Identifying Industry Margins with Unobserved Price Constraints: Structural Estimation on Pharmaceuticals

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Abstract

We provide a method allowing identification of margins in an oligopoly price competition game when prices may not be freely chosen in some markets, for example due to regulation. We use our identification strategy to study the effects of regulatory constraints in the pharmaceutical industry. 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, Germany and France) with varying regulatory constraints. We use the market for anti-ulcer drugs to identify whether regulation in France truly affects margins and prices and relate regulatory reforms to industry pricing equilibrium. Empirical results show that firms were especially constrained in price setting after the different reforms in 2004. Counterfactual simulations show that total spending significantly increased because of the new price regulation by displacing part of the demand from generics to branded drugs.

Key words: empirical IO, price constraints, Bertrand competition, regulation, pharmaceuticals, antiulcer drugs.

JEL Codes: L10, I18, C18

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1 Introduction

Understanding the role played by regulatory constraints is of major importance in an industry like pharmaceuticals where regulation is heavily present in many countries throughout all stages of drug development and commercialization. In many countries, prescription drugs are subject to price negotiation with the national health care system, while in other countries prices are freely set by pharmaceutical companies. The latter is the case of the US, where prices are not regulated once drugs obtain approval by the Food and Drug Administration (FDA). On the contrary, France is considered as heavily regulating pharmaceuticals. Indeed, 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. The different reforms may have affected pharmaceutical manufacturers' price setting and squeezed margins. Reduced form evidence suggests that some specific regulatory changes that occurred in France since late 2003 seem to have reduced prices. However, these difference-in-difference evidence may be a mere consequence of demand changes or supply shocks. Structural estimation is thus needed to interpret these results and to verify whether regulation has really constrained prices or if observed price changes are simply due to demand or supply conditions.

We provide the first structural estimation of price-cost margins in a regulated market with price constraints and show how to identify unknown possibly binding constraints thanks to three different markets with varying regulatory constraints (US, Germany and France). Once the demand shape is identified (with usual conditions for identification of a flexible demand model for differentiated products), the identification strategy relies on the assumptions about the price competition game played by firms and the knowledge that some markets are not price constrained (here US and Germany), while others may be constrained (France). The method allows us to infer whether constraints are binding and to identify price-cost margins even in those markets, provided demand can be identified.

We then investigate whether the price setting regulation mechanism in France actually imposes binding constraints on the market for anti-ulcer drugs. We evaluate the counterfactual free pricing equilibrium and thus identify changes in prices, demand and spending due to the different regulation along the period from 1997 to 2007. We find that there is significant consumer heterogeneity, that demand is price elastic and that drug quality and being branded both affect demand. Empirical results show that margins have increased over time in France but that firms were especially constrained in price setting after 2004.

In the literature on demand estimation for pharmaceuticals, Berndt, Bui, Railey and Urban (1995) use a simple log-log demand model to explore the role played by different forms of marketing for H2 anti-ulcer treatments in the US while Berndt, Kyle and Ling (2003) estimate a log-log demand model to examine the utilization of H2-antagonist drugs after patent expiration. Rizzo (1999) used a similar approach 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. Other works use discrete choice demand models. For instance, Azoulay (2002) uses a logit model to show how product market competition in the H2 subclass was shaped by advertising efforts and quality of scientific information. Berndt, Pindyck and Azoulay (2003) use a logit model, as do Crawford and Shum (2005), who study the effect of uncertainty regarding drug effectiveness, as well as of experience and learning in the Italian market for prescription anti-ulcer drugs. Donohue and Berndt (2004) or Stern (1996) use nested logit demand models, Arcidiacono, Ellickson, Landry and Ridley (2013) extend the nested logit by allowing for unobserved preferences to be correlated across nests (brand type, subclass, molecule and form) and account for copayments and rebates, which bias both the price faced by consumers and the price paid by the insurance companies to drug manufacturers. Ellison, Cockburn, Griliches and Hausman (1997) estimate the elasticity between branded and generic versions of four antibiotics (cephalosporins) with a multistage budgeting demand model. Brekke, Holmås and Straume (2013) find a strong relationship between the margins of brand-names and generics and their market shares in Norway, and suggest that pharmacy incentives are crucial for promoting generic sales.

Demand estimation in empirical IO usually emphasizes the role of consumer heterogeneity through random coefficient logit models (Berry, 1994; Berry, Levinsohn and Pakes, 1995; Nevo, 2000 and 2001). Random coefficient logit models provide richer and more plausible substitution patterns than logit and nested logit models. They have been applied to estimate the demand for cars (Berry et al. 1995, and, more recently, Verboven, 2011), for ready-to-eat cereals (Nevo, 2000 and 2001), for mineral water (Bonnet and Dubois, 2010), among others. However, such demand models have been rarely used to estimate demand for pharmaceuticals. A notable exception is Dunn (2011), who estimates a random coefficient logit model to construct a quality-adjusted price of anti-cholesterol drugs and investigate its evolution over time. Applying the same methodology, Yin (2012) estimates demand drivers for antidepressants on US individual-level data.

We expect the complexity of demand drivers to create high heterogeneity in demand parameters that must be taken into account in the aggregate demand estimation. As the demand may be affected by patients' preferences and copayments, by pharmacists' incentives to substitute brand-name drugs to generic versions, by physicians' incentives to prescribe cheap, expensive or pharmacists' most profitable drugs, we use a flexible random coefficient logit demand model to allow heterogeneity in tastes for drugs characteristics and for price disutilities.

On the supply side, fixed costs are usually much larger than variable costs in drug production. Indeed, the long and difficult process needed to come up with a finished drug and 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 and up to 1 billion $US in expenses per successful molecule (DiMasi, Hansen and Grabowski, 2003). The remainder of the cost consists of intellectual property protection and compliance to strict rules governing safety standards, clinical trials and regulatory approval processes. Regulation of the pricing of pharmaceuticals in many countries makes price setting decisions not entirely under the control of the firm. The regulator typically wants to balance the need for cheap access to drugs by patients and the necessity for firms to recoup the investments made during the R&D phase.

It has been shown that regulation of the pharmaceutical sector affects strategic incentives and behavior of the industry. For instance, Danzon and Chao (2000) 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 counterproductive. Kyle (2007) shows that price controls have important effect on pharmaceutical launches because drugs invented by firms headquartered in countries using price controls reach fewer markets and with longer delays than products that originate in countries without price controls. Scott-Morton (1999) investigates the determinants of entry in the pharmaceutical market and emphasizes the importance of firm 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. Filson (2012) focuses on the impact of the introduction or removal of price controls across countries on the introduction of new drugs, consumer welfare and firm value, simulating a dynamic equilibrium model. 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. Chaudhuri, Goldberg and Jia (2006) find that price regulation is not enough to compensate for the welfare losses originated from global patent protection: the enforcement of product patents provided by the TRIPS Agreement is estimated to negatively affect consumer surplus for a specific type of antibiotics (quinolones) in India. Brekke, Grasdal and Holmås (2009) and Brekke, Holmås and Straume (2011) study the impact of the change of price cap regulation to reference pricing in 2003 for a sub-sample of off-patent products in Norway.

Concerning the supply side, we model the role of regulation in limiting and steering the price setting decisions of the firms. Indeed, price regulation in France is composed of several regulatory constraints: some are akin to price cap regulations, others (mostly after 2004) are reference pricing regulations, meaning that some reimbursement price of drugs are fixed according to the prices of other reference groups of drugs. The diverse regulatory rules and the sometimes implicit rules imposed by the regulator are taken into account on the firm side of our model by simply formulating that firms are not free to choose prices to maximize their profit as in usual oligopolistic models. In addition to the explicit regulatory constraints that evolved along time, the regulator may arbitrarily impose some price cap, which is unknown to the econometrician and that may or may not be binding for pharmaceutical companies. Thus, the magnitude of this price-ceiling and the fact that it is binding or not for firms is unknown. Our modeling and identification strategy allows such price constraints to be unknown and to change across drugs and periods. We model the existence of price constraints in the firms profit maximization strategy and identify those potential constraints thanks to the existence of some unconstrained markets (for example the US, or Germany or some periods in France) and to some cost restrictions of drugs across markets.

This new identification strategy has not yet been used in the IO literature. Relatedly, Salvo (2010) estimates market power in the Brazilian cement industry where firms are also constrained in price setting because of the threat of entry by foreign producers, which poses an observable ceiling to the price that domestic competitors can set. Brenkers and Verboven (2006) study how constraints on international markup differentials introduced after liberalizing the distribution of cars in Europe affect the market equilibrium. After estimating the demand for cars before liberalization and thus without price constraints, they simulate a new price equilibrium imposing a given maximum difference of markups across countries. Our identification strategy under unobserved constraints could thus be used in the context of markets where prices may be affected by inequality constraints on markups across markets.

The paper is structured as follows. Section 2 describes the market for anti-ulcer drugs, the data used and explains the major points of the reforms in France. Section 3 shows how we can

identify price-cost margins in an oligopoly model when demand is known, provided that we observed unconstrained markets together with constrained markets. Section 4 describes the demand model and its estimation. Results are discussed in Section 5. Section 6 presents counterfactual price equilibrium and savings calculations absent the regulation of price setting in France. Finally, section 7 concludes.

2 Market, Data and Regulation

2.1 Regulatory Framework in France

The pharmaceutical market in France shares some characteristics with other industrialized countries, especially 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 a large part of the price of prescription drugs. Moreover, more than 90% of the population has supplementary insurance, which used to cover 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 of 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 starting in 2003 introduced a number of major changes,

partially liberalizing some prices and rationalizing the process for the setting of others (especially hospital prices).

In France, the authorization of market entry of drugs is granted by the Agency for the Safety of Health Products (*Agence Française de Sécurité Sanitaire des Produits de Santé*, AFSSAPS). In order to obtain reimbursement by social insurance, two additional steps must be performed for prescription drugs. The first is the evaluation of the reimbursement level of the drug; the second is the actual price setting, which is regulated. Drugs that are reimbursed must be included in a so-called *positive list* 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 measures the absolute medical benefit of the drug and is based on considerations on both drug characteristics and disease class characteristics (this medical benefit is called *SMR* for *Service Médical Rendu* in French). The second refers to the progress in treatment brought by the drug in terms of efficacy, side effects and/or ease of use as compared to existing products in its class (this improved medical benefit is called *ASMR* for *Amélioration du Service Médical Rendu* in French). If the SMR attributed by the "Transparency Commission" is high enough, the drug is included in the positive list and reimbursement is set at 15**%,** 35%, 65% or 100%, depending on the SMR level. Since 2004, a major role in the decision on the reimbursement rate has been played by UNCAM (National Union of Sickness Insurance Funds).

