994, and $(\beta + \gamma_t + \rho_j + \theta_{j,t})$ for other countries j in year t = 1995 – 2003 (Danzon and Chao, 2000a; Timur et al., 2010).

As explained previously, Germany is used as the baseline country because it is the least regulated market for both manufacturer prices and pharmacy margins and it has the most products in the sample. This fully interacted model yields the same coefficient estimates with separate, country-specific regressions.

This study uses panel data analysis in order to estimate the model. As Gujarati (2003) says, "panel data methods are used because they can give 'more informative data, more variability, less collinearity among variables, more degrees of freedom and more efficiency." In the case of panel data analysis, fixed effects estimators are considered to be quite efficient. The econometric model used in this analysis accounts for the endogeneity of market entry by employing a fixed effects model, which controls for all observed and unobserved time varying and time-constant variables, and the econometric model also takes advantage of the panel data to eliminate both observed and unobserved heterogeneity and to remedy the problems with error terms. Thus fixed effects model explicitly accounts for endogeneity that resulting from time variant and time-invariant omitted variables. In order to see if it is safe to use fixed effects, the analysis also performs the Hausman test indicating that, since fixed effects model is consistent when observed explanatory variables and unobserved effects are correlated, but random effects model is inconsistent, a statistically significant difference is interpreted as evidence in favor of the fixed effects model.

Table 5 reports fully interacted regressions for product-level prices for 1994 and 2003,

which allows all parameters to differ across countries. Table 6 reports results with the fully interacted model for generic competition variable, in five countries for all years between 1995 and 2003.

Chapter 5

Empirical Results

This chapter reports research results of this analysis. The first section describes summary statistics of the analysis at the product level and molecule level. The second section summarizes the empirical results for quasi-hedonic price regressions. And, finally the third section reports the fully interaction model estimations at the product level.

5.1 Descriptive Statistics

Table 1 reports summary statistics for the product-level variables and Table 2 lists summary statistics for the molecule-level variables, by country. Since the unit of observation in Table 1 is the product, some molecules have more observations than others. This analysis categorizes the variables in the tables as quality characteristics and competition (market) characteristics.

The mean Price per product shows some variations across countries. As reported in Table 1, the SU price (Local Euro) ranges from €0.21 in France, €0.23 in Spain, €0.31 in Italy, to €0.52 in Germany, and €0.62 in the United Kingdom.

Quality characteristics are summarized in the first section of Table 1. The mean Strength per product does not differ significantly across countries. Strength ranges from 0.05 in Germany and the United Kingdom to 0.12 in France, with an overall mean of 0.07. More effective

molecules are assumed to have a higher level of strength, implying a positive relationship between strength and price.

The overall mean for Molecule Age is 22 years, ranging from 16 years in Spain to 24 years in Germany and the United Kingdom. The high sample mean age for all countries reflects the influence of a few very old molecules (Danzon and Chao, 2000a). As Timur (2010) says "molecule age is expected to be inversely related with price, since newer treatments are typically introduced precisely because they are more effective, and thus have higher value, than older treatments."

Form Code includes different types of tablets, capsules, ampoules, powders, drops, syrups, syringes, and liquids, along with different strengths and pack sizes suggesting a positive relationship with price. The overall mean is 2.50, ranging from 1 in France, Italy and Spain to 3 in Germany and the United Kingdom.

Competition (market) characteristics are summarized in the second section of Table 1. The average SU Pack Size ranges from 27 in Italy to 90 in Germany, with an overall mean of 64. Mean Pack Size is significantly lower in France, Italy, and Spain, which require more unit pack dispensing than Germany and the United Kingdom. Economies of scale at the manufacturer level will imply a negative relationship between price and pack size.

Generic Competitors are manufacturers of products containing the molecule, including originators, licensees, parallel imports and generics. The overall mean is 12, ranging from 4 in France, 5 in Spain, 6 in Italy, and 6 in the United Kingdom to 18 in Germany. Germany has the highest number of generic competitors in the sample consistent with the high mean age of the sample, which also reflects laxer regulations in Germany. This implies that global molecules are the most valuable ones and attract the most products per molecule.

Consistent with this, the mean of Therapeutic Substitute Molecules (molecules in the ATC categories) is higher in Germany than in France, Italy, Spain and the United Kingdom. Therapeutic Substitute Molecules also reflect increased availability of substitutes that range from 13 in the United Kingdom to 19 in Germany, with an overall mean of 17.

Generic Entry Lag at the product level is longer for Germany (11 years) compared with 9 years or less for the other countries. Relatively high Generic Entry Lag values for Germany suggest a relatively large number of recent generic entrants. A longer average entry lag implies that generics continue to enter later in the life of the molecule in Germany than in the regulated countries. Danzon and Chao (2000a) points out that in the regulated countries, generic entry (when it occurs) is disproportionally by licensees. As licensees would typically enter early in a molecule life, this is consistent with the shorter average entry lag in the four more heavily regulated countries.

Finally, Therapeutic Substitute Molecule Entry Lag ranges from 13 in the United Kingdom to 19 in Germany, Italy, and Spain with the highest number of years from the launch of the molecule to the launch of the first molecule in the therapeutic category.

5.2 Quasi-hedonic Price Regressions

Tables 3 and 4 contain the product level and molecule level results of fixed and random effects estimations of Equation 1 respectively. Quasi-hedonic price regressions define all variables in the log form; therefore each coefficient in the model is interpreted as the elasticity of price with respect to the quality and competition (market) characteristics. The model yields the expected coefficients with consistent fixed and random effects results.

Consistent with the expectations, the average SU price rises significantly with product strength. Since most of the countries in the sample use reference pricing system, this product-specific feature structures a positive relationship between strength and therapeutic effectiveness. The estimations show that a 10% increase in product strength raises price by 1–1.5%, under both the fixed effects model and random effects model.

Fixed effects model yields little information for molecule age variable; the plausible reason is that fixed effects model considers only within-molecule age variation that changes separately from the fixed year and molecule effects only via the non-linearity of the log transformation (Danzon and Chao 2000a; Timur et al. 2010). On the other hand, the random effects model yields consistent estimates for the relationship between price and molecule age since it considers cross-molecule variation. The significantly negative coefficient in Table 3 implies that relative therapeutic value declines with age as more effective products are introduced in the market. Accordingly, a 10% increase in age reduces price by about 6% in the random effects model.

As shown in Table 3, form code, reflecting choice and convenience available to patients, suggests a positive relationship with price in the fixed effects model. This means that with fixed prices, introduction of a new formulation might provide an opportunity for manufacturers to renegotiate prices upward (Timur, 2010). In other words, manufacturers have an incentive to introduce new forms where expected prices are sufficient to cover the fixed costs of introducing a new form. Random effects model yields a negative relationship with price since it does not allow arbitrary correlation between the observed explanatory variables and the unobserved effect. The fixed effect model is therefore more robust than the random effect model (Wooldridge, 2001).

In the competition characteristics, price decreases substantially with pack size, which indicates economies of scale in packaging, EMEA packaging and labeling regulations, and use in reference pricing calculations (Timur et al. 2010). Both fixed effects and random effects models show that the price of a 10% larger pack size will be lower by about 2.5-3.5%.

