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The Effects of Price Regulation on Pharmaceutical Industry Margins: A Structural Estimation for Anti-ulcer Drugs

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Comments Welcome

Abstract

The objective of this paper is to study the effects of price regulation on competition in the pharmaceutical industry. We provide a method allowing to identify margins in an oligopoly price competition game even when prices may not be freely chosen by firms. We use our identification strategy to study the effects of regulatory constraints on prices in the pharmaceutical industry which is heavily regulated in particular in France. We use data from the US, Germany and France to identify country specific demand models and then recover price cost margins under the regulated price setting constraints on the French market. To do so, we estimate a structural model on the market for anti-ulcer drugs in France that allows us to explore the drivers of demand, to identify whether regulation really affects margins and prices and to relate regulatory reforms to industry pricing equilibrium. We provide the first structural estimation of price-cost margins on a regulated market with price constraints and show how to identify unknown possibly binding constraints thanks to three different markets (US, German and France) with varying regulatory constraints. The identified margins show that margins have increased over time in France but that firms were specially constrained in price setting after 2004.

Key words: empirical IO, regulation, price constraints, pharmacy, antiulcer drugs.

JEL Codes: L10, I18

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1 Introduction

The objective of this paper is to study the effects of price regulation on competition in the pharmaceutical industry. We provide a method allowing to identify margins in an oligopoly price competition game even when prices may not be freely chosen by firms. We use our identification strategy to study the effects of regulatory constraints on prices in the pharmaceutical industry, which is heavily regulated in some countries, and particularly in France. We use data from the US, Germany and France to identify country specific demand models and then recover price cost margins under the regulated price setting constraints on the French market. To do so, we estimate a structural model on the market for anti-ulcer drugs in France that allows us to explore the drivers of demand, to identify whether regulation really affects margins and prices and to relate regulatory reforms to industry pricing equilibrium. We provide the first structural estimation of price-cost margins on a regulated market with price constraints and show how to identify unknown possibly binding constraints thanks to three different markets (US, German and France) with varying regulatory constraints. The identification strategy relies on the usual conditions for identification of a flexible demand model for differentiated products, on the assumptions about the price competition game played by pharmaceutical firms but specifically on the knowledge that some markets are not price constrained (here US and Germany) while others may be constrained (France). With such method, we are able to identify whether the price setting regulation mechanism in France really makes price constraints binding and by how much. We can evaluate the counterfactual pricing equilibrium and thus identify changes in prices, demand and spending due to the different regulation along time between 1997 and 2007. With data from 1997 to 2007, we find that being branded and some measure of drug quality matter for the demand, while there is significant consumer heterogeneity and price elasticity in demand. The identified margins show that margins have increased over time in France but that firms were especially constrained in price setting after 2004.

Investigating the actual role exerted by regulatory constraints is of major importance in an industry, like the pharmaceutical one, where regulation is heavily present. The role played by regulation in limiting and steering firms' and users' behavior comes from the importance of the good this industry is based on, health. In order to guarantee the safety of the drugs being manufactured and sold, the process of drug production is standardized everywhere and is required to go through a series of stages, starting from a set of rigorous clinical trials and ending with the approval of the new drug by national or international agencies. In several countries, drugs that are subject to prescription also need to go through price negotiation and reimbursement decisions by the national health system and private insurances.

This is the case of France, which is a clear example of heavily regulated pharmaceutical market. Due to rising drug expenditures in the 1990s, French pharmaceutical regulation underwent a process of reform, which since 2003 has introduced major changes: reference pricing of branded drugs to generics, campaigns to encourage the use of generics, a system of rigorous prescription rules, a new process of price negotiation. However, the many measures introduced make the actual result of such a complex set of regulatory changes difficult to evaluate. Different reforms may have changed the shape of the demand

for drugs, steering preferences and perceptions of patients and physicians, and affecting pharmaceutical manufacturers behavior on price setting, on cost reduction, or margin squeezing.

To carry out our analysis, we choose to focus on the anti-ulcer drugs market, one of the leading therapeutic classes worldwide. Its double-digit growth over time was driven by the presence of several blockbusters and on fierce competition, based on subsequent innovations and on the coexistence of different generations of drugs. Recently, the patent of several of these top-selling drugs expired and generics started to enter the market, inducing originator companies to accelerate the introduction of new products. Interestingly, some (but not all) drugs in this class were subject to some specific regulatory changes introduced by the French reform. All of these factors make this class especially suited for analyzing the effects induced by the reform on the demand and supply for anti-ulcer drugs.

Estimate demand precisely for pharmaceutical products is crucial, due to the implications this has on a number of issues, such as public health, public expenditures for health-related topics, incentives to innovate by public and private organizations. However, it is not an easy task and poses several challenges. First, understanding the factors driving preferences and actual purchase decisions is not straightforward in a market where the decision maker and the buyer/user do not usually coincide (physician vs. patient). This feature is stronger for prescription drugs, for which the patient is required to consult with a physician who decides on the appropriate product. In the economic literature, this fact is often blamed for the emergence of potential agency problems, with the doctor acting as a double agent (Pauly, 1968; Hellerstein, 1998), often not being aware of the prices of the products she prescribes (Danzon, 1997). Sometimes the user is neither the actual decision maker nor the payer of the drug. This happens in those countries where the health insurance system (either private or public) reimburses at least part of the price of some pharmaceutical products. This fact, plus the actual absence of a real substitute to drugs, has traditionally made the demand price-inelastic (Crawford and Shum, 2005), though the advent of generics may be softening this issue. These peculiarities make demand estimation particularly challenging, since one needs a flexible model to enhance these peculiarities, but such flexibility must not compromise model tractability or become too burdensome in terms of data needs.

Similarly, when modeling the supply side, the researcher must account for a number of peculiarities of this market. First, the cost structure of the firms, mainly represented by fixed costs. This originates from the long and difficult process needed to come up with a finished drug. The huge and risky investments in research contribute to most of the costs and duration of the process of drug innovation, which is estimated to take at least 10 years for up to 1 billion USD expenses per successful molecule (DiMasi, Hansen and Grabowski, 2003). The rest of the costs is made up by intellectual property protection and by compliance to strict rules in terms of safety standard, clinical trials and regulatory approval process. An additional challenge in supply estimation is posed by regulation of the pricing of pharmaceuticals, which makes price setting decisions not entirely under the control of the firm. This mechanism aims at finding a balance between the need for access to drugs by patients (preventing that the little elasticity

of demand is exploited with excessive prices) and the necessity for firms to recoup for the investments made during the R&D phase through a congruous price.

This work structurally estimates demand and supply for anti-ulcer drugs in France in the period 1997-2007 and investigates the effects exerted by the regulatory reform, trying to overcome the difficulties illustrated above. On the demand side, flexibility and tractability are achieved through a model of discrete choice for differentiated products which places strong emphasis on consumers' heterogeneity. On the supply side, we allow firms to be constrained in their price setting decisions by regulation and we identify unknown possibly binding constraints thanks to three different markets (US, German and France) with varying regulatory constraints. This allows us to quantify the magnitude of such constraints and to estimate counterfactuals of prices, margins, savings and welfare. With our approach, we are able to show how regulation limited the increase in margins after 2004.

This paper is structured as follows. Section 2 briefly illustrates the literature on demand estimation in the pharmaceutical market, especially focusing on the modeling chosen in each work. Section 3 describes the market for anti-ulcer drugs in France and explains the major points of the reform; it also presents the data used. Sections 4 and 5 describe, respectively, the models chosen for demand and supply. Results are discussed in section 6 and we show counterfactual price equilibrium absent the regulation of price setting in France. Finally, section 7 concludes.

2 Literature

The first group of contributions relevant for this work explores the role played by regulation in shaping strategic incentives and behavior on the supply side. For instance, Danzon and Chao (2000) investigate the effect of regulation of manufacturer prices and retail pharmacy margins on price competition. They find that generic competition is effective in driving prices down only in regimes with limited regulatory intervention on prices (namely US, UK, Canada and Germany), while in countries with strict price or reimbursement rules (France, Italy, and Japan) generic competition is ineffective and may be counter-productive. More recently, Danzon and Epstein (2008) have emphasized the negative effect exerted by external referencing on launch timing and pricing of new drugs. Both the long process caused by strict regulation of the price and the cross-country linkages induced by external referencing create spillover incentives for a firm not to launch in lower-price referenced countries until a higher price is negotiated somewhere else. The very recent work by Filson (2012) also focuses on the impact of the introduction or removal of price controls across countries. By using a dynamic equilibrium model of the pharmaceutical industry, parametrized using industry facts, he simulates the effect on the introduction of new drugs, consumer welfare and firm value in different scenarios, where the US and other non-US countries would change their approach to price regulation of drugs. Its predictions show that price controls that fail to compensate firms for the introduction of high-quality drugs result in a significant decrease in the number of new drugs and in large welfare losses at a global scale. However, abandoning price controls

especially hurts domestic consumers and this may explain why many countries still use them, despite their inefficiency.