The SMR and ASMR rates are also used in the negotiation of the price of the drug between the manufacturer and the Economic Committee for Health Products (CEPS - *Comité Economique des Produits de Santé*) which is the name of the regulator since 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 (called TFR for *Tarif Forfaitaire de Responsabilité* in French), linking the reimbursement of originator drugs to the price of their generic counterparts. In 2004 external referencing was also introduced, ensuring that prices are set in line with those in four neighboring countries (Italy, Germany, UK

and Spain). Finally, since 2006, the price of all drugs in a class must be reduced when generics become available or when they have been on the market for at least 24 months. The purpose of all of these measures was to reduce the price level of reimbursable drugs, 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 (2009). First, some campaigns were launched, addressed to patients, to increase awareness and convey the idea that generics are safe equivalents of branded drugs. In addition, due to the limited application of generic substitution, introduced in 1999, some agreements were signed between doctors and the health insurance system in order to increase prescription of generics. In 2001, a commitment to use the international chemical name of the medicine in prescriptions was introduced (INN, International Nonproprietary Name). However, since only 8.5% of all prescriptions showed the INN (Grandfils and Sermet, 2006), another agreement was signed in 2006, encouraging physicians to prescribe drugs for which generic alternatives are available. Table 1 summarizes the regulatory changes between 1997 and 2007 that affected the anti-ulcer market in France (where a presentation of a drug is a combination of its format and packaging size).

Table 1: Regulatory Changes of Anti-ulcer Market in France since 1997

Date	Event in France for the Anti-ulcer Drugs Class
September 2003	Introduction of reference pricing (TFR) for some presentations of Cimetidine and Ranitidine.
March 2004	Revision of TFR: decrease of 0.02-0.04 € per box for Cimetidine and Ranitidine.
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.

2.2 The Anti-Ulcer Drugs Market

The analysis focuses on the anti-ulcer prescription drugs market during 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 that can be thought of as three different generations of drugs treating

ulcer and ulcer-related conditions. The subclass of histamine antagonists (H2) gathers anti-ulcer treatments of the first 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, the proton-pump inhibitors (PPI). These drugs, instead of blocking the reception of histamine, act at the source of acid secretion, inhibiting it for a longer time. This subclass includes several derivatives of benzimidazole (Omeprazole, Lansoprazole, Pantoprazole and Rabeprazole among the most diffused) and has been considered to be superior to H2 and other existing drugs. Astra Zeneca's Omeprazole compound, called Losec (or Prilosec), was the world top-selling drug during several years. Finally, the third subclass is a residual category, which includes prostaglandins, mainly used for prevention and treatment of peptic ulcer in the elderly.

The anti-ulcer market 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 having to include drugs from other therapeutic classes among competitors. In addition, during the period of study, the market experienced patent expiration of major blockbusters and several entry waves of generics, which started populating the French market in early 2000s.

2.3 Data and Descriptive Statistics

We use data from IMS Health about all wholesale transactions (revenues and quantities sold from each drug in a country-year) for the period 1997-2007. One observation (drug-country-year triplet) is uniquely identified by detailed information on the name of the medicine, the manufacturing firm, the active ingredient, the therapeutic form and information on its brand type (originator, licensed or generic drug).

Since reported transactions are at the wholesale level, there is no way to identify to which segment (pharmacies or hospital) the drug was sold. However, we can obtain an average wholesale price from the figures on quantities (in standard units) and revenues per year (in $ US). Data were aggregated at the therapeutic form level, in order to avoid distinguishing the different methods of administration of exactly the same drug (say, tablet and effervescent capsules, for instance). We use these IMS data for both quantities and revenues for France, Germany and the US but also use the wholesale average prices in Italy, Spain and the UK, as these prices, with the German ones, have been used for external reference pricing of French drugs since 2004 (see Section 5 below). We also use the website *www.theriaque.org* (approved by the regulatory agency HAS) to gather additional information on indications and side effects of each drug, as well as their medical benefit levels in France (SMR and ASMR) for each indication.

Between 1997 and 2007, a total of 69 different drugs were sold in France by 31 different companies: among them, 11 are branded firms, the remaining 20 are generic manufacturers. More than half of the drugs, 36, belong to the PPI subcategory (A02B-C), which represents 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. Conversely, Misoprostol, Nizatidine, Esomeprazole, Pantoprazole and Rabeprazole were always sold only under their branded version. In Germany and the US, the number of drugs is slightly higher than in France in some periods but all drugs sold in France are always sold in these two other countries (except for a few drugs Pantozol and Inipomp already present in France in 1997 and 1998, and Lansoprazole based Takepron only present in France and Germany).

There is not much variation in the levels of medical benefit (SMR) and improvement in medical benefit (ASMR), which are respectively II (important) and V (inadequate) for most of the drugs

in this class. The reimbursement level is set at 65% for all drugs in the class (except for some old drugs with 35% reimbursement since 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 sold 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. 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 side effects (Nexium's peculiarity).

Table 2: Summary Statistics for France

	Number of drugs			Quantity	Market Share		Price	Revenue
Year	All	Branded	Generics	(1000 std units)	Branded	Generics	($US/std unit)	(1000 $US)
1997	13	11	2	604 038	99.97%	0.03%	1.72	1 017 868
1998	13	11	2	612 932	99.97%	0.03%	1.63	1 228 439
1999	14	11	3	706 451	99.96%	0.04%	1.62	1 507 404
2000	27	12	15	809 615	99.82%	1.18%	1.10	1 126 381
2001	27	12	15	918 680	99.00%	1.00%	0.95	1 301 936
2002	29	13	16	1 064 382	99.02%	0.98%	0.97	1 477 346
2003	30	13	17	1 179 154	98.43%	1.57%	0.95	1 661 251
2004	47	13	34	1 285 490	86.73%	13.27%	0.87	1 720 953
2005	47	13	34	1 391 362	78.30%	21.70%	0.87	1 695 253
2006	51	13	38	1 523 885	74.10%	25.90%	0.82	1 695 385
2007	63	13	50	1 593 450	71.11%	28.89%	0.74	1 656 660

Notes: Price is the average price per standard unit in $US across all drugs. Revenue is total revenue of the class.

Two pieces of evidence are especially noteworthy in Table 2. The first is the significant increase in the number of drugs marketed, from less than 15 during the initial three years (1997-1999), to more than sixty in 2007. This increase is driven by the entry of generics, whose market share rose significantly during the period. Only two generics were on the market in 1997, with a negligible market share. During the early 2000s, several Ranitidine- and Cimetidine-equivalents entered the market (Zantac and Tagamet lost patent protection in the '90s), but generics still represented a residual category in terms of volumes and revenues. In 2004, a second entry wave took place by generics of the world top-selling drug Losec (Astra Zeneca's Omeprazole) and generics started becoming real competitors of their branded rivals. In 2007 generics represented nearly 30% of the whole anti-ulcer drugs market in France, around 60% in Germany and 50% in the US (see Tables A1 and A2 in appendix A.2).

The second interesting consideration is that in France generic entrants do not appear to have cannibalized sales of their branded competitors, but may have instead created a new segment of past non-users because market size increased. Indeed, aggregate quantity more than doubled during the period, with much of the increase due to generic entry, but sales of branded products increased even more. The evolution of revenues is slightly different, from 1997 to 2007 revenues increased by 62%, but this increase is not steady, with a peak in 2004, the year in which most of the measures included in the reform were introduced. Conversely, the average price decreased steadily over the period. This is likely to be due to the subsequent entry waves of generics and the regulation of prices.

3 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. Kyle (2007) and Danzon and Chao (2000) have shown that delays in entry can strategically happen, but we will assume that these market entry decisions are orthogonal to unobserved demand shocks in markets and rather driven by regulatory characteristics of markets (including pricing regulation like reference pricing). Therefore, our demand estimates are not biased by the delays in some drugs entry across countries: it is not because a market has a low demand shock in a given year that the companies will delay entry, but rather because the country is not the highest-price country and thus firms prefer to enter first in high-price countries. We can consider that pricing decisions are "static" compared to entry decisions and that these two levels of decisions can be analyzed separately. Moreover, most entries in our data are coming from generics (except for two branded drugs in 2000 and 2002), so they will not be affected by the branded drugs pricing anticipations. 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 and companies may lead to a price equilibrium not far from profit maximization equilibria (Grandfils, 2008). The price approved by the regulator is often the one proposed by the

manufacturer in the first place through a procedure called "depot de prix" (Grandfils and Sermet, 2006). This seems to signal that, despite regulation, the price remains a decision mainly taken by the company. However, companies may anticipate price constraints imposed by the regulator and unobserved negotiations may also happen before the official price setting.

3.1 Free Pricing Equilibrium

We consider first the case of free price setting, which will be the most relevant for the US and for Germany but could also be the equilibrium outcome for France. In this case, it is well known how profit maximizing prices should be set and how marginal costs can be identified if the demand shape is observed.

Denote Π_{rt} the profit of multiproduct firm r in period t. This variable profit (fixed costs and other R&D costs are not affecting pricing decisions) can be written as

$$\Pi_{rt} = \sum\nolimits_{j \in F_r} (p_{jt} - c_{jt})\, q_{jt}(\mathbf{p}_t)$$

where p_{jt} is the price of drug j, c_{jt} is the constant marginal cost of product j, $q_{jt}(\mathbf{p}_t)$ is the quantity of drug j demanded given the vector $\mathbf{p}_t$ of all drug prices, and F_r is the set of drugs produced by firm r.

We consider that firms maximize profits by choosing prices simultaneously after observing the demand factors. 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 r must satisfy the first-order condition

$$q_{jt} + \sum\nolimits_{k \in F_r} (p_{kt} - c_{kt}) \frac{\partial q_{kt}\left(\mathbf{p}_t\right)}{\partial p_{jt}} = 0, \quad \text{for all } j \in F_r$$

which can be written as

$$q_{jt}\mathbf{1}_{\{j \in F_r\}} + \sum\nolimits_{k \in F_r} (p_{kt} - c_{kt}) \frac{\partial q_{kt}\left(p_t\right)}{\partial p_{jt}} = 0, \quad \text{for all } j, r$$

where $\mathbf{1}_{\{j \in F_r\}} = 1$ if $j \in F_r$ and 0 otherwise.

