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Abstract: The purpose of this paper 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. 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 set for 10 years (1994-2003), in order to estimate the effect of generic entry on drug prices at the product level. Both within and across these countries, different interventions are being applied to in-patent and off-patent markets during 10 years of the study period. 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. Accordingly, this analysis finds that generic entry has a negative effect on prices in countries with free pricing originator market, whereas in European Union (EU) countries with strict price and reimbursement regulation, generic competition is ineffective and/or counterproductive. Low regulated prices for originator products do not encourage generic entry following patent expiration. This finding is consistent with less generic firms and less competitive late entrants in regulated environments. Thus, strict price regulation undermines price competition in the off-patent sector, and cost savings from post-patent competition are not realized in countries with strict pricing and reimbursement policies.

Highlights (for review)

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Generic Competition and Price Regulation in Pharmaceuticals: Evidence from the European Union

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Abstract

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Jel Codes: D22, I11, I18, L11, L51, L65

1. Introduction

In recent decades, one of the priorities of the European Union (EU) health care system has been 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. Pharmaceutical pricing and reimbursement regulatory 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.

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.

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 paper examines the extent of competition between generic products and therapeutic substitutes under different regulatory regimes in the EU pharmaceutical industry. In particular, the study 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 more 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.

The remainder of the paper is organized as follows: Section two provides a background of the EU pharmaceutical market to identify the implications of pricing and reimbursement regulations. Section three summarizes a literature review describing the nature of off-patent market competition. Section four outlines the data and research strategy implemented in this study. Section five presents empirical results. Section six provides concluding remarks and suggestions for future research related to this topic.

2. Generic Drug Market and Regulation 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., 2013). Because of the irregularity that exists within this industry, 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., 2013). 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. 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). 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).

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). Countries within the EU use formalized pricing regulations to control generic prices, which support generic uptake following the patent's expiration (See Table 7 in the Appendix). The most commonly used regulatory policies are reference pricing and price caps (Vandoros et al., 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 et al., 2013). Moreover, both within and across these countries, different interventions are being applied to in-patent markets (See Table 7 in the Appendix). For example, in Germany, markets for on-patent drugs are largely unregulated and prices are set relatively freely. In the UK, originator medicine prices are free from direct regulatory intervention, but are subject to a rate of return regulation, where drug companies are allowed to make a profit of up to 21 percent return on capital invested. France, Italy, and Spain, on the other hand, use direct price controls for originator drugs, where fixed maximum pharmaceutical prices are set.

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.

3. Literature

This paper 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. The differences in these empirical results can be explained by heterogeneity in the methodologies used, the range of products considered, the study periods chosen, and the methods of estimation.

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, Jönsson, (1994) and Vandoros 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 et al., (1992), Rizzo et al., (2009) 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.

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.

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 (Magazzini et al., 2004). 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 et al., 1991; Grabowski et al., 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 (Magazzini et al., 2004).

In contrast, Garattini et al., (2000) and Rovira et al., (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 (1996) 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). Brekke (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. Podnar'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 and market incentives in the form of price competition between generic medicines and competition between originator and generic medicines by medication class.

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%.

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 paper focuses on how drug prices change over time as a consequence of generic competition, taking into consideration different regulatory regimes across the countries examined.

4. The pharmaceutical market

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 (i.e., generic firms), which operate in the off-patent market post-patent expiry (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: improving innovation with intensive research and development; auditing the quality of drugs for public health; managing the costs of pharmaceutical expenditures. 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 (Scherer, F. M., 2000).

4.1. 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 8 in the Appendix, similar to 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. 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.

4.2. 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. 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.

4.3. Descriptive Statistics of IMS Data

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 et al., (2011) 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."

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
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

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.

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

5. An empirical examination of generic competition

This study investigates the effect of generic entry on pharmaceutical prices by employing two different

empirical research strategies in a reduced form. The first section explains the nature of the quasi-hedonic regressions model and the second section describes the fully interacted model in detail.

5.1. 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 (Timur et al., 2011).

This study examines the price models through quasi-hedonic regressions for three reasons (Danzon and Chao, 2000a; Timur et al., 2011). 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 (Timur et al., 2011).

As defined in Danzon and Chao, (2000a) and Timur et al., (2011), 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., 2011). 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).

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).

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 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., 2011). 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.

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)**
Therapeutic Substitute Molecules (ln)	0.5159 (0.0992)***	0.4861 (0.0955)***
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 parentheses.
*, ** and *** reflect significance at the 1, 5 and 10% levels, respectively.

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 et al., 2011). 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., 2011). 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 et al., 2011).

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.

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)
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 parentheses.
*, ** and *** reflect significance at the 1, 5 and 10% levels, respectively.

5.2. 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., 2011).

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. 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. 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 complete annual results with the fully interacted model for the major variable of interest - generic competition - in five countries between 1994 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., 2011); 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.

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.

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 et al., 2011). 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 et al., (1992) 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 (Sloan et al., 2012).

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., (2013) 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 relatively 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 1994 to 2003), the magnitude of this negative effect monotonically increases (from -0.0263 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 0.1332 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 price of the originator drug prices and generic drug prices) which is observed in the data. In addition, the market share of the generics would have also increased over time, which would have further lowered the average price.

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
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)

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

*, ** 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	0.0981	0.1808*	0.1104*	0.0923*
	(0.173)	(0.447)	(0.005)	(0.007)	(0.004)
1996	-0.0081***	0.0684***	0.1849*	0.1083*	0.0876*
	(0.094)	(0.056)	(0.002)	(0.004)	(0.002)
1997	-0.0579*	0.0382*	0.1687*	0.1076*	0.0794*
	(0.004)	(0.006)	(0.000)	(0.000)	(0.000)
1998	-0.0882*	0.0087*	0.1504*	0.0960*	0.0712*
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
1999	-0.1079*	0.0316*	0.1780*	0.0966*	0.0605*
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
2000	-0.1188*	0.0373*	0.1915*	0.0844*	0.0564*
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
2001	-0.1336*	0.0394*	0.1584*	0.0663*	0.0338*
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
2002	-0.1581*	0.0329*	0.1242*	0.0235*	0.0152*
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)

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

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.

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.

6. Conclusion

This study 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 their regulation systems rather than to 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 et al., 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.

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. 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 cannot obtain a production permit immediately, it takes time due to regulatory delay for the approval of drug in the industry, and 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 paper focuses on an empirical analysis of generic competition and prices, considering the role of several fundamental features of the European pharmaceutical market. Second, this study does not look at comparisons of price levels across countries, but focuses on price changes within countries. Third, this study does not analyze the determinants of generic entry; this would be an important and interesting issue for future research. Fourth, 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). Finally, 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.

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Appendix A.

Table 7. 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 8. 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)

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