Another branch of the literature which is interesting for the current analysis investigates the determinants of entry in the pharmaceutical market. For example, Scott-Morton (1999) emphasizes the importance of firms heterogeneity (defined mainly as differences in efficiency, specialization and experience), market size and drug characteristics in driving entry of generic drugs (treating a chronic disease is especially profitable). Kyle (2006) points out a major role played by the interaction between country- and firm-specific characteristics in the launch of new products: market profitability, competition level, experience and specialization of the firm are especially important, with a major advantage from being a domestic company.

In general, this work refers to the literature that estimates demand for pharmaceuticals. Usually these contributions show some common characteristics. All of them analyze a specific country-class market, mainly the US market for anti-ulcer drugs, antidepressants and antibiotics. Despite major differences in the topic under investigation, the approaches followed in modeling demand are often quite similar, all aimed at emphasizing product differentiation.

Some contributions estimate demand with a simple log-log specification, in which the log of quantity is regressed over the log of price and on other variables of interest. The estimated coefficients in this approach are interpretable as elasticities. For instance, this specification is applied by Berndt, Bui, Railey and Urban (1995) in exploring the role played by different forms of marketing in the US market for H2 anti-ulcer treatments in the period 1977-1994. Their analysis emphasizes the effectiveness of detailing (the practice of visiting physicians to promote the product) and the role played by price and quality measures (efficacy, dosage, interactions, side effects, number of indications) in driving demand. A similar approach is used by Rizzo (1999) and, more recently, Capella et al. (2009) to explore respectively the role of detailing in decreasing price elasticity and the limited impact of direct-to-consumer advertising on price elasticity in five therapeutic classes.

Most works use discrete choice models to estimate demand. Some apply a logit specification. For instance, Azoulay (2002) uses a logit with instrumental variables for price to show how product market competition in the H2 subclass in the period 1977-1993 was shaped by advertising efforts and quality of scientific information. The same model is used in Berndt, Pindyck and Azoulay (2003) to explore whether consumption externalities were among the success factors of Zantac (the second mover in the H2 anti-ulcer class). Their methodology is quite peculiar and involves three stages to estimate a dynamic demand model: for the estimation of market shares they use a multinomial logit. A logit is also used by Crawford and Shum (2005), who show the role played by uncertainty about the effectiveness of a drug and by experience and learning in the Italian market for prescription anti-ulcer drugs.

Other contributions apply a nested logit model, in order to emphasize product differentiation and estimate more precisely substitution patterns among drugs sharing common characteristics. The nesting structure tries to reflect a prescription process in which the physician chooses to prescribe a specific drug within a class or subclass; lately, at the dispensing phase, the pair pharmacist-patient decides on generic

substitution. Donohue and Berndt (2004) especially focus on the prescription phase, to investigate how direct-to-consumer advertising and detailing affect the choice of antidepressant medications. Ellison, Cockburn, Griliches and Hausman (1997) model demand and compute elasticity between branded and generic versions of four antibiotics (cephalosporins). Their nested logit specification has the choice of the molecule as the top nest and the decision about generic substitution as the bottom nest. They show how elasticity is higher between generic substitutes than between therapeutic substitutes and how price sensitivity is higher at the dispensing than at the prescribing stage. Despite using a very similar model, different findings are reported by Stern (1996) for four therapeutic categories (gout therapies, sedatives, minor tranquilizers and oral antidiabetics). His results display how branded drugs of the same category are relatively strong substitutes but are often substantially differentiated from their generic competitors, though major differences arise across therapeutic classes.

A more recent approach to demand estimation has emphasized the role of consumer heterogeneity through random coefficient logit models. Seminal works in this literature are those by Berry (1994), Berry, Levinsohn and Pakes (1995), hereafter BLP, and Nevo (2000, 2001). Random coefficient logit models, also called mixed logit, are especially tempting to use due to their ability to emphasize consumer heterogeneity and provide richer and more plausible substitution patterns than logit and nested logit models. However, their flexibility comes to the cost of increased computational difficulty. They have been successfully applied to estimate the demand for cars (BLP and, more recently, Verboven, 2011), for ready-to-eat cereals (Nevo, 2000 and 2001), for mineral water (Bonnet and Dubois, 2010), among others. To the best of our knowledge, this approach has not been used to estimate demand for pharmaceuticals yet. More recently, the work by Knittel and Metaxoglou (2008) has pointed out some problems with mixed logit numerical performance and has suggested to use a large number of starting values and different minimization algorithms. Similarly, Dubé, Fox and Su (2011) have provided an alternative method to the estimation of these models, by replacing BLP's nested fixed point algorithm with a constrained minimization, where the market share condition constraint takes the place of BLP's contraction mapping.

When modeling the supply side, this work accounts for the role of regulation in limiting and steering the price setting decisions of the firms. This is reflected in a supply model where firms are not free to maximize their profit function as in usual oligopolistic models, but are subject to a price cap, which is unknown: the magnitude of this ceiling and the fact that it is binding or not are allowed to change across drugs, depending on drug characteristics. To the best of our knowledge, such approach is new to the IO literature and has never been employed either in the drug pricing literature, or in works studying the role of regulation in other industries. The very recent paper by Salvo (2010) has followed a similar approach in the estimation of market power in the Brazilian cement industry. In his work, the constraint is not imposed by regulation, but it is the threat of entry by foreign producers that poses a ceiling to the price that domestic competitors can set. Ignoring this constraint leads to biased and inconsistent estimates of market power, which is always found to be lower than in reality.

3 Market, Data and Regulation

3.1 Regulatory Framework In France

The pharmaceutical market in France shares some characteristics with other industrialized countries, especially with those characterized by heavy regulation. Some French specificities are however noteworthy. France has historically displayed high levels of pharmaceutical expenses. A reason for it is often found in a traditionally strong preference, by French patients and physicians, for branded drugs at the detriment of generic equivalents, considered for long as mere inferior or even unsafe substitutes. Such behavior was presumably encouraged by a welfare system, covering nearly the whole French population, which reimburses at least a part of the price of the drugs (the so called *ticket modérateur*). However, it is reported that more than 90% of the population has supplementary insurance, which usually covers the whole price (Nguyen-Kim, Oz, Paris and Sermet, 2005). In addition, the late introduction of generic substitutability at the pharmacy level (only in 1999) has encouraged the perpetuation of a strongly branded-oriented system of prescription and purchase. All of these factors are said to be the cause for a very low demand elasticity to price. Nevertheless, French prices for drugs have remained for long below the level displayed in other European markets, especially Germany and UK (Nguyen-Kim et al., 2005).

In the early 2000s, the level of pharmaceutical expenses in France doubled with respect to the previous decade (reaching 30 billion euros in 2004), increasing more rapidly than anywhere else in Europe (Nguyen-Kim et al., 2005). This situation accelerated the project of a reform of the pharmaceutical regulatory system, aimed at reducing public expenditures for drugs, which represented a fifth of total public expenditures on health.

Drug prices in France were historically regulated, but the reform started in 2003 introduced a number of major changes, partially liberalizing some prices and rationalizing the process for others (especially hospital prices). The process of drug commercialization starts by obtaining an authorization of market entry (*Autorisation de mise sur le marché*, AMM) granted by the Agency for the Safety of Health Products (*Agence française de sécurité sanitaire des produits de santé*, AFSSAPS). This step is enough for OTC drugs and for some prescription drugs, which are immediately available for purchase once the AMM is granted at a price decided by the producer.

In order to obtain reimbursement by social insurance, two additional steps must be performed. The first is the evaluation of the reimbursement suitability and level of the drug; the second is the actual price setting, which is regulated. The final step is the publication in the *Journal Officiel*, after which the drug can be readily commercialized.