Then, with the following matrix and vector notations

$$\mathbf{q}_t = \begin{bmatrix} q_{1t} \\ \vdots \\ q_{J_t t} \end{bmatrix}, \quad \mathbf{p}_t = \begin{bmatrix} p_{1t} \\ \vdots \\ p_{J_t t} \end{bmatrix}, \quad \mathbf{c}_t = \begin{bmatrix} c_{1t} \\ \vdots \\ c_{J_t t} \end{bmatrix}$$

$$D_r = \begin{bmatrix} \mathbf{1}_{1 \in F_r} & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & \mathbf{1}_{J_t \in F_r} \end{bmatrix}, Q_{p_t} = \begin{bmatrix} \frac{\partial q_{1t}(\mathbf{p}_t)}{\partial p_{1t}} & \dots & \frac{\partial q_{J_t t}(\mathbf{p}_t)}{\partial p_{1t}} \\ \cdot & \cdot & \cdot \\ \frac{\partial q_{1t}(\mathbf{p}_t)}{\partial p_{J_t t}} & \cdot & \frac{\partial q_{J_t t}(\mathbf{p}_t)}{\partial p_{J_t t}} \end{bmatrix}$$

we have in matrix form

$$D_r \mathbf{q}_t + D_r Q_{p_t} D_r \left(\mathbf{p}_t - \mathbf{c}_t \right) = 0$$

and, with abuse of notation[1], the usual formula for all firms r :

$$D_r \frac{\mathbf{p}_t - \mathbf{c}_t}{\mathbf{p}_t} = - \left[D_r Q_{p_t} D_r \right]^{-1} D_r \frac{\mathbf{q}_t}{\mathbf{p}_t} \tag{1}$$

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

3.2 Price Constrained Profit Maximization Equilibrium

Let us now consider the effects of price regulation on the pricing equilibrium. In France, regulation amounts to impose implicitly some price-ceiling on drugs, either because of explicit constraints on prices (like the reference pricing rules in France) or because of implicit constraints coming from price negotiation between the regulator and the industry. These different constraints are such that for a set R_t of potentially price constrained drugs, the price p_{jt} must belong to a set R_{jt}. If the only constraint is that the price p_{jt} must be lower than $\overline{p}_{jt}$, then $R_{jt} = \left[0, \overline{p}_{jt}\right]$. Other constraints on p_{jt} can come from a maximum revenue constraint imposed by the regulator who anticipates some expected demand.

Then, firm r's constrained maximization program, given other firms pricing strategies, is:

$$\begin{aligned} \max_{\{p_{jt}\}_{j \in F_r}} \Pi_{rt} &= \sum\nolimits_{j \in F_r} \left(p_{jt} - c_{jt} \right) q_{jt}(\mathbf{p}_t) \\ s.t. \quad p_{jt} &\in R_{jt} \qquad \forall j \in F_r \cap R_t \end{aligned}$$

[1] Division is element by element division of vectors of identical size.

We assume that each constraint $p_{jt} \in R_{jt}$ can be written $\Psi_{jt}(\mathbf{p}_t, \mathbf{c}_t, \mathbf{q}_t) \geq 0$ where Ψ_{jt} is a vector valued function. This is always possible provided the set R_{jt} is the union of a finite number of intervals.

Remark that the set of constraints R_{jt} for all j in $F_r \cap R_t$ can be endogenous in the sense that it can depend on quantities and prices chosen at equilibrium by all firms. For example, regulatory rules can be such that some price cap is implemented if some drugs sales are too low or lower than some predefined value: this has been the case in France with reference pricing (TFR), which is enforced when generic sales are considered to be too low. Whether price constraints are exogenous or endogenous is irrelevant for our method, since we will develop an identification method under the assumption that constraints are unobserved.

Then, assuming that technical conditions for a pure-strategy Bertrand-Nash equilibrium in prices to exist are satisfied, the first-order conditions are

$$q_{jt} + \sum\nolimits_{k \in F_r} (p_{kt} - c_{kt}) \frac{\partial q_{kt}(\mathbf{p}_t)}{\partial p_{jt}} = \lambda_{jt} \mathbf{1}_{\{j \in R_t\}} \qquad \forall j \in F_r$$

with

$$\lambda_{jt} = \Lambda'_{jt} \nabla_{p_{jt}} \Psi_{jt}(\mathbf{p}_t, \mathbf{c}_t, \mathbf{q}_t)$$

where Λ_{jt} is (vector) of Lagrange multipliers of price constraints $\Psi_{jt}(\mathbf{p}_t, \mathbf{c}_t, \mathbf{q}_t) \geq 0$ ($\Leftrightarrow p_{jt} \in R_{jt}$).

The first order conditions can be written in matrix form

$$D_r(\mathbf{p}_t - \mathbf{c}_t) = -\left[D_r Q_p(\mathbf{p}_t) D_r\right]^{-1} D_r(\mathbf{q}_t - \boldsymbol{\lambda}_t)$$

where $card(R_t)$ elements of $\boldsymbol{\lambda}_t$ are unknown strictly positive (unknown binding constraints) but $J_t - card(R_t)$ elements are zero (by abuse of notations, the inverse of the matrix $[D_r Q_p(\mathbf{p}_t) D_r]$ being the inverse of firm r square block of $Q_p(\mathbf{p}_t)$), where J_t is the number of goods in market t.

Thus, $\boldsymbol{\lambda}_t$ being unknown, even with demand estimates, prices and market shares, one cannot identify price-cost margins without further assumptions. Theoretically, the net effects on prices of regulation are ambiguous and will depend on all own and cross-price elasticities of demand. A price reduction of a drug can affect other drugs not constrained because of cross-price elasticities of demand. Actually, using first order conditions, for each vector $\boldsymbol{\lambda}_t$, we have price-cost margins

or marginal cost $c_{jt}(\boldsymbol{\lambda}_t)$ as a known function of $\boldsymbol{\lambda}_t$ (depending on demand, prices and quantities demanded). Using super-script r for pre and post-multiplication by D_r (which puts to zero all non firm r rows or columns), the first order conditions can also be written as

$$\mathbf{c}_t^r(\boldsymbol{\lambda}_t^r) = \mathbf{p}_t^r + Q_p^r(\mathbf{p}_t)^{-1}(\mathbf{q}_t^r - \boldsymbol{\lambda}_t^r) \tag{2}$$

We can see that, if the matrix $Q_p^r(\mathbf{p}_t)$ is invertible, for any marginal cost vector $\mathbf{c}_0$ it is always possible to find $\boldsymbol{\lambda}_t^r$ such that $c_t^r(\boldsymbol{\lambda}_t^r) = c_0$, using $\boldsymbol{\lambda}_t^r = Q_p^r(\mathbf{p}_t)(\mathbf{p}_t^r - c_0) + \mathbf{q}_t^r$. Thus we cannot identify marginal costs with no restrictions on $\boldsymbol{\lambda}_t^r$. Also, price constraints have spillover effects across drugs because the marginal cost of good i of firm r depends on the Lagrange multiplier of the constraint of price of j of firm r according to

$$\frac{\partial c_{it}^r(\boldsymbol{\lambda}_t^r)}{\partial \boldsymbol{\lambda}_{jt}^r} = -\left[Q_p^r(\mathbf{p}_t)^{-1}\right]_{i,j} \text{ for } i,j \in F_r$$

We will show now how to add some restrictions to identify the constraints.

Identification can be obtained with weaker assumptions but we can see below a simple example using cost restrictions. Let us first make the following assumption that some unconstrained market are observed:

Assumption U_S: For any $t \in S$, market t is not price constrained, that is

$$\boldsymbol{\lambda}_t = 0$$

We can now add the very simple following cost restriction:

Assumption $C_1(S)$: For any t and t_0 in the set S (with $t_0 \neq t$), the difference Δ_{tt_0} in marginal cost across markets t and t_0 is known

$$\mathbf{c}_{t_0} - \mathbf{c}_t = \Delta_{tt_0}$$

Assumption $C_1(S)$ simply states that for any good the econometrician knows the cost difference for this good between any two markets in the set S.

Proposition 1: With assumptions $U_{\{t\}}$ and $C_1(\{t, t_0\})$, for any firm r, we can "just"-identify $\mathbf{c}_{t_0}^r$, $\mathbf{c}_t^r$ and $\boldsymbol{\lambda}_{t_0}^r$ and have

$$\mathbf{c}_{t_0}^r = \Delta_{tt_0}^r + \mathbf{p}_t^r + Q_p^r(\mathbf{p}_t)^{-1}\mathbf{q}_t^r$$

and

$$\boldsymbol{\lambda}_{t_0}^r = \mathbf{q}_{t_0}^r + Q_p^r\left(\mathbf{p}_{t_0}\right)\left(\mathbf{p}_{t_0}^r - \mathbf{p}_t^r - \Delta_{tt_0}\right) - Q_p^r\left(\mathbf{p}_{t_0}\right)\left[Q_p^r\left(\mathbf{p}_t\right)\right]^{-1}\mathbf{q}_t^r \tag{3}$$

Proof: With assumption $U_{\{t\}}$, we can identify $\mathbf{c}_t^r$ in a non constrained market using (1). Then, under assumption $C_1\left(\{t, t_0\}\right)$, we can use (2) to obtain

$$\mathbf{c}_{t_0}^r = \mathbf{p}_{t_0}^r + Q_p^r\left(\mathbf{p}_{t_0}\right)^{-1}\left(\mathbf{q}_{t_0}^r - \boldsymbol{\lambda}_{t_0}^r\right) = \mathbf{c}_t^r + \Delta_{tt_0}^r = \mathbf{p}_t^r + \Delta_{tt_0} + Q_p^r\left(\mathbf{p}_t\right)^{-1}\mathbf{q}_t^r$$

where $\Delta_{tt_0}^r$ is the subvector of firm r marginal costs difference. We can solve for $\boldsymbol{\lambda}_{t_0}^r$, showing that $\boldsymbol{\lambda}_{t_0}^r$ is just identified thanks to prices and quantities in markets t and t_0 and the price elasticities in both markets with 3.□

Remark that the model becomes over-identified as soon as we can impose a stronger assumption than the one that only one market is unconstrained and if we know marginal cost differences between these markets. The cost restriction assumption $C_1\left(\{t, t_0\}\right)$ may be too strong, but a similar idea can be applied and used for identification. Let us consider the following:

Assumption $C_2\left(S, T\right)$: For any $t_0 \in T$, there exists a vector of observed variables $\mathbf{z}$ such that, for all $t \in S$, the vector of marginal costs $\mathbf{c}_t$ satisfies

$$\mathbf{c}_t - \mathbf{c}_{t_0} = \left(\mathbf{z}_t - \mathbf{z}_{t_0}\right)'\delta + \omega_t$$

with

$$E\left(\omega_t | \mathbf{z}_t - \mathbf{z}_{t_0}\right) = 0$$

Assumption $C_2\left(S, T\right)$ simply means that cost differences between markets in the set S and markets in the set T satisfy the cost restriction above such that the difference in costs across any two markets in sets S and T depends linearly on a set of observable differences $z_t - z_{t_0}$ and on unobserved market specific additive mean independent shocks ω_t.