Generic competition is negatively related with price in both fixed effects and random effects models. Generic competition reduces price, as expected, by less than 1% for each 10% increase. Pricing and reimbursement regulations in generic drug market may underestimate the effect of generic competition on price in strictly regulated European Union countries. For instance, the German government allows generic suppliers to formulate and test products and complete product review in another country during the life of patent. It is not unheard of for generics to enter in the German market the day following patent expiration. France, on the other hand, does not allow submission for review of entry documents until the patent expires, delaying launch dates by up to 5 years (Timur, 2010).

The number of therapeutic substitute molecules is significantly positively related to price in both models. As shown in Table 3, the coefficients imply that a 10% increase in the number of therapeutic substitute molecules raises price by 4–5%. Both fixed effects and random effects models yield similar estimations.

The generic entry lag, in years, is a time-invariant market characteristic identified only in the random effects model and it is negatively related with price, as expected, by about 2% for each 10% increase. The therapeutic substitute entry lag, in years, is also a time-invariant market characteristic identified only in the random effects model. Its coefficient is positive, indicating that a 10% increase raises price by 3%.

5.3 Fully Interacted Model

To ease exposition, a detailed discussion of the fully interacted model will only cover 2 years, the first (1994) and last (2003). In the appendix, this study presents results for the other 8 years. Complete annual results for the major variable of interest – generic competition – will be presented and discussed in this section.

5.3.1 Quality Characteristics

Table 5 reports fully interacted regressions for product-level prices for 1994 and 2003, which allows all parameters to differ across countries. Table 6 reports empirical results with the fully interacted model for generic competition variable for all years between 1995 and 2003.

Price increases in *Strength* per SU in all countries and over both years, due to the fact that therapeutic value increases with strength, and strength is a direct measure of relative prices. The elasticity of unit price with respect to strength ranges from 0.03 in France to 0.16 in the United Kingdom.

Molecule Age is significantly negatively related to product price in all five countries. Competitive generic prices in Germany are expected to estimate the marginal cost of production, which is related to the therapeutic value of the molecule (Danzon and Chao, 2000a). Additionally, renegotiation of fixed prices as molecules age is the source of large effects in the more strictly regulated countries (Mossialos et al. 2004; Seget 2003; Timur et al. 2010); consistent with the hypothesis that molecule age is an inverse indicator of relative quality. In the United Kingdom, France, Italy, and Spain the Molecule Age interactions are significantly negative due to regulatory restrictions on post launch price increases and due to weaker generic competition. The Molecule Age elasticity is (-0.96) in Germany, (-0.48) in the United Kingdom,

(-0.56) in France, (-0.21) in Italy, and (-0.54) in Spain. As Danzon and Chao (2000a) says, "the full price-age effect at the product level is the combined effect of its Molecule Age and its Generic Entry Lag relative to the first product in that molecule." Since the Generic Entry Lag coefficient is negative for Germany and positive for other more regulated countries, the full price-age effect at the product level indicates that the price decline with age is more attributable to competition in relatively less regulated market Germany and more to regulation in the United Kingdom, France, Italy, and Spain.

Form Codes are positively related with price in all countries. The number of formulations increases price in Germany and Spain throughout the period, which indicates that introducing line extensions is an effective tool for a price increase in countries that do not allow price increases for established products (Danzon and Chao, 2000a). In France, Italy and the United Kingdom, the price elasticity with respect to the number of forms also indicates a positive relationship for many years since manufacturers have an incentive to introduce new forms where expected prices are sufficient to cover the fixed costs of introducing a new form. The price elasticity with respect to the number of forms in France, Italy and the United Kingdom indicates a negative relationship only for few years, which implies weaker incentives to introduce new forms to get a higher price during those periods of time.

5.3.2 Competition Characteristics

Price significantly decreases with *Pack Size* in all countries and years, implied by economies of scale in packaging, EMEA packaging and labeling regulations, and use in reference pricing calculations. Consistent with this negative estimation, patient co-payment is based on pack size in Germany and maximum price is based on maximum pack size in the

United Kingdom (Timur, 2010). The elasticity of unit price with respect to pack size for Germany is (-0.25), for the United Kingdom is (-0.47), for France is (-0.51), for Italy is (-0.33), and for Spain is (-0.68).

Table 5 and Table 6 report empirical results for the elasticity of unit price with respect to *Generic Competition* at the product level between 1994 and 2003. Germany is the only country that demonstrates a decrease in prices as a result of generic competition. An increase in generic competition by 10% leads to a decrease in drug prices by about 1%-2%. German pharmaceutical markets are relatively least regulated where originator market prices are set freely. Therefore, originator drug prices are higher in Germany. Following patent expiration, generic drugs enter the market at a lower price and introduce price competition to originators due to high price gap between originators and generics. In this case, generic firms are able to steal market share from originators via price competition. Originators often decrease their prices to match with generic drug prices. As time passes, market share of originators also decrease and market share of generic drugs increase. Overall, average price per standard unit decreases in Germany. By contrast, in the United Kingdom, the coefficient of the variable representing generic entry is positive and statistically significant. This means that an increase in generic entry by 10% leads to an increase in prices by between 1.1% and 2.2% over 10 years. This study finds evidence that the generics paradox is present in the United Kingdom, as originator prices increase post-generic entry. In the United Kingdom, originator prices are subject to rate of return regulation i.e. profit controls, which were introduced in 1993. Additionally, price caps were introduced in the United Kingdom at the end of 1990s, and price caps were found not being effective price regulation in lowering drug prices. There is some evidence in the literature that price caps have a positive effect on prices. Frank and Salkever (1997) found that the price of generic products decreases as

a result of price caps regulation. However, while more patients use generics, many still use the originator. The group taking the originator has inelastic demand, providing the producer the incentive to raise price and therefore revenue. Thus, the average price of the drug may be higher with a price cap. In Spain, Italy, and France, where direct price regulations are present, generic entry has a positive effect on prices. A 10% increase in generic entry in these countries leads to an increase in prices by 1.0% or less over all years. In these countries, originator markets are heavily regulated; therefore originator drug prices are low. Following patent expiration, when generics enter the market, they cannot introduce price competition to originators due to low originator prices and they are not able to capture market share from originators by competing via price. In this case, generic competition is typically non-price competition. They cannot compete via price but compete with different form codes and pack size, thus they compete via product differentiation, often with higher price per standard unit. Overall, the prices are not affected negatively by increasing generic competition; consistent with the theory that generic entry does not necessarily lead to a reduction in prices in the regulated markets and may only slow down the increase in these prices. This theory is consistent with the results showing that strict pricing and reimbursement regulations lead to an increase in prices in the United Kingdom and France and also slow down the increase in prices in Italy and Spain throughout the study period. In the regulated markets, fixed prices protect generic entrants from price competition from other generic entrants, thus there is no incentive to lower prices as the number of generic entrants increases.

Evidence of the generic paradox should signal to policy makers that under their regulatory structure, generic entry will not lead to price-reducing competition. Thus, as Vandoros et al. (2012) says, “for generic policies to be successful, a switch to generic alternatives must

take place as early as possible post-patent expiry." In sum, this analysis shows that generic competition effectively reduces prices only in Germany, where originator prices are high and free from regulations. The opposite effect is found in the United Kingdom, Spain, Italy and France. In these regulated markets, as mentioned earlier, there is no incentive to lower prices as the number of generic entrants increases.