Reimbursable drugs are those included in the so-called positive list and the decision on their suitability is taken by the Ministry of Health, after considering the advice from the "Transparency Commission". Evaluation by this Commission, which is part of the High Authority of Health (*Haute Autorité de la Santé*, HAS) since August 2004, is based on two indicators of the drug therapeutic value. The first, the SMR (*Service Médical Rendu*) measures the absolute medical benefit of the drug and is based on considerations on both drug characteristics and disease class characteristics. The second, the ASMR

(*Amélioration de Service Médical Rendu*) refers to the progress in treatment, if any, brought by the drug in terms of efficacy, side effects and/or ease of use as compared to existing products in its class. If the SMR attributed by the Transparency Commission is high enough, the drug is included in the positive list and reimbursement is set at 35%, 65% or 100%, depending on SMR level and on the severity of the illness the drug is aimed at treating. Since 2004, a major role in the decision on the rate of reimbursement has been played by UNCAM (National Union of Sickness Insurance Funds). The positive list is reviewed on a 5-year basis and last revision occurred in 2007.

The information on the SMR and ASMR is also used as a criterion for the negotiation of the price of the drug between its manufacturer and the ministerial agency in charge of it, the Economic Committee for Health Products (*Comité économique des produits de santé*, CEPS), established in 2000. The CEPS establishes the price based on the ASMR level, the anticipated volume of sales and the price of comparable drugs present on the list. In 2003 reference pricing of branded drugs to generics was established (*Tarif forfaitaire de responsabilité*, TFR), linking the reimbursement of originator drugs to the price of their generic counterparts. In 2004 external referencing was also introduced, forcing drug companies to set prices in line with those in neighboring countries, Italy, Germany, UK and Spain. Finally, since 2006, the price of all drugs in a class must be reduced when the patent of one reimbursable drug expires and generics become available. The purpose of all of these measure was to reduce the price level of drugs approved as reimbursable, hence creating savings for the welfare system.

The usage of generics was promoted by the reform not only as a tool to reduce public expenses, but also as a major goal in itself, in line with recommendations of the European Commission (Pharmaceutical sector inquiry, 2009). First, some campaigns were launched, addressed to patients, to increase awareness and convey the idea that generics are perfect equivalents of branded drugs and there is no danger from their use. In addition, due to the limited application of generic substitution, introduced in 1999, some agreements were signed between doctors and the Statutory Health Insurance in order to increase prescription of generics. The first attempt was the 2001 commitment to use the international chemical name of the medicine in prescriptions (INN, International Nonproprietary Name). However, since only 8.5% of all prescriptions showed the INN (Grandfils and Sermet, 2006), in 2006 another agreement was signed, encouraging physicians to prescribe those drugs for which generic alternatives are available.

Date	Event
September 2003	Introduction of TFR for some presentations of cimetidine and ranitidine.
March 2004	Revision of TFR: decrease of 0.02-0.04 $ per box.
April 2005	Revision of TFR: decrease of 0.5 $ for ranitidine.
	Revision of TFR: decrease for ranitidine and cimetidine.
	Introduction of TFR on famotidine.
December 2007	Introduction of TFR for another presentation of cimetidine.

3.2 The Anti-Ulcer Drugs Market

The analysis focuses on the French anti-ulcer prescription drugs market in the period 1997-2007. The market is defined at the therapeutic class level, using the international ATC classification up to the third digit: anti-ulcer drugs are defined as all drugs classified in the A02B category, which comprises three

subclasses, defined by the fourth digit (A02B.A-C). For this market, each subclass can be thought of as a generation of drugs treating ulcer and ulcer-related conditions (for example, the gastroesophageal reflux disease, aka GORD). The subclass of histamine antagonists (H2) gathers anti-ulcer treatments of the first big generation, introduced between the 1970s and 1980s, which treat ulcer symptoms by blocking the action of histamine in the stomach. H2 drugs are based on a number of molecules, the most common of which are cimetidine, famotidine, ranitidine and nizatidine. H2 had a great success in many countries, driven by SmithKline's Tagamet (cimetidine) and Glaxo's Zantac (ranitidine); they remained top sellers until the late 1980s, when a new generation of ulcer treatments was introduced, proton-pump inhibitors (PPI). These drugs, instead of blocking the reception of histamine, act at the source of acid secretion, inhibiting it for a prolonged time. This subclass includes several derivatives of benzimidazole (omeprazole, lansoprazole, pantoprazole and rabeprazole among the most diffused) and, since its introduction, has been considered to be superior to H2 and other existing drugs. Astra Zeneca's omeprazole compound, Losec, was the world top-selling drug during several years. Finally, the third subclass is a residual category, which in France includes prostaglandins, mainly used for prevention and treatment of peptic ulcer in the elderly.

The anti-ulcer market is a good candidate for the study of this work. First, it has long been one of the top selling therapeutic classes worldwide (leading from 1990 to 2003). This was driven by the presence of blockbusters and a competition based on subsequent innovations. Also, as highlighted in previous studies (Crawford and Shum, 2005), the absence of real substitutes to these drugs (hospitalization and surgery are aimed at different conditions) make the market easily identifiable in the A02B category, without the worry of having to include among the competitors drugs belonging to other therapeutic classes. Another interesting peculiarity of this market is the coexistence of products of different types and generations, namely H2 versus PPI. In addition, during the period under study, the market experienced patent expiration of major blockbusters and subsequent entry waves of generics, which started really populating the market in early 2000s. Some of these reasons explain why it was analyzed in previous contributions in the economic literature, which represent an interesting comparison for the results of this work.

3.3 Data and Descriptive Statistics

Most data for this analysis come from IMS Health, providing a dataset with information on wholesale transactions for the period 1997-2007. The revenues and the quantity sold from each drug in a country-year are available, reported respectively in thousand US$ and in standard units. In the dataset, one observation (drug-country-year triplet) is uniquely identified by detailed information: the name of the medicine and the firm manufacturing it, the active ingredient and the ATC classification up to the fourth digit, the therapeutic form and information on its brand type (originator, licensed or generic drug).

The IMS data do not include details on price of the drugs. Since reported transactions are at the wholesale level, there is no way to identify to which segment (pharmacies or hospital) the drug was sold. Hence, only the average wholesale price can be derived from the figures on quantity and revenues per

year. Data were aggregated at the therapeutic form level, in order to avoid that the different method of administration of exactly the same drug (say, tablet and effervescent capsules, for instance) be considered as substitutes.

Additional information on drugs belonging to the French anti-ulcer market was retrieved on the website *www.theriaque.org*: its reliability is guaranteed by its approval by the HAS. The website was used to gather information on indications and counter-indications of each drug in the sample, as well as its SMR and ASMR level for each indication and the resulting reimbursement level (the anti-ulcer class is included in the positive list and is usually reimbursed at 65%).

IMS data are also used to retrieve the prices in Germany, Italy, Spain and UK, which are used as instruments for the price of French drugs (see section 4 below). The countries chosen are those on which the external referencing is based on. Using these prices, however, is not straightforward, but requires a process of adaptation, as explained more in detail in the Appendix.

Add stat on market expansion (total revenue on this market in France over time)

During the eleven years under study (1997-2007), a total of 69 different drugs were commercialized by 31 different companies: among them, 11 are branded firms, the remaining 20 are generic manufacturers. Out of them, only 5 are French firms, where the nationality is identified by the country in which the headquarters are located. More than half of the drugs, 36, belong to the PPI subcategory (A02B-C), which represent the bulk of sales, followed by H2 (A02B-A), with 32 products; prostaglandins (A02B-B) are present with only one drug, Pfizer's Cytotec. French anti-ulcer drugs in this period are based on 10 active ingredients: five PPI (omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole), four H2 (cimetidine, famotidine, nizatidine and ranitidine) and one prostaglandin (misoprostol). For five out of these ten, generic substitutes were or became available: misoprostol, nizatidine, esomeprazole, pantoprazole and rabeprazole were always sold only under their branded version.

In general, there is not much variation in the levels of SMR (*Service Medical Rendu*, the medical benefit) and ASMR (*Amelioration de Service Medical Rendu*, the improvement in medical benefit), which are respectively II (important) and V (inadequate) for most of the drugs in the class. The SMR, in addition to the severity of the illness, defines the reimbursement level, which is set at 65% for all drugs in the class (except for some old drugs in 2007, due to revision of the positive list).

Other quality-related measures refer to the number of formats, indications and side effects. A higher number of formats under which a drug is commercialized is a measure of the quality in that it allows to better suit the needs of heterogeneous patients: this figure varies between one and four different formats in the sample. Not many drugs are sold in a liquid form, which is more common among branded drugs. The number of indications and side effects differs significantly across drugs, from a minimum of two to a maximum of nine indications (Losec and Nexium) and eight counter-indications (Nexium's peculiarity).