Then, we can state the following proposition:

Proposition 2: With assumptions $C_2\left(S, \{t_0\}\right)$, U_S and $J_{t_0} + \dim(\delta) \leq \sum_{t \in S} J_t$, marginal costs $\mathbf{c}_{t_0}$ are identified using (2) where $\boldsymbol{\lambda}_{t_0}$ is identified using the moment condition across all $t \in S$

$$E\left(\omega_t\left(\delta, \boldsymbol{\lambda}_{t_0}\right)\right) = 0 \tag{4}$$

where

$$\omega_t(\delta, \boldsymbol{\lambda}_{t_0}) = \mathbf{p}_t - \mathbf{p}_{t_0} + Q_p(\mathbf{p}_t)^{-1}\mathbf{q}_t - Q_p(\mathbf{p}_{t_0})^{-1}\mathbf{q}_{t_0} + Q_p(\mathbf{p}_{t_0})^{-1}\boldsymbol{\lambda}_{t_0} - (\mathbf{z}_t - \mathbf{z}_{t_0})'\delta$$

provided the matrix $E\left[(z_t - z_{t_0})', Q_p(\mathbf{p}_{t_0})^{-1}\right]_{t\in S}$ has full rank.

Proof: With assumption $C_2(S, \{t_0\})$ and U_S, $\mathbf{c}_t$ is identified using price-cost margins solutions (1) in all non constrained markets S. Then, using (2) and

$$\mathbf{c}_{t_0} = \mathbf{p}_{t_0} + Q_p(\mathbf{p}_{t_0})^{-1}\mathbf{q}_{t_0} - Q_p(\mathbf{p}_{t_0})^{-1}\boldsymbol{\lambda}_{t_0}$$

we have

$$\begin{aligned}\mathbf{c}_t - \mathbf{c}_{t_0} &= \mathbf{p}_t - \mathbf{p}_{t_0} + Q_p(\mathbf{p}_t)^{-1}\mathbf{q}_t - Q_p(\mathbf{p}_{t_0})^{-1}\mathbf{q}_{t_0} + Q_p(\mathbf{p}_{t_0})^{-1}\boldsymbol{\lambda}_{t_0} \\ &= (z_t - z_{t_0})'\delta + \omega_t\end{aligned}$$

Denoting

$$\omega_t(\delta, \boldsymbol{\lambda}_{t_0}) = \mathbf{p}_t - \mathbf{p}_{t_0} + Q_p(\mathbf{p}_t)^{-1}\mathbf{q}_t - Q_p(\mathbf{p}_{t_0})^{-1}\mathbf{q}_{t_0} + Q_p(\mathbf{p}_{t_0})^{-1}\boldsymbol{\lambda}_{t_0} - (z_t - z_{t_0})'\delta$$

the true $\boldsymbol{\lambda}_{t_0}$ should satisfy the moment condition for all $t \in S$

$$E(\omega_t(\delta, \boldsymbol{\lambda}_{t_0})) = 0$$

because $E(\omega_t) = E[E(\omega_t | z_t - z_{t_0})] = 0$. As J_t is the number of goods in market t, we have $\sum_{t\in S} J_t$ non linear equations and $J_{t_0} + \dim(\delta)$ unknown parameters. We assume that $J_{t_0} + \dim(\delta) \leq \sum_{t\in S} J_t$ which will be often the case. Stacking all the $\omega_t(\delta, \boldsymbol{\lambda}_{t_0})$ in $\omega(\delta, \boldsymbol{\lambda}_{t_0})$, the rank condition for identification of parameters is that the matrix $E\left[\frac{\partial}{\partial\delta}\omega(\delta, \boldsymbol{\lambda}_{t_0}), \frac{\partial}{\partial\boldsymbol{\lambda}_{t_0}}\omega(\delta, \boldsymbol{\lambda}_{t_0})\right]_{t\in S}$ has full rank $J_{t_0} + \dim(\delta)$. As

$$\begin{aligned}\frac{\partial}{\partial\delta}\omega_t(\delta, \boldsymbol{\lambda}_{t_0}) &= (z_t - z_{t_0})' \\ \frac{\partial}{\partial\boldsymbol{\lambda}_{t_0}}\omega_t(\delta, \boldsymbol{\lambda}_{t_0}) &= Q_p(\mathbf{p}_{t_0})^{-1}\end{aligned}$$

we need that the matrix $E\left[(z_t - z_{t_0})', Q_p(\mathbf{p}_{t_0})^{-1}\right]_{t\in S}$ has full rank.□

Proposition 2 shows that identification is obtained when all prices are potentially constrained in market t_0 provided that the number of unconstrained markets is large enough. If all markets have

the same number of goods and is larger than $\dim(\delta)$, then two unconstrained markets are enough for identification. The rank condition adds that all columns of the inverse Jacobian matrix with respect to prices in market t_0 are not collinear with the cost shifter differences $z_t - z_{t_0}$.

It is clear that following proposition 2, one can obtain identification with one unconstrained market only if there are enough goods in the constrained market t_0 that are unconstrained. Then $\boldsymbol{\lambda}_{t_0}$ is of lower dimension and potentially $\dim(\boldsymbol{\lambda}_{t_0}) + \dim(\delta)$ can be lower than J_t for an unconstrained market t.

Assumption $C_2(S,T)$ simply makes use of restrictions across markets of marginal costs of drugs. The identification power in our application will come from the fact that there can be relevant and robust cost restrictions across products whose price may be constrained ($j \in R_t$) and other whose price is not constrained ($j \notin R_t$). 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). The previous restrictions include the case where we assume that marginal costs be the sum of a drug effect, a time effect and an uncorrelated deviation $c_{jt} = \phi_j + \delta_t + \omega_{jt}$, or where we assume that marginal costs depend only on the characteristics $m(j)$ of drug j (this characteristic can be the molecule) in a given year and an additive uncorrelated deviation, $c_{jt} = \gamma_{m(j)t} + \omega_{jt}$. Indeed these marginal costs are likely to be market specific because they include packaging costs that can be market specific, as well as transportation costs to each country.

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 enough to capture any substitution patterns among differentiated products. Anti-ulcer drugs can be partitioned into three subclasses, which refer to different generations of products. Older H2 drugs are still widely

used, even if 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 one another, but there exist differences between, say, Cimetidine and Ranitidine. These levels of differentiation stem from objective differences that make one drug more appropriate to treat one condition or more suitable for one type of patient. Given a molecule, there is also product differentiation between branded and generic drugs. This is not justified by a difference in the curative effects, since both have the same active ingredient and are thus are therapeutically equivalent. However, despite being (nearly) perfect substitutes (besides potential differences in excipients, shape and color of the drug that do not compromise efficacy or curative effects for most patients), patients have historically perceived vertical differentiation.

We will start by specifying the utility of using drug $j \in \{1, .., J_t\}$ for patient i in period t as

$$u_{ijt} = \sum\nolimits_k \alpha_i^k x_{jt}^k - \beta_i p_{jt} + \zeta_{jt} + \varepsilon_{ijt} \tag{5}$$

where x_{jt}^k are k drug characteristics, p_{jt} is the price of the drug, ζ_{jt} are drug-period specific effects and ε_{ijt} is the consumer i deviation to the mean utility of taking drug j at period t. Preference parameters α_i^k, β_i are allowed to vary across users i. The model is completed by the inclusion of an outside good, denoted good zero, which corresponds to not using any of the J_t products, with a normalized indirect utility $u_{i0t} = \varepsilon_{i0t}$.

We assume that each user chooses an element in the choice set $\{0, 1, .., J_t\}$ according to the maximum utility (5). This modeling of choices can be seen as a reduced form of a more complex mechanism where patients, prescribers and pharmacists interact. It is thus important that the preference parameters be specific to each user i, because of the unobserved variation in price-sensitivity across users: this may be driven by the patient's choices and their reimbursement scheme; by the prescriber's choice, who may follow the insurance system recommendation to prescribe cheaper drugs; by the pharmacist, who also influences the choice of brand-name versus generic. In particular, in France, the pharmacist's margins are regulated in a way that gives pharmacists a preference for cheaper drugs. Indeed, pharmacists margins decrease by steps in the price of the

drug (26.1% of retail price if below 22.9€, 10% between 22.9€and 150€, 6% above 150€) and are larger for generic than branded drugs (because absolute margins of generics are equal to those of the branded drug and generic price is lower), which may influence their effort in generic substitution when facing the purchasing user. Heterogeneity in preference parameters $\left(\alpha_i^k, \beta_i\right)$ across decision makers in this demand model is thus crucial to capture the aggregate demand shape resulting from these heterogeneous situations.