Looking at the effect of the generic entry on the post generic entry price per standard unit, there are two facts observed in the study. In Germany, where the prices of the originator drugs are high to begin with and where the generic entry leads to a decrease in the price per standard unit, as the time goes by (from 1995 to 2003), the magnitude of this negative effect monotonically increases (from -0.0261 to -0.1775). On the other hand, in the other four more regulated countries, where the prices of the originators are lower before the generic entry and in general the prices per standard unit increase following generic entry, the magnitude of this positive effect decreases over time (from 0.1104 to 0.0006, for instance in the case of Italy).

One possible explanation for the monotonic increase in the negative effect of generic entry in Germany is that over time the generics become more acceptable substitutes for the originator drugs. This would both lead to lower prices for originator drugs post generic entry and lower market shares for these originator drugs. If that is the case in less regulated market Germany, as time passes, the competition brought about by generic drugs become more intense and thus the price of the originators decrease more significantly in response to the entry of the generic drug, lowering the overall price per standard unit (a weighted average of the originator drug prices and generic drug prices) which is observed in data. In addition, the market share of the generics would have also increased over time, which would have further lowered the average price.

There are several possible explanations for why generic drugs become more acceptable substitutes of the originators over time. First, the consumers become more informed of the existence of these generics. Second, the consumers' perception of generics becomes more favorable over time because they become more aware of the fact that generics are indeed good substitutes for the originator drugs. Third, the doctors are more likely to prescribe generics either by their own will (because of either of the reasons mentioned earlier) or because of government regulations (or health insurers) that required them to prescribe generics. Fourth, if the prices of the originators increase sufficiently over time (the prices of new patented drugs do increase significantly), either consumers or doctors or insurers or the regulators are more likely to consider alternatives (to look for them, to purchase them, to prescribe them, to require them to be prescribed, to pass laws that required them to be prescribed, etc.).

On the other hand, in more regulated countries, where the prices of the originators are lower before the generic entry, in general the prices per standard unit increase following generic entry, but the magnitude of this effect decreases over time. One possible explanation is that following patent expiration generics enter the market in different form codes and pack sizes with a higher price per standard unit. As more generics enter the market, they capture market share with product differentiation and increase the price per standard unit. As time passes generics continue to enter with higher price per standard unit but they start to capture smaller market share because they face more stringent spatial competition; more generic entry leaves smaller product space for firms that compete via product differentiation. Therefore, in these regulated countries the prices per standard unit still increase following generic entry, but the magnitude of this positive effect decreases over time.

The above conjecture regarding a possible explanation for the change over time in the effect of the generic entry on the average drug price is only few of the possible explanations, which at this time this study cannot test because of lack of specific data on the evolution over time of the price and market shares of the originator drugs.

As further evidence of generic price competition in Germany, generics enter and compete via price. If market prices are high enough, generic entry will occur in markets with older drugs. Generic entry lag still lowers the prices. For the United Kingdom, France, Italy, and Spain the later entrants receive positive price premiums with the positive elasticity of price with respect to *Generic Entry Lag*, which is consistent with expected regulatory effects in these countries. For these regulated countries, the positive entry lag premium also reflects the relatively small number of generic entrants (mean numbers of generic competitors in these countries are much less than Germany; 6 or less versus 18).

In Table 5, price is positively related to the number of *Therapeutic Substitute Molecules* with an elasticity of (0.49) for Germany indicating that the number of Therapeutic Substitute Molecules does not have a competitive pressure on price. On the other hand, the price elasticity with respect to Therapeutic Substitute Molecules is significantly negative for the United Kingdom (-0.36), France (-0.31), Italy (-0.44), and Spain (-0.11). In these countries, therapeutic reference pricing regulations are present to encourage across-molecule competition by therapeutic substitute molecules. In these regulated countries, there is evidence of competition between therapeutic substitutes in the form of lower prices for successive entrants. Competition, under therapeutic reference pricing, decreases drug prices (Brekke et al. 2007). These countries do not have as much generic competition, although generics are much closer substitutes.

Since the number of Therapeutic Substitute Molecules does not appear to exert competitive pressure on price, the price elasticity with respect to *Therapeutic Substitute Molecule Entry Lag* is positive for Germany (0.30). Consistent with the negative price elasticity with respect to Therapeutic Substitute Molecules, Therapeutic Substitute Molecule Entry Lag is negative for France (-0.23) and Spain (-0.01) indicating that successive entrants receive lower prices.

5.3.3 Summary of Findings

This analysis focuses on how drug prices change over time as a consequence of generic competition. The results suggest that the relationships between the dynamics of drug prices and generic competition are complex and differentiated across EU countries.

The most important factor that increases prices in regulated countries relative to Germany is non-price competition. The relatively small number of generic entrants and fewer generics are consistent with the results found in the regulated pharmaceutical markets: generic entry is not attractive once patent expires due to low regulated prices for originator products. Danzon and Chao (2000a) says that "the incentives for price-competitive generic strategies are less owing to price-insensitive purchasers, and the incentives for price- increasing generic strategies are greater." The estimates of generic competition in Germany show that reference pricing policy and free originator pricing together increase generic entry and price competition. In the United Kingdom, the total generic effect is found to be weaker compared to Germany, due to the lower number of generics per molecule and most importantly due to profit control and price caps regulations.

There is evidence of competition between therapeutic substitutes in the form of lower prices for successive entrants. This study shows that the number of Therapeutic Substitute Molecules has a negative effect on price in the more regulated markets, but this is mostly attributable to regulation rather than competition, since prices of established products are quite effective in regulation of new product prices. Generic price competition does not exist in these regulated countries; even though generics are much closer substitutes. Danzon and Chao (2000a) says, "these pricing and reimbursement regulations cause indistinguishable price incentives for investment in innovative and imitative R&D." The results of this work are consistent with Danzon and Chao's findings that the more regulated countries have produced a large number of minor new products but few truly innovative molecules that have achieved global diffusion.

Germany has a free-pricing originator market. It thus has generic price competition and more generic competitors compared to the other more regulated regimes. The elasticity of product price with respect to Generic Competitors is negative and significant. One would expect more entry and price competition in Germany and the results confirm this. These results agree with other studies that examined other lightly regulated markets (Grabowski and Vernon, 1992 and Ellison et al, 1997). On the other hand, generic entry and product price are positively related in the more regulated markets of this study. These positive elasticities in the United Kingdom, France, Italy, and Spain are consistent with evidence that multi-source suppliers in these countries are usually licensed co-marketers rather than competing generic manufacturers or minor new products that enter to obtain a higher regulated price.

Finally and most importantly, this analysis does not find any evidence that prices decrease as a result of generic entry in the heavily regulated European pharmaceutical markets. The findings are very clear and also show the presence of the generics paradox. Across the four

countries the elasticity estimates for generic competition are positive, but differ in magnitude, with a much larger coefficient in the U.K. than in France, Italy, and Spain.

The number of generic entrants depends on drug prices in the market; when prices are high, firms enter due to higher expected profits (Danzon and Chao, 2000a). This could lead to a reverse causation problem and bias the estimates. Other studies have posited that such a bias would understate the price-lowering effects of generic entry. Thus the true effects in Germany would be more negative, while the positive effects in the other countries are overstated. Danzon and Chao (2000a) makes the claim that this bias would be larger in the less regulated countries. This endogeneity problem in this analysis is limited by two things: First, firms can not obtain a production permit immediately, it takes time due to regulatory delay for the approval of drug in the industry, therefore the number of generic competitors is predetermined when price is set. Second, this study controls for country and product fixed effects as well as interaction between the country and the time effects. Thus, the analysis allows for a great amount of heterogeneity that can be correlated with generic entry.