Year	n_{drugs}	$n_{branded}$	$n_{generic}$	Quantity (1000 std units)	$s_{branded}$	$s_{generic}$	$\overline{p}$ ($/std unit)	Revenue
1997	13	11	2	604038	99.97%	0.03%	1.72	1 038 945
1998	13	11	2	612932	99.97%	0.03%	1.63	999 079
1999	14	11	3	706451	99.96%	0.04%	1.62	1 144 451
2000	27	12	15	809615	99.82%	1.18%	1.10	890 577
2001	27	12	15	918680	99.00%	1.00%	0.95	872 746
2002	29	13	16	1064382	99.02%	0.98%	0.97	1 032 451
2003	30	13	17	1179154	98.43%	1.57%	0.95	1 120 196
2004	47	13	34	1285490	86.73%	13.27%	0.87	1 118 376
2005	47	13	34	1391362	78.30%	21.70%	0.87	1 210 485
2006	51	13	38	1523885	74.10%	25.90%	0.82	1 249 586
2007	63	13	50	1593450	71.11%	28.89%	0.74	1 179 153

Table 1: Descriptive Statistics

Two pieces of evidence are especially noteworthy at a first analysis of the data (Table 1). The first is the significant increase in the number of drugs marketed during the period, from less than 15 during the initial three years (1997-1999), to almost seventy in 2007. This increase is driven by entry of generics, whose market share rises significantly during the period. Only two generics are on the market during the initial part of the sample period, with a negligible market share. During the first entry wave of early 2000s, several ranitidine- and cimetidine-equivalents hit the market (Zantac and Tagamet lost patent protection in the '90s), but generics still represent a residual category in terms of volumes and revenues. Finally, in 2004 generics start becoming real competitors of their branded rivals: after patent expiration of the world top-selling drug, Losec (Astra Zeneca's omeprazole), a second entry wave takes place and in 2007 generics represent between a fourth and a third of the whole A02B anti-ulcer drugs market.

The second interesting consideration is that generic entrants do not appear to have cannibalized sales of their branded competitors, but have instead created a new segment of past non-users, increasing the size of the market. This is clear by observing the pattern of evolution of aggregate quantity, which more than doubles during the period. Much of the increase is due to generic entry, but sales of branded products increase even more (not shown). The evolution of revenues is slightly different: from 1997 to 2007 revenues increase by 60%, but this increase is not steady, with a peak in 2004 (1.72 billion dollars), the year in which most of the measures included in the reform are introduced. Conversely, the average price decreases steadily over the period. This is likely to be due to the subsequent entry waves of generics.

4 Demand Model

4.1 Random utility model

In order to identify the demand shape for pharmaceutical drugs in each market, we estimate a random utility discrete choice model which has the advantage of being flexible and allow product differentiation.

The first layer of product differentiation occurs at the sub-class level. The drugs under study belong to the same therapeutic class, the A02B anti-ulcer category, but to different subclasses, which refer to different generations of products. Older H2 drugs are still widely used, but PPI are usually considered

superior products, while prostaglandins are mainly prescribed for elderly patients. Differences emerge also within a subclass, at the active ingredient level. For instance, H2 anti-ulcer drugs are easily substitutable among each other, but there exist differences between, say, cimetidine and ranitidine. These two levels of differentiation stem from objective differences that make one drug more appropriate to treat one condition or more suitable for one type of patients. The third level of product differentiation is the one between branded and generic drugs. This is not justified by a difference in the curative effects: the two are perfect therapeutic equivalents. However, despite being (nearly) perfect substitutes (besides potential differences in excipients, shape and color of the drug that do not compromise efficacy or its curative effects for most of the patients), for long they have not been perceived as being so. These three types of differentiation may define specific patterns of product interdependence and substitutability and the demand model must be flexible enough to capture them.

We thus use a random coefficient logit model à la Berry, Levinsohn and Pakes (1995). Contrary to the standard logit model, it is not constrained by the IIA assumption, thus allowing to obtain consistent estimates of the demand parameters required for computation of price-cost margins.

Utility is specified as additive separable between an observed and an unobserved part, with

$$U_{ijt} = \alpha_{it} X_{jt} - \beta_{it} p_{jt} + \zeta_{jt} + \varepsilon_{ijt}$$

for $j = 1, .., J$. The model is completed by the inclusion of an outside good, denoted good zero, allowing for the possibility of consumer i not buying any of the marketed products J, and whose indirect utility is normalized to zero: $U_{i0t} = 0$.

Heterogeneity of preferences is captured by random coefficients on all or on a subset of variables, which emphasizes consumer heterogeneity and varies according to $(\alpha_{it}, \beta_{it}) = (\alpha + \sigma_\alpha \nu_{it}, \beta + \sigma_\beta \nu_{it})$, where ν_{it} summarizes all the unobserved consumer characteristics, and σ_α, σ_β characterize how consumer marginal utilities vary according to these unobserved characteristics. Indirect utility can then be redefined as the sum of mean utility $\delta_{jt} = \alpha X_{jt} - \beta p_{jt} + \zeta_{jt}$ and deviations from the mean utility $\mu_{ijt} = (\sigma_\alpha X_{jt} - \sigma_\beta p_{jt}) \nu_{it}$:

$$V_{ijt} = \delta_{jt} + \mu_{ijt}$$

Under the assumptions that ε_{ijt} is independently and identically distributed according to Gumbel (extreme value type I) distribution, the choice probability of alternative j by consumer i is

$$s_{ijt} = \frac{\exp\left(\delta_{jt} + \mu_{ijt}\right)}{1 + \sum_k \exp\left(\delta_{kt} + \mu_{ikt}\right)}$$

Assuming that ν_{it} is normally distributed with p.d.f. φ, the market share of product j, s_{jt} is given by

$$s_{jt} = \int_{A_{jt}} s_{ijt} \varphi\left(\nu_{it}\right) d\nu_{it}$$

where A_{jt} denotes the set of consumers that purchase product j in period t.

Then, the own-and cross-price elasticities of the market share s_j are :

$$\begin{aligned}\frac{\partial s_{jt}}{\partial p_{kt}}\frac{p_{kt}}{s_{jt}} &= -\frac{p_{jt}}{s_{jt}}\int_{A_{jt}}\beta_{it}s_{ijt}\left(1-s_{ijt}\right)\varphi\left(\nu_{it}\right)d\nu_{it} \quad \text{if } j=k \\ &= \frac{p_{kt}}{s_{jt}}\int_{A_{jt}}\beta_{it}s_{ijt}s_{ikt}\varphi\left(\nu_{it}\right)d\nu_{it} \quad \text{otherwise}\end{aligned}$$

4.2 Identification and Estimation

Based on Berry, Levinsohn and Pakes (1995) and Nevo (2000), the identification of such random coefficient logit model can be done on aggregate data with instrumental variables. To do so, one needs instrumental variables supposed to be correlated with prices but not with random demand shocks ζ_{jt}. Actually, one has to take into account the problem of endogeneity of prices. The unobserved demand factors ζ_{jt} are correlated with prices (Berry, 1994; Berry et al., 1995). Ignoring this simultaneity leads to biased results and upward-sloping demand functions. Previous literature has used measures of the degree of competition (Stern, 1996), of costs (Azoulay, 2002), prices for different markets or segments (Azoulay, 2002, and Berndt et al., 2003) as instruments. Other approaches use the characteristics of competing products, excluding those produced by the same firm (Berry et al., 1995). Then, the estimation can be done with Generalized Method of Moments using aggregate data on market shares per product and per period, prices and drug characteristics.

To construct instrumental variables, we regress the price of drugs in Germany, Italy, Spain and UK (countries on which external referencing has been based in France since 2004) on active ingredient dummies, country and year fixed effects. The residuals of this regression are used as instrumental variables for the price in France. The idea is to control for country and time effects and isolate the quality of each drug, proxied by molecule dummies, which is the part of the price more likely to be correlated with demand unobservable. What remains is an approximation of the marginal cost of each drug.

If p_{jt}^c is the price of drug j in country c at period t, we use residuals ε_{jt}^c of the linear regression

$$p_{jt}^c = X_{jt}\gamma_c + \varepsilon_{jt}^c$$

and make the following identification assumption:

$$E\left(\zeta_{jt}\varepsilon_{jt}^c\right) = 0$$

The variables used as regressors capture the most important product characteristics that influence demand (Table 2). Drug-specific variables include the brand type (branded or generic), active ingredient dummies, the number of side effects and formats. Additional dummies are used to indicate whether the drug is still under patent protection and whether it has an indication for the eradication of helicobacter pylori (the major bacterial cause of ulcer) and for co-prescription with non-steroidal anti-inflammatory drugs (NSAID). Interactions between generic and formats and side effects are also used.