Thus, consumer heterogeneity varies according to random coefficients $\left(\alpha_i^k, \beta_i\right)=\left(\alpha^k + \sigma_\alpha^k \nu_i^k, \beta + \sigma_\beta \nu_i^p\right)$, where ν_i^k, ν_i^p summarize all the unobserved consumer characteristics, and $(\sigma_\alpha^k, \sigma_\beta)$ characterize how consumer tastes vary according to these unobserved characteristics. Indirect utility can then be redefined as the sum of a mean utility $\delta_{jt} = \sum_k \alpha^k x_{jt}^k - \beta p_{jt} + \zeta_{jt}$, a deviation from the mean utility $\mu_{ijt} = \sum_k \sigma_\alpha^k x_{jt}^k \nu_i^k - \sigma_\beta p_{jt} \nu_i^p$ and an idiosyncratic error ε_{ijt}:

$$u_{ijt} = \delta_{jt} + \mu_{ijt} + \varepsilon_{ijt}$$

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

$$s_{ijt}\left(\mathbf{x}_t, \mathbf{p}_t, \boldsymbol{\zeta}_t\right) = \frac{\exp\left(\delta_{jt} + \mu_{ijt}\right)}{1 + \sum_k \exp\left(\delta_{kt} + \mu_{ikt}\right)}$$

and the outside good choice probability is

$$s_{i0t}\left(\mathbf{x}_t, \mathbf{p}_t, \boldsymbol{\zeta}_t\right) = \frac{1}{1 + \sum_k \exp\left(\delta_{kt} + \mu_{ikt}\right)}$$

Assuming that $\nu_i = \left(\nu_i^1, .\nu_i^k, ., \nu_i^K, \nu_i^p\right)$ is distributed with p.d.f. φ, the market share of product j, s_{jt} is given by

$$s_{jt}\left(\mathbf{x}_t, \mathbf{p}_t, \boldsymbol{\zeta}_t\right) = \int s_{ijt}\left(\mathbf{x}_t, \mathbf{p}_t, \boldsymbol{\zeta}_t\right) \varphi\left(\nu_i\right) d\nu_i$$

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

$$\frac{\partial s_{jt}}{\partial p_{kt}} \frac{p_{kt}}{s_{jt}} = \begin{cases} -\frac{p_{jt}}{s_{jt}} \int \beta_{it} s_{ijt}\left(1 - s_{ijt}\right) \varphi\left(\nu_i\right) d\nu_i & \text{if } j = k \\ \frac{p_{kt}}{s_{jt}} \int \beta_{it} s_{ijt} s_{ikt} \varphi\left(\nu_i\right) d\nu_i & \text{otherwise} \end{cases}$$

4.2 Identification and Estimation

The identification of such random coefficient logit model can be carried out on aggregate data using moment conditions between constructed demand shock variables ζ_{jt} and some instrumental variables (Berry et al., 1995, and Nevo, 2000). As in the simple logit demand models, one has to take into account the problem of endogeneity of prices correlated with unobserved demand factors ζ_{jt} (Berry, 1994; Berry et al., 1995). Previous estimation of demand models in pharmaceuticals has used instrumental variables usually proposed in empirical IO, like measures of the degree of competition (Stern, 1996), of costs (Azoulay, 2002), or prices for different markets or segments (Azoulay, 2002, and Berndt et al., 2003). Other approaches use the characteristics of competing products, excluding those produced by the same firm (Berry et al., 1995). Then, the estimation can be performed on aggregate data with Generalized Method of Moments using the moment condition

$$E\left[\zeta_{jt}\left(\theta\right)|\mathbf{x}_t, \mathbf{w}_t\right] \tag{6}$$

where $\theta = (\alpha^k, \beta, \sigma_\alpha^k, \sigma_\beta)$ is the vector of parameters and $\mathbf{w}_t$ are cost shifters as in Nevo (2000) and eventually jointly with the supply equation (4) as in Berry et al. (1995).

The quality of instruments is crucial for the consistency and robustness of estimates (Knittel and Metaxoglou, 2012). Thus, following Berry et al. (1999) and Reynaert and Verboven (2014), we use approximations of optimal instrumental variables (Chamberlain, 1987) in order to improve the efficiency of our estimation. These are

$$E\left[\frac{\partial\zeta_{jt}\left(\theta\right)}{\partial\theta'}|\mathbf{x}_t, \mathbf{w}_t\right]$$

Reynaert and Verboven (2014) show that in the case where price equals marginal cost (perfect competition), we can approximate these optimal instrumental variables by using the predicted price $\hat{p}_{jt}$ from the regression $p_{jt} = x_t\gamma_x + w_{jt}\gamma_w + \varepsilon_{jt}$, where w_{jt} are country-specific cost shifters, and derivatives of the mean utility with respect to variance coefficients $\frac{\partial\delta_{jt}(\hat{s}_t,\sigma)}{\partial\sigma_\alpha^k}$, $\frac{\partial\delta_{jt}(\hat{s}_t,\sigma)}{\partial\sigma_\beta}$ (approximated by taking derivatives at the mean instead of the mean of derivatives). These non linear functions of exogenous variables and cost shifters are only approximation of optimal instruments in the case of perfect competition but prove to be quite informative even in the case of imperfect competition.

Reynaert and Verboven (2014) also show that there are small gains to estimate the demand model jointly with non-competitive supply side, and that the simplifying assumption of perfect competition does not lead to much bias in the demand estimates. Here, our supply side is more complex because of the price constraints and thus estimating jointly demand and supply is more difficult.

Drug-specific variables used in the demand specification include the brand type (branded or generic), active ingredient dummies, the number of side effects and formats. Dummies are used for drug indications, namely whether the drug 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 the branded dummy and the number of formats or the number of side effects are also used in the demand model. These variables capture the most important product characteristics that influence demand and are the result of a specification search allowing for more interactions or other product characteristics. The other characteristics that we used and that finally were not significant and were removed from our preferred specification are the age of the drug, whether the drug is domestically produced, whether it is under patent protection, dummies for its format, absolute and improved medical benefits (SMR and ASMR). Descriptive statistics of these variables are shown in Table 3.

Table 3: Summary Statistics on Variables used in Demand Model

	France		Germany		US	
Variables	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
Market share (s_{jt})	0.02	0.04	0.01	0.03	0.01	0.03
Price ($US per Std. Unit) ($p_{jt}$)	0.96	0.86	0.57	0.45	0.99	2.08
Branded (1 if branded, 0 otherwise)	0.37	0.48	0.21	0.41	0.16	0.37
Formats (nb. of therapeutic formats)	1.60	0.90	1.40	0.87	1.41	1.03
Side effects (number of side effects)	3.24	1.69	2.95	1.32	2.67	1.30
Helicobacter (1 if indication, 0 otherwise)	0.75	0.44	0.56	0.53	0.35	0.48
NSAID (1 if indication, 0 otherwise)	0.24	0.43	0.24	0.42	0.24	0.43

As we explained above, several sorts of instrumental variables can be used and allow the model to be overidentified. Hausman style instrumental variables are used for example in Azoulay (2002), and Berndt et al. (2003). Using data from other countries, we also implement such a strategy. For example, for France, we use prices of drugs in Germany, Italy, Spain and UK (countries on which

external referencing has been based in France since 2004) or the US as potential instrumental variables. However, the validity of such instruments relies on the fact that prices across markets are correlated because of common cost shocks and not because of common unobserved demand shifters (due to scientific knowledge or manufacturing firms detailing). Thus, we regress the price of drugs in those countries (Germany, Italy, Spain and UK) on active ingredient dummies, country and year fixed effects and use the residuals as instrumental variables for the price in France. Controlling for country and time effects, we isolate the quality of each drug, proxied by molecule dummies, which is the part of the price more likely to be correlated with demand unobservables. What remains is an approximation of the marginal cost of each drug. We also use predicted prices in foreign countries, where those prices are regressed on interactions between firm dummies and exchange rates between US Dollars and respectively Euros, UK Pounds and Swiss Francs (which are the currency of most drug producing countries). Finally, we use producer price indices (producer price index for all pharmaceuticals in France, for antisecretory/antispasmodics for the US, for pharmaceutical preparations in Germany) and wages (in the manufacturing industry for France, in the manufacturing of basic pharmaceutical products and preparations for Germany, in the pharmaceutical manufacturing industry for the US) in each country (coming from the US Bureau of Labor Statistics, Eurostat for Germany, and the French National Statistical Institute INSEE).

5 Estimation Results

5.1 Demand Estimation Results

After some specification search and robustness checks, results of the random coefficient logit model are reported in Table 4. Coefficients are estimated through simulated method of moments. 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. We used different algorithms and starting values for the simulated method of moments. Actually, Knittel and Metaxoglou (2012) have pointed out some numerical problems in the nested fixed point algorithm used to estimate

such model and suggested to use a large number of starting values and different minimization algorithms. Dubé, Fox and Su (2012) provided an alternative algorithm called Mathematical Programming with Equilibrium Constraints (MPEC) that replaces the nested fixed point contraction mapping algorithm with a constrained minimization based on the market share condition. We used both algorithms to check the robustness of our demand estimation as well as approximate optimal instrumental variables as suggested by Berry, Levinsohn and Pakes (1999) and Reynaert and Verboven (2014). As in Reynaert and Verboven (2014), our estimates are very robust to starting values and simulation draws once we use the optimal instrumental variables approximation.

Year and active ingredient dummies were included in the estimation but are not reported in Table 4. 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 (higher for PPIs, lower for drugs based on older molecules). Branded drugs show a competitive advantage in all three countries, even though the effect is not significant in Germany. Similarly, having an indication for the eradication of helicobacter pylori has on average a positive effect except for Germany and indication for co-prescription with NSAID has a positive effect in the US while negative in France. Being sold under larger number of formats has a positive effect in all countries even if not significant in France. Surprisingly, in France, the number of side effects has positive effects on sales for branded drugs but negative for generics while it is the contrary in the US.

Estimates of heterogeneity of coefficients are reported in columns denoted "sigma". We have random coefficients for 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 in all three countries and for the therapeutic indications mainly in France, showing that consumers have heterogeneous valuations for these indications. Conversely, the valuation for branded is heterogeneous across individuals even if always positive.

Table 4: Estimation results of Random Coefficient Logit Model

Random Coefficient Logit	France		Germany		US	
	mean	sigma	mean	sigma	mean	sigma
Price	-3.72***	1.79***	-8.28***	4.18***	-2.68***	1.08***
	(0.52)	(0.19)	(1.08)	(0.88)	(0.53)	(0.21)
Branded	4.20***	0.17	1.19	0.74	11.86***	3.90
	(1.37)	(1.04)	(1.24)	(1.65)	(1.15)	(2.71)
Nb. formats	0.43		0.77***		0.19**	
	(0.28)		(0.13)		(0.08)	
Generic*nb. formats	0.54***		0.54***		1.73***	
	(0.31)		(0.17)		(0.21)	
Nb. side effects	0.60**		-0.05		-2.20***	
	(0.26)		(0.37)		(0.23)	
Generic*nb. side effects	-0.78***		-0.35		2.14***	
	(0.28)		(0.40)		(0.32)	
Helicobacter indication	2.64***	2.08**	-1.76	1.32***	4.03***	0.18
	(0.29)	(0.90)	(1.02)	(0.45)	(0.48)	(2.04)
NSAID indication	-1.59***	7.40***	-0.78	2.15	1.70***	1.73
	(0.55)	(1.65)	(1.16)	(2.29)	(0.46)	(1.60)
Year fixed effects	Yes		Yes		Yes	
Molecule fixed effects	Yes		Yes		Yes	
Obj. function	0.22		1.09		7.63	

Notes: Standard errors in parentheses under each coefficient. *, **, *** mean significance at 10%, 5% and 1% levels.