There are few important points that need to be emphasized at this point. First, this study does not look at comparisons of price levels across countries, but focuses on price changes within countries. Second, this study does not analyze the determinants of generic entry (see NERA, 1998). This would be an important and interesting issue for future research. This paper focuses on a preliminary analysis of generic competition and prices, considering the role of several fundamental features of the European pharmaceutical market.

Chapter 6

Conclusions

This chapter summarizes the main findings regarding generic competition in the European Union pharmaceutical market. Additionally, limitations and future research are outlined at the end.

6.1 Main Findings

This study focuses on the microeconomic decisions of pharmaceutical firms, including competition between branded and generic products. The firms' strategies reflect the actual and anticipated decisions of rivals and of governments.

The empirical analysis used comprehensive IMS data for five countries over 10 years (1994-2003) to estimate the effect of generic competition on drug prices at the level of the individual product. Generic competition has a significant negative effect on price for Germany, whereas for the countries with strict price regulation (the United Kingdom, France, Italy, and Spain), the number of generic competitors has either no effect or a positive effect on prices. Danzon and Chao (2000a) says, "this is consistent with evidence that in countries with strict regulation, generic competitors are predominantly either licensed co- marketers or ''new'' versions of old molecules that manufacturers introduce in order to obtain a price increase." On the other hand, in countries with relatively free pricing regime, successive generics enter at lower

prices, and prices at the product levels are negatively related to the number of generics.

There is also evidence for therapeutic competition in the form of lower prices for successive entrants in regulated markets. The number of Therapeutic Substitute Molecules does appear to reduce prices in the United Kingdom, France, Italy and Spain, where the effect is more consistent with their regulatory systems than with competition.

As a conclusion, this study examines whether generic price competition exists in regulated European pharmaceutical market. The analysis finds empirical evidence that the price lowering benefits from generic competition do not occur in the presence of certain regulations. When including all five countries in panel data models, this study finds evidence that generic price competition is not present in the United Kingdom, France, Italy, and Spain as prices increase with generic entry post-patent expiry. The only country in which generic entry leads to lower prices is Germany.

In unregulated markets, generic price competition provides cost savings to health insurers. However, this situation does not hold in regulated pharmaceutical markets since regulations restrict price competition. The findings in this work agree with Danzon and Chao (2000a) and suggest that regulations undermine price competition and sacrifice potential cost savings due to generic entry.

Not all differences are due to market regulations. Pammolli et al. (2002) note that the health care services, provisions, and medical traditions vary widely across countries. Surely, this will also affect the effects of generic entry on prices.

Finally, generic price competition can create strong incentives for innovation within the European pharmaceutical market, allowing higher prices and profits for innovative on patent products (Pammolli et al., 2002). On the other hand, in the regulated markets, strict price

regulation undermines generic price competition, and this reduces the positive effects of generic competition on innovation within pharmaceuticals (Sloan, Health Economics, 2012).

6.2 Limitations

This research has several limitations that should be emphasized. First, the data set used in this study focuses on ten years between 1994 and 2003. This study yields interesting results for regulated European market, and since the regulatory environment has changed over time, future research can focus on the same topic by considering the early 2010s, when patents of many widely prescribed products expire.

Second, quality and market characteristics employed in the empirical analysis are based on the measurability of variables in the data set. A different competition characteristic factor, such as an "index" variable considering all the different regulations and reimbursements in different countries, may be very useful in order to better capture the generic price competition (Timur, 2006).

Third, although this study has identified certain factors like returns to age, therapeutic substitutes, and competition, controlling for these measured factors leaves some unmeasured country effects. For instance, the contribution of patent expiration and other factors to these unexplained differences is an important subject for future research.

Fourth, as explained in previous chapters, exchange rate fluctuations are controlled through IMS fixed euro standard unit prices, thus the role of exchange rate changes must be investigated separately (Timur, 2006).

Finally, even though they are the largest markets, this analysis focuses only on 5 of the 28 members of the European Union.

6.3 Future Research

Future research should address several of the limitations mentioned above. Heterogeneity in drug prices due to different pricing and reimbursement regimes has provided arbitrage opportunities across countries. This is called "parallel trade (PT)", which is a legal activity within a single pharmaceutical market. Parallel imports have an important effect on price differences. As a follow up of this work, the theoretical and empirical work could be extended to the impact of the parallel imported products on pharmaceutical prices in the regulated markets.

Continued research in this area should study the competition of PT by using comprehensive IMS data for the five largest European pharmaceutical markets – the United Kingdom, Germany, France, Italy, and Spain. The impact of PT on price competition across different countries has been discussed for a long time, but the literature has contradicting results. Therefore, future research can focus on the price competition by examining the parallel traders' incentives to deviate from the price of the originator products and can analyze if the price of the original products will be affected negatively as a result of parallel traded products. The paper should also consider the different pricing and reimbursement regulations applied to parallel traded products to examine the effect of PT on prices. This analysis will inform policy makers about whether cost savings are realized in countries with strict regulatory systems as a result of parallel trade activities.

Finally, continued research in this area would give a better understanding of the dynamic price competition in the pharmaceutical industry in the EU.

Table 1. Overall Mean; (Overall), [Within] Standard Deviation Values; N Unit of Observation: Products, Retail Pharmacy, 1994 – 2003

Variable	Germany	France	United Kingdom	Italy	Spain	Overall
SU Price (Local Euro)	0.5208 (1.1888) [0.1871] 5039	0.2116 (0.2051) [0.0135] 1022	0.6290 (3.1275) [0.1456] 945	0.3109 (0.7629) [0.1189] 1822	0.2337 (0.2597) [0.0478] 1298	0.3584 (1.3227) [0.1513] 10126
Quality:						
Strength(g)	0.0529 (0.0884) [0.0089] 5039	0.1276 (0.4011) [0.0046] 1022	0.0523 (0.0831) [0.0101] 945	0.0939 (0.1468) [0.0295] 1822	0.0768 (0.1375) [0.0145] 1298	0.0708 (0.1663) [0.1041] 10126
Molecule Age	24.0784 (13.4493) [2.8724] 8160	21.4869 (11.8051) [2.8732] 1530	24.5141 (14.3001) [2.8733] 1410	21.9339 (10.9312) [2.8937] 2650	16.8350 (11.1338) [2.8730] 1910	22.6181 (12.9345) [3.0572] 15660
Form Code	3.3351 (4.4552) [2.0342] 8240	1.1574 (1.1126) [0.6454] 1550	3.0574 (4.5637) [1.4828] 1410	1.2215 (1.1186) [0.5444] 2650	1.3994 (1.4475) [0.7835] 1910	2.5061 (3.7171) [1.7960] 15760
Competition:						
Pack Size	90.0948 (22.3983) [6.7413] 5039	33.1120 (13.4247) [2.0104] 1012	68.4500 (83.7458) [51.6193] 945	27.8134 (15.7158) [2.7000] 1822	40.9572 (16.9818) [2.6861] 1298	64.8498 (41.7574) [21.1523] 10116
Generic Competition	18.4353 (16.3496) [5.0843] 8240	3.9309 (3.6622) [2.0654] 1550	5.5673 (6.1620) [1.7857] 1410	6.6290 (6.4981) [2.1331] 2650	4.9062 (5.2283) [3.9564] 1910	12.2327 (14.0546) [4.5613] 15760
Generic Entry Lag	10.8625 (11.2981) [0] 8150	8.9935 (12.3641) [0] 1540	7.2205 (18.2439) [0] 1360	8.6981 (10.4850) [0] 2650	6.3979 (7.7276) [0] 1910	8.6002 (11.7480) [0.6012] 15610
Therapeutic Substitute Molecule	19.5940 (7.4819) [1.4054] 8240	14.4954 (4.7608) [1.2526] 1550	13.0198 (4.0079) [1.3880] 1410	16.6022 (5.3471) [1.5518] 2650	15.1722 (6.2132) [1.2986] 1910	17.4654 (6.9412) [1.7413] 15760
Therapeutic Substitute Molecule Entry Lag	18.6639 (15.9104) [0] 7290	15.7381 (11.1827) [0] 1260	13.1951 (9.7283) [0] 1230	19.5043 (10.6759) [0] 2280	19.2616 (11.7163) [0] 1720	18.1219 (13.8951) [0.6987] 13780