Variables	Description	Exp. sign	Mean	Std Dev.
market share s_{jt}	market share by year	/	0.02	0.04
price p_{jt}	average price by year	(−)	0.96	0.86
Variables X_{jt}				
branded	dummy: 0=generic, 1=branded	(+)	0.37	0.48
formats	number of therapeutic presentations	(+)	1.60	0.90
side effects	number of side effects	(−)	3.24	1.69
helicobacter	dummy: 0=no indication, 1=indication	(+)	0.75	0.44
nsaid	dummy: 0=no indication, 1=indication	(+)	0.24	0.43

Table 2: Variables and descriptive statistics

Our structural model allows to interpret the estimated sign of the coefficients as the way drug characteristics affect utility. For example, one would expect the two measures of indications, formats and branded to affect positively demand. Conversely, a large number of side effects is expected to reduce demand.

5 Supply Model and Identification of Margins

We consider an oligopoly model with a given market structure, taking entry decisions as exogenous. Indeed pharmaceutical innovation involves long R&D delays, decided many years in advance, and generic entry is constrained by patent protection. We can thus consider that pricing decisions are "static" compared to entry decisions and that these two levels of decisions can be analyzed separately. We thus focus on pricing with an exogenously given market structure.

Then, even if price setting is regulated in France, pharmaceutical companies may manage to choose prices that maximize profit. Actually, lobbying and negotiations between the regulator (CEPS) and companies may lead to price equilibrium not far from profit maximization equilibria. In particular, the fact that the price approved by the CEPS is in most cases set at the level proposed by the manufacturer seems to be a signal that, despite regulation, the price remains a decision mainly taken by the company.

We thus consider first the case of free price setting, which will be the most relevant one for US and Germany but could also be for France.

5.1 Profit Maximization Equilibrium

Denote Π_i the profit of multiproduct firm i in a given period (the time subscript t is dropped for ease of presentation). This variable profit (fixed costs and other R&D costs are not affecting pricing decisions) can be written as

$$\Pi_i = \sum\nolimits_{j \in S_i} (p_j - c_j)\, q_j(p)$$

where p_j is the price of drug j, c_j is the marginal cost of product j, $q_j(p)$ is the quantity of drug j demanded given the vector p of all drug prices, and S_i is the set of drugs owned by firm i.

We consider that firms maximize profits by choosing prices simultaneously after observing the demand factors (and in particular also the demand shocks ζ_j unobserved by the econometrician). As the assumption on the demand specification imply no dynamic effects in the demand, assuming that the cost

function of the drug manufacturer does not have any dynamic effects too, maximizing the expected sum of intertemporal profits by choosing each period the prices of drugs is thus equivalent to maximizing profit period by period.

Then, each firm i chooses the prices of all its drugs in order to maximize profit. Assuming that technical conditions for a pure-strategy Bertrand-Nash equilibrium in prices to exist are satisfied and that equilibrium prices are strictly positive, the price of any product j sold by firm i must satisfy the first-order condition

$$q_j + \sum\nolimits_{k \in S_i} (p_k - c_k) \frac{\partial q_k(p)}{\partial p_j} = 0, \quad \text{for all } j \in S_i$$

which can be written as

$$q_j \mathbf{1}_{j \in S_i} + \sum\nolimits_{k \in S_i} (p_k - c_k) \frac{\partial q_k(p)}{\partial p_j} = 0, \quad \text{for all } j, i$$

Then, with the following matrix and vector notations

$$q = \begin{bmatrix} q_1 \\ \vdots \\ q_J \end{bmatrix}, \quad p = \begin{bmatrix} p_1 \\ \vdots \\ p_J \end{bmatrix}, \quad c = \begin{bmatrix} c_1 \\ \vdots \\ c_J \end{bmatrix}$$

$$D_i = \begin{bmatrix} \mathbf{1}_{1 \in S_i} & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & \mathbf{1}_{J \in S_i} \end{bmatrix}, Q_p = \begin{bmatrix} \frac{\partial q_1(p)}{\partial p_1} & \dots & \frac{\partial q_J(p)}{\partial p_1} \\ \cdot & \cdot & \cdot \\ \frac{\partial q_1(p)}{\partial p_J} & \cdot & \frac{\partial q_J(p)}{\partial p_J} \end{bmatrix}$$

we have in matrix form

$$D_i q + D_i Q_p (p - c) = 0$$

and the usual formula for all i :

$$D_i \frac{p - c}{p} = - \left[D_i Q_p \right]^{-1} D_i \frac{q}{p}$$

giving price cost margins for all products as a function of demand shape, prices and quantities.

Remark that in the case of monopoly pricing, which amounts to assume that one firm would own all drugs and choose all prices to maximize total profit, we would have:

$$\frac{p - c}{p} = -Q_p^{-1} \frac{q}{p}$$

where $Q_p \frac{p}{q}$ is the price elasticity of demand.

Also, if firms choose prices in order to maximize profits product by product, drug by drug independent profit maximization would lead to the following price-cost margins:

$$D_i \frac{p_i - c_i}{p_i} = - \left(\left[Q_p \right]_{i,i} \right)^{-1} \frac{q_i}{p_i}$$

Thus, given demand estimates and the observation of prices and market shares, one can obtain price-cost margins per product and per year, just by solving the system of first order conditions obtained above.

5.2 Regulation and constrained profit maximization equilibrium

Let's now consider that price regulation amounts to impose implicitly some price-ceiling on drugs, either because of explicit constraints on prices (like the TFR rules in France) or because of implicit constraints coming from price negotiation between the regulator and the industry. These price ceilings are such that for each drug in a set of potentially constrained price R, the price p_j must be lower than a maximum price $\overline{p}_j$, such that the firm i constrained maximization program is:

$$\begin{array}{rcll} \max\limits_{\{p_j\}_{j\in S_i}} \Pi_i & = & \sum\nolimits_{j\in S_i} (p_j - c_j)\, q_j(p) & \\ s.t. \quad p_j & \leq & \overline{p}_j & \forall j \in S_i \cap R \end{array}$$

Assuming that technical conditions for a pure-strategy Bertrand-Nash equilibrium in prices to exist are satisfied and that equilibrium prices are strictly positive, the price of any product j sold by firm i must satisfy the first-order condition

$$q_j + \sum\nolimits_{k\in S_i} (p_k - c_k) \frac{\partial q_k(p)}{\partial p_j} = \lambda_j \mathbf{1}_{\{j\in R\}}, \quad \text{for all } j \in S_i$$

where λ_j is the Lagrange multiplier of price constraint.

These first order conditions can be written as we have in matrix form

$$D_i (q - \lambda) + D_i Q_p (p - c) = 0$$

and then

$$D_i \frac{p-c}{p}(\lambda) = -\left[D_i Q_p\right]^{-1} D_i \frac{(q-\lambda)}{p}$$

Thus, λ being unknown, even with demand estimates, prices and market shares, one cannot identify price-cost margins. We know that

$$\lambda_j > 0 \Rightarrow p_j = \overline{p}_j \text{ and } \lambda_j = 0 \Rightarrow p_j < \overline{p}_j$$

but $\overline{p}_j$ also unknown.

Theoretically, net effect on prices of regulation is ambiguous and will depend on all own and cross price elasticities of demand. Price reduction of a drug can affect other drugs not explicitly constrained because of cross price elasticity of demand

However, for each vector λ_t, from first order conditions, we have price-cost margins or marginal cost $c_{jt}(\lambda_t)$ as a known function of λ_t (depending on demand, prices and quantities demanded).

Then, identifying restrictions can be used to reduce the degree of underidentification. For example, one can assume that

$$c_{jt} = Z'_{jt}\delta \qquad \text{for some vector } Z_{jt}$$

Then, the identified set of Lagrange multipliers $\lambda_t = (\lambda_{1t}, .., \lambda_{Jt})$ is the set solution to the following minimization:

$$\min_{\{\lambda_t\}_{t=1,..,T}} \sum\nolimits_{j,t} \left[c_{jt}(\lambda_t) - Z'_{jt}\left(Z'_{jt}Z_{jt}\right)^{-1} Z'_{jt} c_{jt}(\lambda_t)\right]^2$$

where $\left(Z'_{jt}Z_{jt}\right)^{-1} Z'_{jt}c_{jt}\left(\lambda_t\right)$ is the OLS estimate of δ.