The estimates of elasticities provided by the demand model in France capture flexible substitution patterns. Mean own-price elasticity across products and years is -3.49 and ranges from -11.5 to -1.33. On the whole, generics show lower own-price elasticities than branded drugs (-3.00 on average versus -4.18), consistent with pharmacy substitution. However, there is much more variation across generics than across branded drugs. Elasticities also change over time. Table 5 displays own-price elasticities for a sample of major branded drugs in four years in France. Elasticities for new branded drugs decrease 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 Nexium, Lanzor and Takepron, for example: their pattern seems to suggest that it took time for physicians and patients to know their availability and quality. Conversely, older drugs display more stable own-price elasticities (Zantac, Tagamet and Cytotec). Own-price elasticities for US and Germany are given in Tables A3 and A4 in appendix A.2.

Table 5: Own-Price elasticities of main branded drugs (France)

Drug	Sub-class	1997	2000	2004	2007
Losec	PPI	-1.44	-0.89	-3.39	-4.01
Nexium	PPI			-4.87	-2.56
Lanzor	PPI	-8.48	-4.91	-4.13	-3.73
Takepron	PPI	-7.46	-4.84	-4.12	-3.57
Tagamet	H2	-2.14	-1.47	-1.66	-1.64
Zantac	H2	-2.20	-3.14	-1.86	-2.11
Raniplex	H2	-4.24	-3.34	-2.98	-2.10
Cytotec	Prost.	-0.46	-0.76	-0.87	-1.49

Notes: PPI: Proton Pump Inhibitors. H2: H_2 receptor antagonist. Prost.: Prostaglandin.

Nexium entered after 2000.

Table 6 reports own- and cross-price elasticities for a sample of drugs in France for 2004. Some results are expected, others are instead surprising. First, PPI branded drugs are the ones that usually have the largest cross price elasticities with other drugs, showing that the branded and even generic PPI drugs are close substitutes, but they also have quite significant cross price elasticities with H2 drugs. The price elasticity of Losec with respect to Nexium is the largest (2.79) and larger than the price elasticity of Nexium with respect to Losec (1.29), consistent with the fact that Losec is more expensive than Nexium in all markets. On the contrary, H2 drugs are less substitutable with other H2 drugs or non H2 drugs. However, substitutability relationships also 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 Mylan (not shown in Table 6). Price elasticities for US and Germany are given in Tables A5, A6 in appendix A.2. Own-price elasticities are in general larger in the US and Germany than in France. The picture is less clear for cross-price elasticities, as they are sometimes larger in one country, sometimes smaller.

Table 6: Own and Cross-Price elasticities for a sample of drugs, 2004 (France)

Sub-Class	H2	H2	PPI	PPI	PPI	H2	H2	PPI
Branded/Generic	Branded	Branded	Branded	Branded	Branded	Branded	Generic	Generic
Company	Axcan	Glaxo	AstraZ	AstraZ	Eurom.	Pfizer	Sandoz	Sandoz
Molecule	Cimet.	Rani.	Ome.	Esom.	Lanso.	Miso.	Rani.	Ome.
Drug Name	Tagamet	Zantac	Losec	Nexium	Lanzor	Cytotec	Generic	Generic
Tagamet	-1.66	0.03	0.17	0.09	0.27	0.001	0.002	0.02
Zantac	0.01	-1.86	0.31	0.15	0.47	0.00	0.01	0.03
Losec	0.001	0.01	-3.39	1.29	0.08	0.01	0.001	0.12
Nexium	0.002	0.01	2.79	-4.87	0.08	0.00	0.004	0.02
Lanzor	0.01	0.06	0.27	0.13	-4.13	0.00	0.004	0.02
Cytotec	0.001	0.001	1.46	0.77	0.002	-1.63	0.001	0.66
Rani. Novt	0.01	0.07	0.35	0.17	0.50	0.000	-2.23	0.03
Ome. Novt	0.003	0.02	2.17	1.06	0.08	0.09	0.001	-4.72

Notes: Each column is the price elasticity of demand for the drug in first row with respect to the drug named in first column.

Company names: Glaxo is GlaxoSmithKline. AstraZ is Astra Zeneca. Eurom. is Euromed.

Molecules: Rani. is Ranitidine, Ome. is Omeprazole, Esom. is Esomeprazole, Lanso. is Lansoprazole. Miso. is Misoprostol.

5.2 Reduced Form Evidence

Once the demand is estimated, the aim is to use our supply side model to obtain price-cost margins and marginal costs and test whether some price constraints are actually binding for pharmaceutical firms. Indeed, several regulatory events in France might have made the constraints on the price setting of drugs more stringent. In particular, the introduction of reference pricing may have put more pressure on the pricing of drugs. Reference pricing was implemented at the end of 2003 in France and links the reimbursement level of some branded drugs to the price of their generic versions. In 2004 and 2005 three anti-ulcer drugs were subject to this rule (Tagamet, Zantac and Raniplex), and a fourth was added in 2006 (Pepcidine). Then, since 2006 a decrease in the price for all drugs in a subclass has been imposed once generic drugs enter or when they have been on the market for at least 24 months. This has concerned anti-ulcer drugs Losec since 2006 and Lanzor and Takepron starting in 2007.

As a first test, it is interesting to look at the determinants of prices of drugs within this class across markets, to investigate whether these potential price constraints have affected the pricing of drugs in France. For that, we defined the group of drugs denoted TFR as those drugs that have been subject to the reference pricing rule (called "Tarif Forfaitaire de Responsabilité" in French -

TFR) starting in 2004 in France, and we also denoted "Price Decrease" the dummy variable for the group of drugs that could be subject to the rule coming from imposed price decreases after generic entry in France. Of course these two rules are supposed to have affected the price of drugs in France only and not in Germany and the US, but these drugs could also be different from other drugs within the anti-ulcer market.

Table 7 reports the regression of the price of drugs on drug characteristics, on the drug group dummies "TFR" and "Price Decrease", on the interaction between these group dummies and the dummy for whether the time period is after the regulatory event (2004 for TFR and 2006 for price decrease) and finally on the interaction between the dummy variable for France after the start of the regulatory event and these group dummies. The coefficients of these last interactions can be interpreted as the effect of the regulatory event in France on prices. In column (1), we added country fixed effects, molecule fixed effects and year fixed effects to this regression: we find that while the group of drugs subject to the two regulatory rules are slightly more expensive (although the effect is not significant), the interaction of the group "TFR" with the regulatory period after 2004 shows that this group has experienced a raise in price; yet, the interaction with the French dummy shows that in France these drugs became cheaper when each of this regulations was implemented. The effect is only significant for TFR, though. When adding interactions between country and year fixed effects or country and molecule fixed effects in columns (2) and (3), results remain similar. Finally, column (4) shows the same result with country-molecule-year fixed effects, so that the effects of drug characteristics and regulation are identified from variations within a molecule-country-year triplet. Table 7 also shows that branded drugs are more expensive, whereas drugs with more side effects or with Helicobacter or NSAID indications are cheaper (results are similar with log price as the dependent variable).

Finally, even if this reduced form difference-in-difference evidence confirms that these regulatory events seem to have reduced prices, it is however at the condition that counterfactual prices would have been similar. It is indeed possible that demand changed during these years, leading to lower prices or that specific cost shocks have also affected the equilibrium pricing. It seems thus that

structural estimation will help interpreting those results and also test whether regulation has really constrained prices or if observed price changes are simply due to demand or supply conditions.

Table 7: Reduced Form Regression of Prices

	(1)	(2)	(3)	(4)
Variables	Price	Price	Price	Price
Drug Characteristics				
Branded	1.306	1.605*	1.473*	2.123
	(0.835)	(0.813)	(0.871)	(1.321)
Nb. Side Effects	-0.217	-0.259	-0.330*	-0.520
	(0.203)	(0.202)	(0.191)	(0.322)
Formats	-0.0407	-0.0457	-0.0492	-0.0878
	(0.107)	(0.0997)	(0.112)	(0.146)
Helicobacter Indication	-0.0946	-0.116	2.145***	-0.198
	(0.182)	(0.182)	(0.143)	(0.238)
NSAID Indication	-0.441*	-0.336	-11.61***	-0.248**
	(0.249)	(0.237)	(0.107)	(0.120)
Drug Group Dummies				
Group "TFR"	-0.588	-0.826	-0.846	-0.862
	(0.542)	(0.542)	(0.632)	(0.769)
Group "Price Decrease"	-0.115	-0.346	-0.164	-0.302
	(0.563)	(0.558)	(0.638)	(0.727)
Drug Group Dummies * After				
"TFR" * After	0.503*	0.587**	0.764**	0.831**
	(0.291)	(0.262)	(0.290)	(0.380)
"Price Decrease" * After	0.00826	0.233	0.0482	0.566
	(0.471)	(0.374)	(0.360)	(0.584)
Regulatory Event in France				
"TFR" * After * France	-0.741**	-0.637*	-1.128***	-1.263**
	(0.357)	(0.358)	(0.391)	(0.469)
"Price Decrease" * After * France	-0.570	-0.561	-0.255	-0.370
	(0.411)	(0.384)	(0.305)	(0.583)
Country FE	Yes			
Molecule FE	Yes	Yes		
Year FE	Yes			
Country*Year FE		Yes	Yes	
Country*Molecule FE			Yes	
Country*Molecule*Year FE				Yes
Observations	2,114	2,114	2,114	2,114
R-squared	0.707	0.733	0.772	0.804

Notes: Standard errors are clustered by country-molecule. *, **, *** mean significance at 10%, 5% and 1% levels. Dependent variable is price in $US. Data for France, Germany, US from 1997 to 2007.