Table 2. Overall Mean; (Overall), [Within] Standard Deviation Values; N Unit of Observation: Molecule, Retail Pharmacy, 1994 – 2003

Variable	Germany	France	United Kingdom	Italy	Spain	Overall
SU Price (Local Euro)	0.7079 (2.9756) [0.2363] 1535	0.2446 (0.2186) [0.0180] 998	0.9954 (3.8324) [1.2219] 954	0.2792 (0.2735) [0.0433] 1105	0.2272 (0.3161) [0.0382] 993	0.5039 (2.2513) [0.9162] 5585
Quality:						
Strength(g)	0.1529 (0.4583) [0.0299] 1535	0.1426 (0.4109) [0.0045] 998	0.1097 (0.4174) [0.1090] 954	0.1390 (0.3861) [0.0391] 1105	0.2176 (0.7000) [0.0146] 993	0.1524 (0.4850) [0.1997] 5585
Molecule Age	20.7951 (15.8138) [2.8731] 1660	18.9521 (12.7938) [2.8735] 1150	22.3972 (19.0603) [2.8736] 1070	20.1222 (13.9323) [2.8733] 1350	18.5000 (12.2250) [2.8734] 1190	20.1651 (14.9874) [5.2916] 6420
Form Code	10.1146 (15.6971) [3.3044] 1770	2.3647 (2.6718) [1.0148] 1190	6.1398 (8.5647) [2.4327] 1080	2.4629 (2.7911) [1.0604] 1350	2.5075 (3.1166) [0.9489] 1190	5.1150 (9.6884) [7.7632] 6580
Competition:						
Pack Size	85.4489 (29.0398) [8.7029] 1535	34.2039 (16.6044) [7.3645] 998	84.7038 (124.8797) [72.1947] 954	28.0996 (10.8393) [2.1203] 1105	40.7264 (16.9137) [3.4093] 993	56.8663 (60.6243) [50.7921] 5585
Generic Competition	5.9858 (9.8455) [3.1336] 1770	1.9781 (2.6833) [1.4446] 1190	1.8527 (2.4395) [0.8506] 1080	2.3325 (3.1603) [1.0555] 1350	2.5974 (4.1714) [1.7986] 1190	3.2203 (6.0340) [4.8851] 6580
Therapeutic Substitute Molecule	22.3135 (8.0338) [1.6718] 1770	14.4495 (5.2413) [1.2616] 1190	13.7027 (3.8900) [1.4225] 1080	15.3681 (5.1608) [1.5743] 1350	15.1512 (6.2689) [1.3172] 1190	16.7577 (7.0020) [4.1716] 6580
Therapeutic Substitute Molecule Entry Lag	20.2767 (14.8938) [0] 1120	15.9090 (10.5595) [0] 880	17.4069 (12.3608) [0] 860	19.5825 (12.8462) [0] 1030	19.0434 (12.4329) [0] 920	18.5800 (12.9081) [3.8204] 4810

Table 3. Quasi-Hedonic Price Regression Results Unit of Observation: Products, Retail Pharmacy, 1994-2003

	Fixed Effects	Random Effects
Quality Characteristics:		
Strength (ln)	0.1344 (0.0328)**	0.0885 (0.0226)**
Molecule Age (ln)	-0.0393 (0.0580)***	-0.6796 (0.0926)***
Form Code (ln)	0.0089 (0.0248)**	-0.0506 (0.0366)**
Competition Characteristics:		
Pack Size (ln)	-0.2526 (0.0555)***	-0.3396 (0.0687)***
Generic Competition (ln)	-0.0263 (0.0403)**	-0.0276 (0.0125)**
Generic Entry Lag (ln)		-0.1776 (0.0626)***
Therapeutic Substitute Molecules (ln)	0.5159 (0.0992)***	0.4861 (0.0955)***
Therapeutic Subst. Molecule Entry Lag (ln)		0.3010 (0.0458)**
N	8,773	3,524
R^2 (within)	0.5376	0.3540

The dependent variable is the log of the SU euro price. p-values in parantheses.
, ** and * reflect significance at the 1, 5 and 10% levels, respectively.*

Table 4. Quasi-Hedonic Price Regression Results Unit of Observation: Molecules, Retail Pharmacy, 1994-2003

	Fixed Effects	Random Effects
Quality Characteristics:		
Strength (ln)	0.3023 (0.000)*	0.2160 (0.001)*
Molecule Age (ln)	0.1248 (0.029)**	-0.2031 (0.001)*
Form Code (ln)	-0.0987 (0.081)***	0.0653 (0.193)
Competition Characteristics:		
Pack Size (ln)	-0.3605 (0.000)*	-0.3924 (0.000)*
Generic Competition (ln)	-0.1240 (0.014)**	-0.0607 (0.030)**
Therapeutic Substitute Molecules (ln)	0.2718 (0.014)**	0.0623 (0.570)
Therapeutic Subst. Molecule Entry Lag (ln)		0.1103 (0.475)
N	3,263	2,480
R^2 (within)	0.6369	0.3689

The dependent variable is the log of the SU euro price. p-values in parantheses.
, ** and * reflect significance at the 1, 5 and 10% levels, respectively.*

Table 5. Product Level Pharmaceutical Prices: Log Price Per Unit Fully Interacted Model – Fixed Effect, 1994 – 2003

Variable	Year	Germany	France	U.K.	Italy	Spain
Quality:						
Strength (ln)	1994	0.1344*	0.0619**	0.1580*	0.1126*	0.1557**
		(0.004)	(0.015)	(0.000)	(0.003)	(0.011)
	2003	0.1259*	0.0353*	0.1598*	0.0596*	0.1502*
		(0.001)	(0.006)	(0.000)	(0.000)	(0.004)
Molecule Age (ln)	1994	-0.6797*	-0.0970*	-0.4834	-0.0367*	-0.5392*
		(0.000)	(0.001)	(0.180)	(0.000)	(0.000)
	2003	-0.9603*	-0.5663*	-0.3968*	-0.2144*	-0.7134*
		(0.003)	(0.000)	(0.001)	(0.000)	(0.000)
Form Codes (ln)	1994	0.0089***	0.1763**	0.0004	-0.0787**	0.1400***
		(0.080)	(0.014)	(0.157)	(0.024)	(0.085)
	2003	0.0756*	-0.0538*	-0.0207*	0.0728*	0.1458*
		(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Competition (Market):						
Pack Size (ln)	1994	-0.2527*	-0.5135*	-0.4787*	-0.3385*	-0.6818*
		(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
	2003	-0.2198*	-0.4273*	-0.5768*	-0.3294*	-0.8127*
		(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Generic Competition (ln)	1994	-0.0263**	0.0973**	0.2252*	0.1332*	0.1052*
		(0.022)	(0.017)	(0.003)	(0.003)	(0.001)
	2003	-0.1775*	0.0374*	0.1118*	0.0006*	0.0039*
		(0.000)	(0.000)	(0.000)	(0.000)	(0.000)