Some of these cost restrictions, depending on Z_{jt}, will simply make use of restrictions across markets t of marginal costs of drugs. The identification power in our application will come form the fact that there can be relevant and robust cost restrictions across products whose price is constrained ($j \in R$) and other whose price is not constrained ($j \notin R$). Here it can be either because of restrictions on the marginal costs of the same drug across periods (before and after some regulatory changes), or because of restrictions on costs of drugs across countries, some regulated (France) and others not price constrained (US or Germany).

Then, each $\hat{\lambda}_{jt}$ allows to infer if the price constraint is binding for drug jt and $\hat{\lambda}_t$ allows to obtain the marginal costs $c_{jt}\left(\hat{\lambda}_t\right)$ under the constrained equilibrium.

Among the different possible cost restrictions of the form $c_{jt} = Z'_{jt}\delta$, that we could be willing to impose, we can consider the following special cases to reduce the degree of underidentification of marginal costs. We can assume that marginal costs be the sum of a drug effect and a time effect $c_{jt} = \gamma_j + \delta_t$. We can assume that marginal costs depend only on the characteristics $m(j)$ of drug j at period t(this characteristic can be the molecule), $c_{jt} = \gamma_{m(j)t}$.

Finally, one could also consider inequality restrictions like imposing that marginal costs be positive or zero and below price

$$0 \leq c_{jt} \leq p_{jt}$$

Then, we could identify the following set

$$\left\{\{\lambda_t\}_{t=1,..,T} | 0 \leq c_{jt}\left(\lambda_t\right) \leq p_{jt} : t = 1,..,T\right\}$$

Once we have obtained $c_{jt}\left(\hat{\lambda}_t\right)$, we will see that we can identify the counterfactual equilibrium prices without the regulatory constraint by simulating $c_{jt}\left(0\right)$.

6 Estimation Results

6.1 Demand Estimation Results

Results of the mixed logit model are reported in Table 3. Time and active ingredient dummies were included in the estimation but are not reported in Table 3. Year dummies are not always significant, but their sign captures a positive trend (negative coefficients are associated to earlier years, while positive and increasing coefficients are estimated after 2000). Active ingredient dummies are usually significant and their sign reflects perceived quality of different drugs. Branded drugs show a competitive advantage, even though the effect is not always significant. Similarly, having an indication for the eradication of helicobacter pylori and for co-prescription with NSAID has a positive effect, as well as being sold under several presentations. Surprisingly, the number of side effects does not seem to discourage purchase, but it does so for generic drugs. This result may be driven by the simplistic way side effects are defined, by just their number, without accounting for their seriousness.

Coefficients are estimated through a simulated method of moment. The simulations are used to compute the predicted aggregated market shares with 100 simulation draws using normalized Halton draws. This type of draws was preferred to more common (pseudo)random draws due to their superior performance. Train (2003) shows how results are similar with 100 Halton draws to using 1000 random draws, but standard errors are lower.

Estimates of heterogeneity of coefficients around the mean are reported in columns denoted sigma. In this specification, four variables have a random coefficient: the price, the dummy variable for being branded and the two measures of therapeutic indications (helicobacter and NSAID). Heterogeneity seems to play a role especially for the price coefficient for France and the US and for the therapeutic indications for the three countries. Conversely, the valuation for branded does not change much across individuals for France and the US while it is very heterogenous for Germany.

Random Coefficient Logit	France		Germany		US	
	mean	sigma	mean	sigma	mean	sigma
price	−4.61	2.26	−10.76	1.82	−3.63	2.33
	(2.00)	(0.87)	(3.80)	(3.95)	(1.80)	(1.08)
branded	4.36	1.59	−4.77	7.57	11.71	0.12
	(1.95)	(1.80)	(3.20)	(4.97)	(2.96)	(9.38)
formats	0.31		0.88		0.45	
	(0.58)		(0.19)		(0.20)	
generic*formats	0.92		0.53		1.13	
	(0.37)		(0.24)		(0.30)	
side effects	0.61		0.17		−1.68	
	(0.30)		(0.52)		(0.83)	
generic*side effects	−0.85		−1.36		2.14	
	(0.32)		(0.67)		(1.03)	
helicobacter	2.63	2.27	−8.03	4.97	3.11	1.47
	(0.41)	(3.28)	(5.67)	(2.63)	(1.57)	(2.60)
nsaid	−0.19	3.94	−4.75	5.87	1.62	4.79
	(0.36)	(1.22)	(5.71)	(9.35)	(3.33)	(10.61)
constant	−5.47		6.26		−6.08	
	(1.61)		(2.14)		(1.17)	

Table 3: Estimation results of Random Coefficient Logit Model

6.2 Elasticities

The estimates of elasticities provided by the Mixed Logit model in France are able to capture real substitution patterns. In general, own price elasticities are estimated to be quite low, especially for some products. Mean own price elasticity across products and years is -4.84 and ranges from values smaller than -25 to -1.16. On the whole, generics show lower own price elasticities than branded drugs, though the difference is not large (-4.42 against -5.53). However, there is much more variation across generics than across branded drugs.

Elasticities evolve over time. Table 4 displays own-price elasticities for a sample of major branded drugs in four years in France. Elasticity for new branded drugs decreases gradually after some time on the market, indicating a role for learning by physicians and patients (Crawford and Shum, 2005). This

fact is clear at inspection of the elasticities for Inipomp and Nexium: their pattern suggests that it took time to physicians and patients to know their availability and quality. Conversely, older drugs display pretty stable own price elasticities (Zantac, Tagamet and Cytotec).

Drug		1997	2000	2004	2007
Losec		-12.85	-7.80	-8.01	-7.53
Nexium		-	-	-8.63	-5.22
Inipomp		-7.73	-7.67	-5.83	-5.01
Zantac		-3.12	-4.43	-3.00	-2.88
Tagamet		-2.62	-2.26	-2.77	-2.30
Cytotec		-1.37	-1.75	-1.80	-1.65

Table 4: Own-price elasticities of a sample of branded drugs (France)

Table 5 displays cross-price elasticities in France for a sample of drugs for the year 2004. Some of its results are expected, others instead are quite surprising. First, these drugs do not seem to be very close substitutes, as for a 1% price increase of any of these drugs, the highest benefit is an increase by 1.5% in sales. The fact that this figure is found between Losec and Nexium is in line with expectations, given that Nexium and Losec are based on very similar molecules. Similarly, the benefit in sales increase is proportional for drugs based on the same active ingredient (Omeprazole Serv and Losec) and is relatively high also for drugs belonging to the same ATC category (Losec, Nexium and Inipomp). However, the Mixed Logit uncovers substitutability relationships that go beyond ATC subclass or active ingredient and show how, for example, patients are quite willing to switch to Losec if the price of Zantac increases, instead of buying the closest alternative, i.e. Ranitidine Myla. Other cross price elasticities for France , US and Germany are given in Tables A1, A2, A3, A4 in appendix A.2.

	Losec	*Nexium*	*Inipomp*	*Zantac*	*Tagamet*	*Cytotec*	*Ome. Serv*	*Ran. Myla*
Losec	-8.01	0.72	0.70	0.19	0.04	0.04	0.20	0.03
Nexium	1.49	-8.63	0.69	0.19	0.04	0.01	0.20	0.03
Inipomp	1.00	0.48	-5.83	0.13	0.03	0.03	0.02	0.02
Zantac	0.49	0.23	0.22	-3.00	0.01	0.01	0.06	0.01
Tagamet	0.44	0.21	0.20	0.06	-2.77	0.01	0.06	0.01
Cytotec	0.29	0.14	0.13	0.04	0.01	-1.80	0.04	0.01
Ome. Serv	1.00	0.48	0.46	0.13	0.03	0.03	-6.15	0.02
Ran. Myla	0.49	0.24	0.23	0.06	0.01	0.01	0.07	-3.10

Table 5: Cross elasticities for a sample of drugs, 2004 (France)

6.3 Margins and Costs

After estimating own- and cross-price elasticities, we can estimate price-cost margins under the two different supply models considered. Inspection of the evolution of price-cost margins and the differences obtained using different models should shed some light on the actual role played by regulation in price-setting decisions of the firms.