5.3 Structural Estimation of Margins and Costs

We now turn to our structural estimation of the supply model. After estimating own- and cross-price elasticities, we can estimate price-cost margins under the two different supply models considered: free pricing (section 3.1) or price constrained profit maximization (section 3.2). In the case where we allow prices to be possibly constrained, we estimate the structural model proposed in section 3.2 using Proposition 2, where we assume that firms pricing is not constrained in the US, in Germany[2] and for some drugs and years in France. As explained above, several regulatory events in France have possibly increased the constraints on the price setting of drugs. We focus on the introduction of reference pricing in late 2003, which directly affected four anti-ulcer drugs (Tagamet, Zantac and Raniplex since 2004 and Pepcidine since 2006). Also, anti-ulcer drugs Losec, Lanzor and Takepron could have been subject to the price decrease rule after 2006, because of generic entry in the corresponding subclass. Given these regulatory rules, we allow the price of these drugs to be potentially constrained during those periods. In order to identify marginal costs under this price constrained model, we know from Proposition 2 that we need to impose some cost restrictions across constrained and unconstrained markets. We assume that the marginal cost of drugs is the sum of a time invariant drug effect common across countries, some country-year effects and an uncorrelated additive deviation. We can then use the non-linear least squares method as described in Proposition 2 with all drugs in our sample in France, Germany and the US.

Inspection of the evolution of price-cost margins and the differences obtained using the two models should shed some light on the actual role played by regulation in the price-setting decisions of the firms. Table 8 displays the averages per year of the estimated price-cost margins (as a percentage of price) for this constrained model as well as for the free pricing model. They do not differ before 2004 because we allow prices to be constrained for some drugs only after 2004. We can see that the average price-cost margin is 7 to 10% lower with price constraints than without starting in 2004, but this average masks some differences across drugs. Actually, the difference in

[2] Remark that not using German data (thus not assuming anything on the pricing game in Germany) but only taking the US as a reference market, we find the same results with slightly less precisely estimated marginal costs. We thus prefer to use German data as well, even if we do not allow price constraints coming from reference pricing to affect the pricing game on the German market.

average price-cost margin across models for branded drugs is in general smaller than for generics, showing that price constraints are also significantly affecting drugs non directly targeted by the TFR regulation. Interestingly, if we look at the average margins for branded drugs versus generics, we see that margins decrease for branded drugs while they increase for generics especially after 2003, a result that could not be seen without taking into account the possibility that some prices are constrained. Conversely, in the free pricing model, margins increase in a similar way for generics but also slightly for branded drugs (while it appears that they decrease when one takes into account the possible price constraints). The difference is quite significant, with average estimated margins of 40% instead of 50% (if free pricing is assumed) in 2007. The free pricing model estimates increasing average markups over time, as suggested by Berndt et al. (2003) (where marginal costs in the US have been estimated to be small and decreasing after patent expiration) and Arcidiacono et al. (2013) for generics. In France, with a free pricing assumption, we would find a similar increase (especially for branded drugs) if we had not taken into account the fact that prices may have been constrained. Under the constrained pricing model, we see that average margins have been low, especially for branded drugs.

Table 8: Average price-cost margins (France)

Year	All Drugs		Branded		Generic	
	Free	Constr.	Free	Constr.	Free	Constr.
1997	45%		47%		28%	
1998	44%		41%		58%	
1999	37%		39%		28%	
2000	50%		45%		53%	
2001	51%		48%		54%	
2002	50%		43%		57%	
2003	53%		47%		57%	
2004	44%	35%	39%	35%	46%	35%
2005	45%	37%	41%	35%	47%	38%
2006	49%	36%	41%	31%	51%	38%
2007	50%	40%	41%	32%	53%	42%

Notes: Free and Constr. stand for free and constrained price equilibrium. Columns are merged when both models are identical by definition. Margins as a percentage of price.

Table 9 reports some average price-cost margins for the drugs based on the main molecules. It shows the margins under the free pricing model and the price constrained model. On average, Cimetidine, Famotidine, Ranitidine, Esomeprazole, and Misoprostol are the five molecules for which

the price constraints seem to have the largest and most significant effect. The first three are molecules that have some drugs in the potentially price constrained set, while Misoprostol seem to be indirectly affected in equilibrium. Indeed, even if some drugs may not be price constrained, their equilibrium price may be constrained by other drugs price constraints. This can result in different estimated margins under one model or the other, even for drugs with some active ingredients (molecules) that are not constrained. Other molecules like Omeprazole and Lansoprazole are on average not significantly affected by the possible price constraints on some of their versions. Remark also that, under the free pricing model, the margin for Misoprostol is inconsistently estimated to be higher than 100%, something that our model is able to correct to obtain more plausible margins.

Table 9: Average price-cost margins by molecule (France)

		Some price	All Drugs		Branded Drugs		Generic Drugs	
Sub-Class	Molecule	Constr. drug	Free	Constr.	Free	Constr.	Free	Constr.
H2	Cimetidine	Yes	87%	50%	61%	41%	94%	52%
	Ranitidine	Yes	44%	38%	38%	39%	45%	38%
	Famotidine	Yes	50%	38%	39%	27%	61%	42%
	Nizatidine	No	29%	26%	29%	26%		
PPI	Omeprazole	Yes	36%	33%	65%	39%	31%	33%
	Esomeprazole	No	54%	46%	54%	46%		
	Lansoprazole	Yes	33%	34%	23%	20%	52%	44%
	Pantoprazole	No	21%	21%	21%	21%		
	Rabeprazole	No	24%	23%	24%	23%		
Prost.	Misoprostol	No	122%	67%	122%	67%		

Notes: Margins as a percentage of price. Empty cells when there is no generic version of the molecule named in the corresponding row.

Except for a few generics of Cimetidine and the unique prostaglandin drug, margins are below 50% and many between 20 and 40%. Generics of Cimetidine, Famotidine and Lansoprazole show higher margins than branded versions. 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 and Famotidine (Arcidiacono et al., 2013). Markups also vary substantially across molecules.

Table 10: Average margins for drugs possibly subject to price constraints (France)

Sub-Class	Molecule	Drug	2003	2004		2005		2006		2007	
				Free	Constr.	Free	Constr.	Free	Constr.	Free	Constr.
H2	Cimetidine	Tagamet	70%	60%	42%	57%	39%	67%	38%	61%	44%
	Ranitidine	Zantac	41%	54%	37%	52%	42%	50%	37%	47%	39%
	Ranitidine	Raniplex	32%	34%	37%	39%	38%	48%	41%	48%	39%
	Famotidine	Pepcidine	34%	35%		36%		37%	24%	34%	29%
PPI	Omeprazole	Losec	78%	48%		42%		42%	31%	48%	34%
	Lansoprazole	Lanzor	28%	29%		30%		33%	20%	37%	18%
	Lansoprazole	Takepron	24%	24%		24%		26%	19%	28%	17%

Notes: Free stands for free pricing equilibrium. Constr. stands for constrained price equilibrium.

Columns merged when both models identical by definition. Margins as percentage of price.

In Table 10, examination of margins drug by drug further confirms that drugs subject to reference pricing and to price decreases show lower margins than when ignoring the potential effects of regulation on prices. The effects on price are very small from 2004 to 2005 for Raniplex, indicating that the price constraints were not binding the price setting for this drug, which became really affected by price setting constraints only starting in 2006. For other drugs, the price constraints have significant effect on equilibrium margins. For some drugs, the effect is very large and estimated margins much lower. For example, Tagamet and Zantac seem to have much lower margins starting from 2004. The model is able to identify some large effect of regulation on prices while the free pricing model is not. When one looks at the prices of Zantac (see below in Table 12), it can be seen that it dropped by 23%, from 0.74 to 0.57 between 2003 and 2004 while it increased by 21% for Tagamet (0.43 to 0.52) for example. Thus, it is possible that the pressure on the price of Zantac (Ranitidine) managed to bring its price closer to its marginal cost while at the same time Tagamet (Cimetidine), in the same H2 sub-class, increased its price. As shown in Table 10, we also find that margins of PPI drugs decreased substantially in 2006 and in 2007, a fact which seems very plausible given that prices decreased in 2006 and 2007. Again, this is something that the free pricing model is unable to identify with estimated margins for PPI that would be constant or would have even increased slightly after 2006. Finally, Table 11 shows marginal costs estimates under the free pricing and constrained pricing models. For Raniplex, our model with potential price constraints is able to estimate marginal costs that seem to be larger than under the free pricing model and that do not drop dramatically after the price decrease later on. According to the free

pricing model, Zantac would have a decrease in marginal cost in 2004 while it is not the case if we take into account the potential price constraint. The same happens for Raniplex, which suggests our model is better at identifying marginal costs.

Overall, these results seem to indicate that our model is capturing some effects on the drugs subject to reference pricing and to price decreases. Accounting for potentially binding price constraints is thus important when estimating market power through price-cost margins.

Table 11: Marginal costs for drugs possibly subject to price constraints ($US/std. unit) (France)

Sub-			2003	2004		2005		2006		2007	
Class	Molecule	Drug		Free	Constr.	Free	Constr.	Free	Constr.	Free	Constr.
H2	Cimetidine	Tagamet	0.13	0.20	0.23	0.23	0.26	0.16	0.21	0.18	0.21
	Ranitidine	Zantac	0.44	0.26	0.55	0.27	0.45	0.29	0.45	0.31	0.39
	Ranitidine	Raniplex	0.58	0.55	0.57	0.45	0.52	0.31	0.41	0.31	0.38
	Famotidine	Pepcidine	0.59	0.58		0.57		0.56	0.60	0.56	0.61
PPI	Omeprazole	Losec	0.39	0.92		1.04		0.97	1.37	0.83	1.36
	Lansoprazole	Lanzor	0.86	0.86		0.85		0.77	0.92	0.68	0.84
	Lansoprazole	Takepron	0.93	0.94		0.94		0.87	0.95	0.78	0.86

Notes: Free stands for free pricing equilibrium. Constr. stands for constrained price equilibrium.

Columns are merged when situation is identical by definition, under both models.