Table 5 (cont.) Product Level Pharmaceutical Prices: Log Price Per Unit Fully Interacted Model – Fixed Effect, 1994 – 2003

Variable	Year	Germany	France	U.K.	Italy	Spain
Generic Entry Lag (ln)	1994	-0.1776*	0.2651*	0.2813**	0.0547*	0.0877*
		(0.005)	(0.002)	(0.018)	(0.008)	(0.003)
	2003	-0.1777*	0.2650*	0.2812**	0.0548*	0.0877*
		(0.005)	(0.002)	(0.018)	(0.008)	(0.003)
Therapeutic Substitute Molecules (ln)	1994	0.5159**	-0.3138*	-0.1373**	-0.4497*	-0.0478**
		(0.016)	(0.000)	(0.031)	(0.000)	(0.039)
	2003	0.4970**	-0.0932*	-0.3608*	0.1193*	-0.1134**
		(0.032)	(0.000)	(0.000)	(0.000)	(0.029)
Therapeutic Substitute Molecules Entry Lag (ln)	1994	0.3011*	-0.2353*	0.3196*	0.3072**	-0.0112*
		(0.000)	(0.000)	(0.003)	(0.040)	(0.002)
	2003	0.3010*	-0.2354*	0.3196*	0.3071**	-0.0111*
		(0.000)	(0.000)	(0.003)	(0.040)	(0.002)

Adjusted R^2=0.539; p-values in parantheses.
, ** and * reflect p < 0.01, p < 0.05 and p < 0.10 respectively.*

Table 6. Product Level Pharmaceutical Prices: Generic Competition Log Price Per Unit, Fully Interacted Model

Year	Germany	France	United Kingdom	Italy	Spain
1995	-0.0261 (0.173)	0.0981 (0.447)	0.1808* (0.005)	0.1104* (0.007)	0.0923* (0.004)
1996	-0.0081*** (0.094)	0.0684*** (0.056)	0.1849* (0.002)	0.1083* (0.004)	0.0876* (0.002)
1997	-0.0579* (0.004)	0.0382* (0.006)	0.1687* (0.000)	0.1076* (0.000)	0.0794* (0.000)
1998	-0.0882* (0.000)	0.0087* (0.000)	0.1504* (0.000)	0.0960* (0.000)	0.0712* (0.000)
1999	-0.1079* (0.000)	0.0316* (0.000)	0.1780* (0.000)	0.0966* (0.000)	0.0605* (0.000)
2000	-0.1188* (0.000)	0.0373* (0.000)	0.1915* (0.000)	0.0844* (0.000)	0.0564* (0.000)
2001	-0.1336* (0.000)	0.0394* (0.000)	0.1584* (0.000)	0.0663* (0.000)	0.0338* (0.000)
2002	-0.1581* (0.000)	0.0329* (0.000)	0.1242* (0.000)	0.0235* (0.000)	0.0152* (0.000)
2003	-0.1775* (0.000)	0.0374* (0.000)	0.1118* (0.000)	0.0006* (0.000)	0.0039* (0.000)

Adjusted R^2=0.539; p-values in parantheses.

, ** and * reflect $p < 0.01$, $p < 0.05$ and $p < 0.10$ respectively.*

Table 7. National Controls for Pharmaceuticals on the Supply-Side

COUNTRY:	NATIONAL HEALTH SYSTEMS: *	PRICING:	REIMBURSEMENT:
Germany	GKV, statuary health insurance covers 88% of the population. Most of the remaining population had private insurance.	Price freedom for new products	a) Reference price for off-patent sector (products subjected to generic competition; reference price for identical molecule only) b) Drug budgets with caps re-introduced in 1999. c) Negative list d) Positive list
UK	The National Health Service since 1948 financed through central government.	a) PPRS: Agreement with industry on profit control, renewed in 1999 for a five-year period b) Price cut, as part of PPRS, of 4.5% c) Free price modulation by 2001.	a) Negative List b) Homogeneous budget given to PCGs c) Practice guidelines d) Guidance on cost-effectiveness by NICE, influences prescribing
France	Universally covered (99% of the population) by statuary health insurance.	a) Price fixing through negotiation (productgs medical value, prices of comparable medicines, volume sales and conditions used) b) Comparisons with other European Countries for iinnovativej products c) Periodic price reductions for new and expensive products d) Price freedom has been introduced since 2003**	a) Comite Economique du Medicament decides on reimbursable prices on advice from Transparency committee b) Positive List c) Medical References d) Targets for igate-keepingj GP e) Pharmacoeconomic guidelines under development f) Prices of generics 30% lower than those of the original
Italy	SSN: National Health Service. Funds are supplemented by local taxes and health service charges.	a) Average European Price (all EU countries) for ioldj products and products registered with the national procedure; AEP is calculated on ex-manufacturergs price (excl. VAT), of top five selling equivalents, including generics. b) Price negotiation (contractual model) for new and innovative products (for drugs registered with EMEA or for those for which AEP cannot be calculated) c) Price freedom for non-reimbursable drugs d) Generics are priced at least 20% below the original e) Frequent use of price cuts/freezes	a) Positive list b) Reference listing and same prices for same drugsg principle for off-patent drugs c) Formal requirement for economic evaluation during price negotiations d) Guidelines and protocols defined and managed at local level e) Official earmarked budget for innovative drugs introduced in 1998, representing 1% of national drug budget
Spain	The National statuary health insurance	a) Price control trough negotiation on a cost-plus basis b) International price comparisons c) Price-volume agreement for expensive products	a) Positive list b) Negative list c) Reference pricing for estimating maximum reimbursement for multi-source products

(Timur 2006), (Kanavos 2001), (Seget 2003), (Blachier and Kanavos), (Jommi), (Kullman), (Mossialos et al. 2004)

Table 8. Summary of Approaches in the Regulation of Pharmaceutical Prices by Originator and Generic Drugs (2003)

Countries:	Market segment	Free Pricing	Direct Price Controls	Use of international price comparisons	Profit Controls	Reference Pricing
France	Originator		X	X		
	Generic					X
Germany	Originator	X				
	Generic					X
Italy	Originator		X	X		
	Generic					X
Spain	Originator		X	X		
	Generic			X		X
UK	Originator				X	
	Generic		X			

(Timur 2006), (Mossialos et al. 2004)

Table 9. Demand-Side Policies (Prescribing, Dispensing and Consumption) in the Member States

Country:	Positive List	Negative List	Budget	Guidelines / Monitoring	Generic Prescribing	Substitution	Incentives	Co-payment
France	Yes	No	Yes	Yes	Yes (limited-gatekeepers)	Yes	Yes (gatekeepers)	%
Germany	No (but planned)	Yes	Yes	Yes	Yes	Yes	Yes	Flat Fee
Italy	Yes	No	Yes	Yes	No	Yes	No	% + flat fee
Spain	Yes	Yes	No	Yes	Yes (limited)	No	No	% up to a max per item
UK	No	Yes	Yes	Yes	Yes (limited)	No	Yes	Flat

(Timur 2006), (Kanavos 2001)