6.3.1 *Unconstrained price-setting*

Although marginal costs for drugs have been estimated to be small and to decrease after patent expiration (see, for example, Berndt et al., 2003)

First, no markups are estimated to be above 1 (see Table 6 below) and the mean across drugs and years is 28%. Thus, there seems to be some degree of market power. Half of the values are below 25% and, except for a few generics of cimetidine showing very high levels of markups in later years (between 80 and 90%), the rest of the drugs show margins below 50%. Generics systematically show higher margins than branded versions, with a mean of 33% against 22%. Similarly, some molecules appear to be more profitable than others to sell, as they repeatedly display higher levels of markups, both for branded and for generic manufacturers (cimetidine is a clear example in Table 6). However, for some active ingredients generic firms display a significant comparative advantage in their production. It is again the case of cimetidine and, to a less extent, omeprazole and lansoprazole. This fact is not surprising: it is common wisdom in the industry that generic firms display lower marginal costs than branded manufacturers and this is especially true for older molecules, such as cimetidine.

Molecule	Average	Branded	Generic
Cimetidine	54%	38%	58%
Ranitidine	28%	25%	29%
Famotidine	29%	25%	38%
Omeprazole	20%	11%	22%
Lansoprazole	16%	14%	35%
Average price-cost margins by molecule			

Table 6

Interestingly, average markups are estimated to increase over time, as suggested by previous models. The increase is significant, from 24% in 1997 to 33% in 2007, and mainly occurs in 2006. This effect is driven by an increase in the margins for generics, while branded drugs show more stable markups.

6.3.2 *Constrained price-setting*

We now assume that regulation may impose some price cap to some drugs in France. This has been implemented since 2004 in France through reference pricing, which links the reimbursement level of some branded drugs to the price of their generic versions. In 2004 and 2005 only two anti-ulcer drugs were affected by this measure (Tagamet and Zantac), and a third was added in 2006 (Pepcidine). In addition, since 2006 the price for all drugs in a subclass is imposed to decrease once generic drugs enter or when they have been on the market for at least 24 months. This amounts in our model to an additional price constraint on three drugs (Losec, Lanzor and Takepron). Thus, we impose that the price of these drugs only can be capped and we test our hypothesis by estimating the Lagrange multiplier for each of them. In order to recover it, we assume that the marginal cost depends on the active ingredient of the drug. We estimate them through non-linear least squares.

Year	Average		Branded		Generic	
	Unconst.	Constr.	Unconst.	Constr.	Unconst.	Constr.
1997	24%	24%	24%	24%	25%	24%
1998	22%	22%	19%	19%	36%	37%
1999	21%	21%	21%	21%	21%	21%
2000	28%	29%	22%	22%	33%	34%
2001	29%	30%	22%	23%	34%	36%
2002	28%	30%	22%	23%	33%	36%
2003	28%	30%	21%	22%	33%	35%
2004	26%	25%	21%	16%	29%	29%
2005	26%	25%	21%	15%	29%	30%
2006	33%	32%	26%	18%	37%	32%
2007	33%	-	25%	-	37%	-
Average price-cost margins						

Table 7

Table 7 reports a comparison of average margins by year estimated with each of the two models. Markups do not differ significantly depending on the model used: the average is slightly below 28% as in the unconstrained model, and the evolution over time reflects an increasing pattern. However, since 2004 margins estimated using the price-constrained model are always below those obtained by the unconstrained model. This is more obvious when comparing results for branded drugs. Since 2004 margins for branded drugs are systematically lower than in the model ignoring regulation and the effect is quite strong. However, even margins for generics are estimated to be lower than with the unconstrained model for year 2006.

Molecule	Unconstr.	Constr.
Cimetidine	54%	54%
Ranitidine	28%	26%
Famotidine	29%	28%
Nizatidine	18%	18%
Omeprazole	20%	19%
Esomeprazole	14%	13%
Lansoprazole	16%	14%
Pantoprazole	14%	13%
Rabeprazole	16%	16%
Misoprostol	56%	59%
Average price-cost margins by molecule		

Table 8

It is interesting to note how margins by active ingredient reflect the constraints. Margins for famotidine, ranitidine, omeprazole and lansoprazole are estimated to be slightly lower than with the unconstrained model (see Table 8), while for other molecules there is not a clear pattern. Inspection of margins drug by drug (not reported) further confirms that drugs subject to reference pricing and to price decreases are correctly estimated to enjoy lower margins than when ignoring regulation after 2004.

Drug	2003		2004		2005		2006	
	Un.	Con.	Un.	Con.	Un.	Con.	Un.	Con.
Tagamet	41%	44%	34%	30%	31%	29%	41%	36%
Pepcidine	20%	20%	20%	20%	19%	19%	22%	16%
Losec	14%	13%	12%	11%	11%	11%	13%	13%
2003-2006 margins for regulated drugs								

Table 9

Year	Average		Branded		Generic	
	Unconst.	Constr.	Unconst.	Constr.	Unconst.	Constr.
1997	24%	24%	24%	24%	25%	24%
2000	28%	29%	22%	22%	33%	34%
2003	28%	30%	21%	22%	33%	35%
2004	26%	25%	21%	16%	29%	29%
2005	26%	25%	21%	15%	29%	30%
2006	33%	32%	26%	18%	37%	32%

Average price-cost margins

Table 10

On the whole, these results seem to suggest that our model is capturing some effects on the drugs subject to reference pricing and to price decreases. Accounting for regulation is thus important when estimating market power and our results, though far from estimating a binding constraint, are indicative of the fact that firms are not completely free to choose the price.

Year	Average		Branded		Generic	
	Unconst.	Constr.	Unconst.	Constr.	Unconst.	Constr.
1997	22.8%	-	22.7%	-	23.4%	-
1998	26.1%	-	22.9%	-	43.9%	-
1999	22.0%	-	22.0%	-	21.7%	-
2000	32.7%	-	25.2%	-	38.7%	-
2001	32.6%	-	24.7%	-	39.0%	-
2002	31.7%	-	24.5%	-	37.6%	-
2003	32.0%	-	24.3%	-	38.0%	-
2004	30.9%	30.6%	25.1%	22.4%	33.4%	34.2%
2005	31.9%	31.2%	25.4%	21.1%	34.9%	35.9%
2006	34.2%	33.2%	26.1%	19.3%	37.5%	38.8%
2007	35.5%	34.9%	27.2%	22.0%	39.6%	41.1%

Table 11: Average price-cost margins

Molecule	France		US		Germany	
	Branded	Generic	Branded	Generic	Branded	Generic
Cimetidine	42.1%	66.1%	24.6%	109%	23.4%	21.9%
Famotidine	27.1%	40.6%	10.1%	214%	13.8%	18.7%
Nizatidine	19.6%	-	13.5%	47.5%	13.5%	-
Ranitidine	27.5%	32.8%	15.8%	283%	27.9%	12.5%
Esomeprazole	15.1%	-	8.5%	-	28.7%	-
Lansoprazole	16.0%	38.1%	9.1%	-	15.7%	0.05%
Omeprazole	13.0%	23.8%	8.2%	22.5%	17.0%	14.5%
Pantoprazole	15.1%	-	11.7%	9.5%	17.0%	-
Rabeprazole	18.3%	-	10.6%	-	26.0%	-
Misoprostol	61.8%	-	36.2%	58.3%	15.8%	-

Table 12: Average price-cost margins by molecule in the 3 countries

Drug	2004		2005		2006		2007	
	Un.	Con.	Un.	Con.	Un.	Con.	Un.	Con.
Tagamet	40%	42%	38%	37%	42%	39%	44%	39%
Zantac	37%	6%	37%	5%	35%	6%	35%	29%
Raniplex	25%	12%	29%	0.5%	34%	-22%	35%	-22%
Pepcidine	23%	-	23%	-	23%	21%	24%	22%

Table 13: 2004-2007 margins for regulated drugs

Drug	2004		2005		2006		2007	
	Un.	Con.	Un.	Con.	Un.	Con.	Un.	Con.
Tagamet	40%	41%	38%	37%	42%	39%	44%	39%
Zantac	37%	2%	37%	1%	35%	2%	35%	30%
Raniplex	25%	11%	29%	1%	34%	-24%	35%	-21%
Pepcidine	23%	-	23%	-	23%	21%	24%	22%
Losec	14%	-	13%	-	13%	-	14%	-11%
Lanzor	18%	-	18%	-	19%	-	20%	9%
Takepron	18%	-	18%	-	29%	-	20%	5%

Table 14: 2004-2007 margins for regulated drugs

Drug	2004		2005		2006		2007		
	Un.	Con.	Un.	Con.	Un.	Con.	Un.	Con.	
Tagamet	0.31	0.30	0.33	0.34	0.28	0.29	0.27	0.29	
Zantac	0.36	0.53	0.34	0.34	0.37	0.54	0.39	0.42	
Raniplex	0.61	0.72	0.52	0.72	0.39	0.72	0.38	0.72	
Pepcidine	0.68	-	0.68	-	0.68	0.70	0.64	0.66	