Table 10. ATC Therapeutic Categories for Cardiovascular Disease

ATC Code	Category Name
C1A	Cardiac Glycosides and Combinations
C2A	Antihypertensives (of non-herbal origin) Plain: It includes plain antihypertensives and combinations other than those with diuretics, eg combinations of two synthetic antihypertensives or combinations of one synthetic antihypertensive with reserpine.
C3A	Diuretics: Combinations with potassium belong to C3A1, C3A2 or C3A3.
C4A	Cerebral and Peripheral Vasotherapeutics: This group includes all products (including citicoline) which are mainly recommend for cerebral vascular diseases or peripheral circulatory disorders excluding venous diseases. Combination products are only classified in this group if they do not belong to group C1-C3, C7-C11.
C7A	Beta-Blocking Agents, Plain: Includes, eg acebutolol, alprenolol, amosulalol, arotinol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucumolol, bufetolol, bunitrolol, bupranolol, butofilolol, carazolol, carteolol, carvedilol, celiprolol, cloranolol, dilevalol, esmolol, indenolol, labetolol, levobunolol, mepindolol, metipranolol, metoprolol, nadolol, nifenalol, nipradilol, oxprenolol, penbutolol, pindolol, practolol, propranolol, sotalol, tertanolol, tilisolol, timolol, toliprolol.
C8A	Calcium Antagonists, Plain
C9A	Ace Inhibitors, Plain : Angiotensin-Converting-Enzyme inhibitors. It includes eg alacepril, benazepril, captopril, cilazepril, delapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril.
C10A	Cholesterol and Triglyceride Regulating Preparations: Includes all products regulating cholesterol and triglycerides only. Combinations with products of group C4 should be classified here.

(Timur 2006), (Jacobzone 2000)

Table 11. Largest Pharmaceutical Markets in the World, National Currency (million), growth: US$, NC

		2000			2001			2002			2003		
Rank 03	Country	Mill NC	+($)	+NC	Mill NC	+($)	+NC	Mill NC	+($)	+NC	Mill NC	+($)	+NC
1	USA	150,952	14	14	176,748	17	17	197,602	12	12	219,522	11	11
2	Japan	6,231,585	8	2	6,502,706	-7	4	6,603,811	-2	2	7,059,335	12	7
3	Germany	18,157	-8	6	19,921	7	10	21,515	14	8	24,631	30	14
4	France	18,111	-6	9	19,418	4	7	20,183	9	4	22,583	27	12
5	Italy	11,990	-1	15	13,441	9	12	14,136	11	5	15,592	25	10
6	United Kingdom	7,380	0	7	8,180	5	11	9,111	16	11	10,386	20	14
7	Spain	7,711	2	18	8,349	5	8	9,174	16	10	10,794	34	18
13	Australia	5,452	0	11	6,227	2	14	6,854	16	10	8,088	30	18
17	Belgium	2,722	-7	8	2,862	2	5	3,049	12	7	3,521	31	15
18	Poland	11,013	12	22	11,913	15	8	12,373	4	4	14,407	18	16
19	Greece	1,504	-1	19	1,805	15	20	2,281	33	26	2,898	44	27
20	Sweden	19,690	0	11	21,051	-5	7	22,737	15	8	24,711	22	9
21	Switzerland	2,971	-4	8	3,279	10	10	3,517	16	7	3,926	26	12
23	Austria	1,766	-9	6	1,864	3	6	2,038	15	9	2,284	27	12
24	Portugal	1,702	-6	8	1,848	5	9	1,998	14	8	2,183	24	9
29	Finland	1,071	-5	10	1,201	9	12	1,330	17	11	1,491	27	12
33	Denmark	7,105	-5	10	7,782	6	10	8,799	19	13	9,762	26	11
35	Norway	6,945	-3	9	7,742	9	11	8,912	30	15	9,384	16	5
36	Czeck Republic	28,254	0	11	29,896	7	6	32,763	27	10	38,138	29	16

(Timur 2006), (Pammolli et al. 2004)

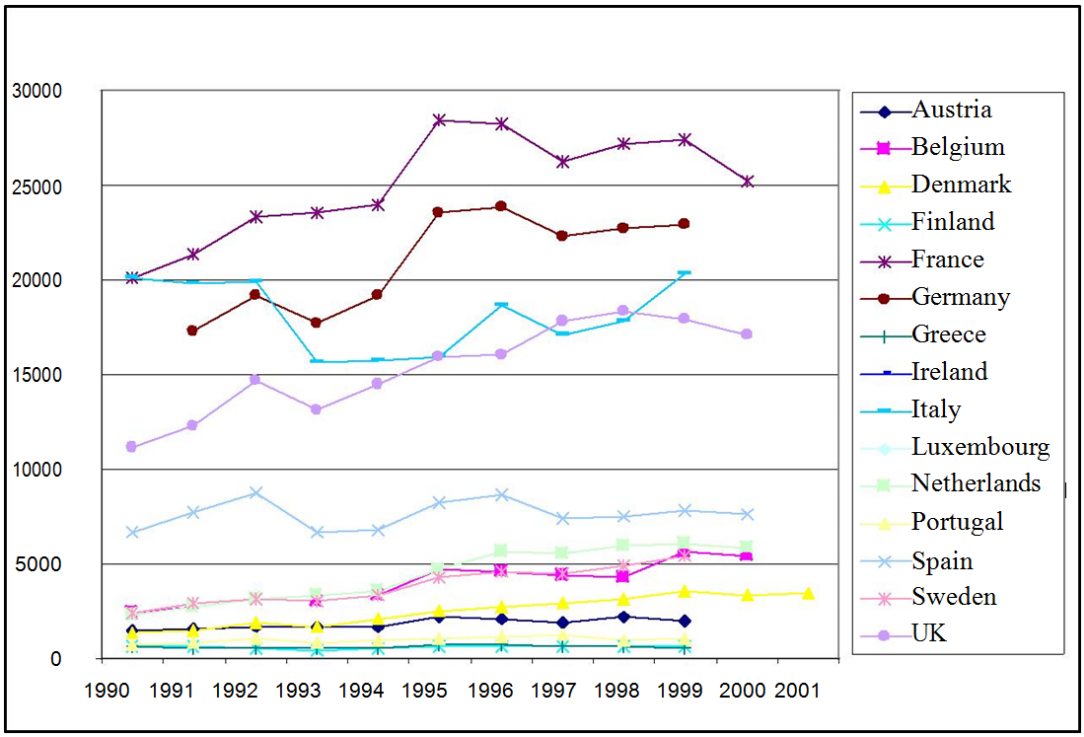

Figure 1. Pharmaceutical Production in the EU (In million dollars at exchange rate)
Source: OECD Health Data (2003)

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Appendices

Appendix A: Tables

Table A.1. Product Level Pharmaceutical Prices: Strength Log Price Per Unit, Fully Interacted Model

Year	Germany	France	United Kingdom	Italy	Spain
1995	0.1325 (0.009)	0.0666 (0.051)	0.1407 (0.004)	0.1008 (0.000)	0.1482 (0.002)
1996	0.1314 (0.014)	0.0602 (0.074)	0.1364 (0.004)	0.0979 (0.000)	0.1509 (0.001)
1997	0.1269 (0.014)	0.0636 (0.046)	0.1413 (0.002)	0.0925 (0.000)	0.1498 (0.012)
1998	0.1223 (0.011)	0.0668 (0.030)	0.1517 (0.001)	0.0880 (0.001)	0.1501 (0.022)
1999	0.1237 (0.010)	0.0649 (0.050)	0.1224 (0.001)	0.0901 (0.000)	0.1538 (0.039)
2000	0.1269 (0.008)	0.0596 (0.044)	0.1356 (0.001)	0.0725 (0.000)	0.1516 (0.034)
2001	0.1272 (0.005)	0.0473 (0.032)	0.1212 (0.002)	0.0659 (0.000)	0.1488 (0.019)
2002	0.1311 (0.004)	0.0407 (0.027)	0.1541 (0.000)	0.0541 (0.000)	0.1459 (0.010)

Adjusted R^2=0.539; p-values in parentheses.