Table 15: 2004-2007 marginal costs for regulated drugs - in USD per standard unit

Drug	2004		2005		2006		2007		
	Un.	Con.	Un.	Con.	Un.	Con.	Un.	Con.	
Tagamet	0.31	0.30	0.34	0.34	0.28	0.29	0.27	0.29	
Zantac	0.36	0.56	0.35	0.56	0.37	0.56	0.39	0.42	
Raniplex	0.61	0.73	0.52	0.72	0.39	0.73	0.38	0.71	
Pepcidine	0.68	-	0.68	-	0.68	0.70	0.64	0.66	
Losec	1.51	-	1.55	-	1.45	-	1.37	1.75	
Lanzor	1	-	1	-	0.95	-	0.86	0.98	
Takepron	1.02	-	1.02	-	0.96	-	0.86	1.04	

Table 16: 2004-2007 marginal costs for regulated drugs - in USD per standard unit

7 Conclusion

We have estimated models of demand for anti-ulcer drugs in France, US and Germany in the period 1997-2007, so as to identify the effects exerted by the regulation of prices in France on margins, industry structure and, on the whole, welfare. Models of discrete choice for differentiated products are applied to data on wholesale transactions provided by IMS Health, with an emphasis on consumers' heterogeneity. On the supply side, we assume firms may be constrained by regulation in their price setting decisions on some markets (France).

The analysis of the demand side finds out that being branded and quality of the drug are the major drivers of demand in the period under study, but consumers heterogeneity matters quite significantly. Interestingly, cross price elasticities capture a still imperfect perceived substitutability of generics: as the price of the drug used increases, consumers are predicted to rather switch to a branded competitor than to the generic version of their preferred drug.

On the supply side, our results suggest that price regulation measures introduced after 2003 in France act as a price cap for some drugs, which are estimated to display lower margins than with a model

that ignores regulation. Both models show that margins increased over time, suggesting that firms in this market have some degree of market power. Generics display higher markups along the whole period and regardless of the active ingredient. Moreover, they show a particular competitive advantage in the production of some old molecules. This is not surprising, as it is common wisdom that generic manufacturers have lower costs than their branded competitors. Our constrained profit maximization model uncovers some role played by price regulation in France, focusing on reference pricing and on generic-related price decreases. Results suggest that firms subject to these measures are indeed not completely free to choose the price besides their intense negotiation in price setting with the regulator. Thus, accounting for regulation is crucial to estimate market power and welfare.

We are able to show evidence on which drugs are truly affected by regulation and which constraints are more or less binding (on-patent versus off-patent drugs, branded versus generics, etc.). We finally perform some counterfactual analysis, by simulating price with and without constraint and test what would happen to prices and margins if, for example, price regulation had not existed in France.

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A Appendix

A.1 Data

After adaptation and manipulation of the data, 361 observations were left. One observation is defined as a drug-year pair: Zantac in 1997 is a different observation from Zantac in 1998.

Recovering prices of drugs in other countries proved sometimes to be difficult, due to a number of reasons. First, not all medicines are sold in all countries. Even when a medicine exists abroad, sometimes it is not exactly the same as the one in France or that it is called differently. Also, the patentee may be the manufacturer in its country, but may decide to license it to other firms in other countries: this translates into different names of the medicine and of the company, even though the two drugs coincide. Often, it is easy to identify the same medicine in different countries in the database, but it is present under different therapeutic forms. Even though data are aggregated at the therapeutic form level, this imperfect matching requires additional steps of data checking.

A drug is identified by the matching in France and in the other country of five pieces of information present in the dataset: the name of medicine and/or the name it is given in the company, the active ingredient, the brand type (branded vs. generic) and the patent registration date. The manufacturer was not used as a major criteria, but it was often used for double checking.

When a matching based on these criteria could be found, but the drug in the two countries was not exactly the same, some proxies where used. When a drug is sold under different presentations in different countries, then it is considered to be the same when at least two out of three digits in the code defining the therapeutic form coincide: this criterion guarantees that the main characteristics of each form are preserved (and hence the price abroad is a good instrument for the price in France). When matching for a drug in France and any of the other four countries could not be found, the price used as a proxy was that of a drug showing as many characteristics as possible in common with the French medicine, namely the active ingredient, therapeutic form, brand type. For a couple of products even such correspondence could not be found: the price was then instrumented with the weighted average price in the other three countries.

For generics, it was sometimes very difficult to identify the same drug in France and abroad. In this case, the price of a French unbranded generic was instrumented by averaging the price of all the unbranded generics with the same molecule in the other country.

A.2 Additional Tables

	Tagamet	*Zantac*	*Losec*	*Nexium*	*Inipomp*	*Cytotec*	*Ran. Myla*	*Ome. Serv*
Tagamet	-2.35	0.04	0.41	0.19	0.17	0.02	0.01	0.05
Zantac	0.02	-2.57	0.45	0.21	0.19	0.02	0.01	0.05
Losec	0.06	0.14	-6.73	0.66	0.60	0.05	0.03	0.16
Nexium	0.06	0.14	1.37	-7.32	0.59	0.05	0.03	0.16
Inipomp	0.04	0.09	0.92	0.44	-4.97	0.04	0.02	0.11
Cytotec	0.01	0.03	0.27	0.13	0.11	-1.53	0.01	0.03
Ran. Myla	0.02	0.05	0.46	0.22	0.19	0.02	-2.64	0.05
Ome. Serv	0.04	0.09	0.92	0.44	0.39	0.04	0.02	-5.25

Table A1: Cross elasticities for a sample of drugs, 2004 (France)

	Tagamet	*Zantac*	*Losec*	*Nexium*	*Pariet*	*Cytotec*	*Ran. Novt*	*Ome. Novt*
Tagamet	-2.35	0.04	0.41	0.19	0.18	0.02	0.0	0.03
Zantac	0.02	-2.57	0.45	0.21	0.20	0.02	0.0	0.04
Losec	0.06	0.14	-6.73	0.66	0.63	0.05	0.01	0.12
Nexium	0.06	0.14	1.37	-7.32	0.62	0.05	0.01	0.11
Pariet	0.04	0.10	0.95	0.45	-5.09	0.04	0.01	0.08
Cytotec	0.01	0.03	0.27	0.13	0.12	-1.53	0.0	0.02
Ran. Novt	0.02	0.05	0.51	0.24	0.23	0.02	-2.95	0.04
Ome. Novt	0.04	0.09	0.92	0.44	0.41	0.04	0.01	-5.28

Table A2: Cross elasticities for a sample of drugs, France 2004

	Tagamet	*Zantac*	*Losec*	*Nexium*	*Pariet*	*Cytotec*	*Ran. Novt*	*Ome. Novt*
Tagamet	-4.93	0.06	0.11	0.19	0.70	0.01	0.14	0.05
Zantac	0.0	-7.30	0.16	1.05	0.51	0.01	0.20	0.08
Losec	0.01	0.14	-11.13	1.68	0.83	0.01	0.33	0.13
Nexium	0.01	0.15	0.28	-11.61	0.90	0.01	0.36	0.14
Pariet	0.0	0.11	0.22	1.41	-9.26	0.01	0.28	0.11
Cytotec	0.0	0.04	0.07	0.46	0.23	-3.25	0.09	0.04
Ran. Novt	0.0	0.01	0.02	0.11	0.05	0.0	-0.76	0.01
Ome. Novt	0.0	0.07	0.13	0.87	0.43	0.01	0.17	-6.09

Table A3: Cross elasticities for a sample of drugs, US 2004

	Tagamet	*Zantac*	*Losec*	*Nexium*	*Pariet*	*Cytotec*	*Ran. Novt*	*Ome. Novt*
Tagamet	-4.36	0.01	0.04	0.43	0.02	0.0	0.05	0.09
Zantac	0.0	-6.13	0.06	0.61	0.03	0.01	0.06	0.13
Losec	0.01	0.07	-26.34	2.65	0.14	0.03	0.28	0.55
Nexium	0.01	0.05	0.17	-15.71	0.09	0.02	0.18	0.36
Pariet	0.01	0.05	0.18	1.80	18.01	0.02	0.19	0.38
Cytotec	0.0	0.01	0.04	0.44	0.02	-4.36	0.05	0.09
Ran. Novt	0.0	0.01	0.03	0.31	0.02	0.0	-3.11	0.07
Ome. Novt	0.01	0.04	0.14	1.40	0.07	0.02	0.15	-13.71

Table A4: Cross elasticities for a sample of drugs, Germany 2004