Table A.2. Product Level Pharmaceutical Prices: Molecule Age Log Price Per Unit, Fully Interacted Model

Year	Germany	France	United Kingdom	Italy	Spain
1995	-0.5972 (0.031)	-0.1441 (0.021)	-0.3254 (0.039)	-0.1022 (0.006)	-0.6456 (0.000)
1996	-0.6558 (0.006)	-0.2028 (0.005)	-0.5280 (0.006)	-0.1323 (0.030)	-0.7357 (0.000)
1997	-0.6941 (0.000)	-0.1262 (0.000)	-0.1217 (0.000)	-0.1408 (0.000)	-0.7882 (0.000)
1998	-0.6833 (0.000)	-0.0912 (0.000)	-0.1989 (0.000)	-0.1347 (0.000)	-0.8469 (0.000)
1999	-0.7039 (0.000)	-0.1053 (0.000)	-0.3584 (0.000)	-0.1098 (0.000)	-0.9317 (0.000)
2000	-0.7036 (0.000)	-0.1853 (0.000)	-0.4952 (0.000)	-0.1073 (0.000)	-0.9730 (0.000)
2001	-0.7751 (0.003)	-0.2475 (0.000)	-0.5011 (0.001)	-0.1332 (0.006)	-0.8634 (0.000)
2002	-0.8598 (0.001)	-0.3177 (0.000)	-0.5086 (0.000)	-0.1463 (0.002)	-0.7774 (0.000)

Adjusted R^2=0.539; p-values in parentheses.

Table A.3. Product Level Pharmaceutical Prices: Form Code Log Price Per Unit, Fully Interacted Model

Year	Germany	France	United Kingdom	Italy	Spain
1995	0.0120 (0.064)	0.1882 (0.035)	0.0265 (0.131)	-0.0648 (0.053)	0.1290 (0.123)
1996	0.0093 (0.041)	0.1633 (0.031)	0.0569 (0.042)	-0.0110 (0.007)	0.1399 (0.088)
1997	0.0190 (0.177)	0.1062 (0.067)	0.0274 (0.223)	0.0023 (0.031)	0.2339 (0.094)
1998	0.0342 (0.080)	-0.0776 (0.037)	0.0177 (0.213)	-0.0006 (0.032)	0.1652 (0.025)
1999	0.0428 (0.016)	0.1070 (0.014)	0.0482 (0.040)	0.0085 (0.010)	0.1746 (0.001)
2000	0.0421 (0.003)	0.1071 (0.004)	0.0590 (0.013)	0.0099 (0.002)	0.1876 (0.000)
2001	0.0398 (0.006)	0.1181 (0.007)	0.0139 (0.030)	0.0199 (0.002)	0.1721 (0.001)
2002	0.0571 (0.000)	-0.0602 (0.000)	-0.0044 (0.000)	0.0734 (0.000)	0.1595 (0.000)

Adjusted R^2=0.539; p-values in parentheses.

Table A.4. Product Level Pharmaceutical Prices: Pack Size Log Price Per Unit, Fully Interacted Model

Year	Germany	France	United Kingdom	Italy	Spain
1995	-0.2407 (0.000)	-0.5226 (0.000)	-0.4514 (0.000)	-0.2944 (0.000)	-0.6879 (0.000)
1996	-0.2345 (0.000)	-0.4425 (0.000)	-0.4927 (0.000)	-0.2852 (0.000)	-0.6918 (0.000)
1997	-0.2221 (0.000)	-0.6417 (0.000)	-0.5025 (0.000)	-0.2797 (0.000)	-0.7182 (0.000)
1998	-0.1962 (0.000)	-0.4335 (0.000)	-0.5566 (0.000)	-0.2788 (0.000)	-0.7600 (0.000)
1999	-0.2089 (0.000)	-0.4700 (0.000)	-0.5928 (0.000)	-0.2677 (0.000)	-0.7594 (0.000)
2000	-0.2230 (0.000)	-0.2952 (0.000)	-0.6253 (0.000)	-0.2779 (0.000)	-0.7708 (0.000)
2001	-0.2270 (0.000)	-0.3102 (0.000)	-0.6505 (0.000)	-0.3026 (0.000)	-0.8049 (0.000)
2002	-0.2212 (0.000)	-0.3298 (0.000)	-0.6178 (0.000)	-0.3265 (0.000)	-0.8038 (0.000)

Adjusted R^2=0.539; p-values in parentheses.

Table A.5. Product Level Pharmaceutical Prices: Therapeutic Substitutes Log Price Per Unit, Fully Interacted Model

Year	Germany	France	United Kingdom	Italy	Spain
1995	0.4730 (0.050)	-0.3254 (0.005)	-0.1255 (0.100)	-0.2355 (0.000)	-0.0443 (0.015)
1996	0.4022 (0.039)	-0.2294 (0.002)	-0.1691 (0.100)	-0.2080 (0.000)	-0.0505 (0.009)
1997	0.4360 (0.043)	-0.1140 (0.000)	-0.1185 (0.016)	-0.1072 (0.000)	-0.0674 (0.042)
1998	0.5040 (0.051)	-0.0474 (0.000)	-0.2097 (0.004)	-0.0838 (0.000)	-0.0570 (0.037)
1999	0.4983 (0.049)	-0.0549 (0.001)	-0.1332 (0.026)	-0.1231 (0.000)	-0.0683 (0.036)
2000	0.4922 (0.037)	-0.1279 (0.001)	-0.2450 (0.000)	-0.0585 (0.000)	-0.0622 (0.017)
2001	0.4687 (0.033)	-0.1255 (0.001)	-0.4378 (0.000)	-0.1071 (0.000)	-0.0736 (0.059)
2002	0.4342 (0.041)	-0.1030 (0.001)	-0.4066 (0.000)	0.0835 (0.000)	-0.0897 (0.090)

Adjusted R^2=0.539; p-values in parentheses.

About the Author

Berna Colak obtained her undergraduate degree in International Finance from Istanbul Bilgi University in 2003 and her M.A. degree in Economics from Bogazici University in 2005. After holding positions in the finance industry as a financial auditor and a corporate finance expert in Turkey, she moved to the USA in 2006.

While teaching a wide range of economics courses at the University of South Florida, she started to pursue her Ph.D. degree in Economics in 2009. She received her M.A. degree in Economics in 2011, M.S. degree in Finance in 2012, and Graduate Certificate degree in Statistics in 2014 from the University of South Florida. She held a research scientist position at Moffitt Research Center for one year between April 2012 and March 2013 to apply econometric models to the field of health economics. She won the Provost's Award for Outstanding Teaching at the University of South Florida in 2014. Her major areas of research are Industrial Organization, Health Economics, Applied Econometrics, and International Economics.