6 Counterfactuals of Free Pricing in France

Since our results suggest that the French regulation seems to have constrained the price setting of some drugs after 2004, it would be interesting to investigate the effect of such price constraints on the whole industry equilibrium. This requires the knowledge of the counterfactual situation of free pricing in markets where price constraints have been modeled. Once marginal costs have been estimated using the identification method presented above, one can model and estimate the free pricing equilibrium using the identified demand estimates and first order conditions (1). Table 12 reports the observed price from 2003 to 2007 and the counterfactual prices under free pricing for years where some possible constraints may affect the observed equilibrium (remind that drugs non directly price constrained can be affected by price constraints of other drugs in equilibrium). The results show how the free pricing equilibrium would be very different for some drugs and not for others during the period 2004-2005 when the reference pricing policy started. For example, while Tagamet does not seem to have been affected by such policy in 2004 and 2005, Zantac and

Raniplex do, though at different levels. However, starting in 2006, the price decrease policy appears to have been very effective in decreasing prices of these drugs, even for Tagamet, which has been the least affected. Moreover, PPI drugs not directly affected by possible price constraints in 2004 and 2005 are also affected in equilibrium by price constraints on H2 drugs. The more stringent price constraints introduced in 2006 and targeted at these drugs managed to reduce their price; however, except for Losec, the price never falls below the counterfactual price. Looking at prices of all drugs, we can see that in 2004 half of the drugs had a counterfactual price lower than the observed price, whereas this is true only for 20% of drugs from 2005 to 2007. Drugs whose price increased due to the policy are some generics of Cimetidine, Ranitidine and Omeprazole and branded drugs such as Inipomp, Nexium, Panaxid, Pantozol and Pariet, in addition to those of Table 12 whose price increased.

Table 12: Observed and counterfactual (free pricing) prices ($US/std. unit)

Sub-Class	Molecule	Drug	Price	2003	2004	2005	2006	2007
H2	Cimetidine	Tagamet	observed	0.43	0.52	0.55	0.48	0.47
			counterfactual		0.64	0.65	0.60	0.64
	Ranitidine	Zantac	observed	0.74	0.57	0.56	0.57	0.59
			counterfactual		0.94	0.87	0.81	0.78
	Ranitidine	Raniplex	observed	0.86	0.82	0.72	0.59	0.59
			counterfactual		0.93	0.90	0.81	0.77
	Famotidine	Pepcidine	observed	0.89	0.89	0.89	0.88	0.84
			counterfactual		0.85	0.84	0.84	0.90
PPI	Omeprazole	Losec	observed	1.79	1.77	1.78	1.67	1.59
			counterfactual		1.43	1.45	1.69	1.70
	Lansoprazole	Lanzor	observed	1.20	1.22	1.22	1.15	1.07
			counterfactual		1.09	1.08	1.12	1.02
	Lansoprazole	Takepron	observed	1.22	1.24	1.24	1.17	1.09
			counterfactual		1.14	1.14	1.14	1.03

Notes: We have two rows per drug with observed price per year and counterfactual price below.

Counterfactual cell is empty when equal to observed because counterfactual situation is by definition identical (2003).

By comparing the counterfactual prices in Table 12 with results of the reduced form regression in Table 7, one can assess the importance of structural estimation for predicting counterfactual prices. The reduced form results suggest that, absent TFR, the price of Tagamet, Zantac and Raniplex since 2004 and Pepcidine since 2006 would be US$ 1.26 higher than the observed price (according to coefficient "TFR"*After*France" of column 4 of Table 7). Our model predicts a much smaller increase in prices in the counterfactual situation of no TFR, with differences between observed and

counterfactual prices by few cents of a dollar. The same happens for the drugs subject to price decreases: the structural estimation results show that the observed price would not necessarily be always higher without regulation, as instead the figures in Table 7 suggest (with a quantified effect of price decreases of US$ -0.37, though imprecisely estimated, according to the coefficient "Price Decrease"*After*France of column 4 of Table 7). In addition, the reduced form approach does not allow to pin down the differences across drugs and time: it is clear from Table 12 that the price level and change vary across drugs and years, from a minimum of 4 cents difference for Pepcidine in 2006 up to 37 cents for Zantac in 2004. Lanzor and Takepron would even charge a lower price in the counterfactual situation. Finally and most interestingly, the reduced form estimation completely ignores the spillover effects of regulatory measures towards drugs not subject to TFR or price decreases, i.e. that competitor drugs may react to the regulation-induced price changes by adapting their prices. On the contrary, our model allows to simulate the new price equilibrium of all drugs on the market and shows that while some drugs do not seem to have changed their price when some competitors became subject to TFR and price decreases, others responded by increasing or decreasing it, in line with the substitution patterns estimated by our demand model.

However, in the counterfactual situation of free pricing, even if prices had been higher, consumers would have consumed lower quantities for some of these drugs. On average, one third of drugs experienced increased quantity sales compared to the free pricing equilibrium. Table 13 reports the observed and counterfactual quantities sold for the drugs in Table 12, under the assumption that in the free pricing equilibrium there would not be any volume constraints imposed by the regulator. First, as a consequence of the reduced price of Tagamet, sales of Tagamet increased because of the price constraints, while they would have been much lower under the free pricing equilibrium. We will see later the effect on total expenses on Tagamet which combines price and quantity effects. We can see that substitutions across drugs play an important role, as for example the sales of Raniplex would have been much higher under the free pricing equilibrium in 2004 despite its higher price: substitutions away from Raniplex to other drugs, that were even cheaper due to regulation, reduced its sales in 2004. After 2005, however, the price reduction of Raniplex caused its sales to be

much larger than if its price had been set freely. Similarly, Zantac experienced a 40% decrease in its price due to the price constraint and higher sales as compared to the counterfactual situation. One can also see that Pepcidine, whose price was not directly constrained in 2004 and 2005 (and for which Table 12 shows that equilibrium price under the price constraints affecting other H2 drugs was slightly higher until 2006 and lower in 2007), has been sold less than what it would have been in 2004 and 2005 under the counterfactual free pricing equilibrium, because of substitutions away from Pepcidine, but more in 2006 and 2007. Takepron, whose price would have been lower under the free pricing equilibrium, would have been sold in larger quantities in 2004 and 2005 because of substitution away from PPI drugs to H2 drugs; conversely, it has been sold in larger quantity in 2006 and 2007 than it would have been under free pricing.

Table 13: Observed and counterfactual (free pricing) quantities (1000 std. unit)

Sub-Class	Molecule	Drug	Quantity	2004	2005	2006	2007
H2	Cimetidine	Tagamet	observed	4 158	3 922	2 483	1 595
			counterfactual	2 589	3 026	1 362	528
	Ranitidine	Zantac	observed	570 884	539 173	232 870	172 674
			counterfactual	315 858	357 132	188 219	149 544
	Ranitidine	Raniplex	observed	260 085	319 911	347 954	174 754
			counterfactual	321 043	318 672	287 081	150 988
	Famotidine	Pepcidine	observed	1 405	1 557	933	609
			counterfactual	1 425	1 869	807	298
PPI	Omeprazole	Losec	observed	61 586	62 775	70 254	66 281
			counterfactual	151 055	125 024	80 868	62 600
	Lansoprazole	Lanzor	observed	29 347	26 462	24 952	25 062
			counterfactual	36 738	33 872	22 095	21 631
	Lansoprazole	Takepron	observed	28 010	25 415	38 203	38 827
			counterfactual	31 569	28 311	31 975	32 188

Notes: We have two rows per drug with observed quantities per year and counterfactual quantity below.

One can then compute savings in expenditures on drugs due to the policy by comparing the total realized drug expenditures and the total expenditures under the counterfactual situation. Even if prices were constrained downward, total expenditures may have increased due to the changes in quantity. Analyzing expenses drug by drug, we can see that although only 25% of drugs would have a lower price under free pricing, two thirds of drugs would have had overall lower expenses under free pricing: these expenses represent 81% of total expenses on the 2004-2007 period.

Tables 13, 14 and 15 show the different results in terms of savings compared to the counterfactual situation of free pricing for the specific drugs and molecule directly targeted by the TFR policy

starting in 2004 and the price decreases policies of 2006-2007. Negative savings mean that expenses would have been lower under the counterfactual free pricing. Table 14 reports such savings for the 7 drugs that have been at some point potentially price constrained in our model during the 2004-2007 period. Table 15 displays the savings aggregated over all drugs for the 5 molecules that have some drugs potentially price constrained, including the sub-total for the generic drugs of each of these molecules. Table 16 reports the overall aggregated savings of the current regulatory situation as compared to the free pricing equilibrium. Remark that, contrary to other tables, Table 16 also reports the savings that would have been achieved had the demand not changed in the counterfactual situation but only prices, as predicted by the free pricing. This is a completely ad hoc scenario that is however of some interest if one thinks that demand would not react to the change in price predicted by the free pricing equilibrium.

Table 14: Savings on potentially constrained drugs (in 1000 $US)

Sub-Class	Molecule	Drug	2004	2005	2006	2007	2004-2007
H2	Cimetidine	Tagamet	-2 818	-1 699	-1 706	-1 803	-8 026
	Ranitidine	Zantac	276 214	294 817	141 992	109 594	822 616
	Ranitidine	Raniplex	282 425	275 576	225 826	110 534	894 361
	Famotidine	Pepcidine	-5 398	-3 859	-2 005	-555	-11 816
Sub-total H2			550 423	564 835	364 107	217 770	1 697 135
PPI	Omeprazole	Losec	-315 008	-120 865	-39 696	9 533	-466 035
	Lansoprazole	Lanzor	-111 196	-111 082	-110 138	-82 785	-415 201
	Lansoprazole	Takepron	-135 968	-143 485	-134 503	-123 295	-537 250
Sub-total PPI			-562 172	-375 431	-284 336	-196 546	-1 418 486
Total			-11 749	189 404	79 771	21 223	278 649

Notes: Negative numbers indicate increased expenditures as compared to counterfactual.

Savings may be real (positive) or even negative, as for example some constrained drugs, especially Tagamet, Zantac and Raniplex, have been priced lower than under free pricing but sold in much higher quantities (only in 2006 and 2007 for Raniplex). Actually, it seems that the price constraint that affected Zantac has been eroding sales for Raniplex and their generic versions in 2004. Savings are shown in Table 14 and show that the policy has allowed to save a lot on Raniplex and Zantac. On the contrary, the regulation significantly increased expenditures on PPI drugs such as Losec, Lanzor and Takepron.

Table 15: Savings For Some Molecule (in 1000 $US)

Molecule	Drugs	2004	2005	2006	2007	2004-2007
Cimetidine	All	-7 602	-5 602	-5 239	-5 335	-23 778
	Generics	-4 784	-3 903	-3 533	-3 531	-15 751
Ranitidine	All	588 190	636 621	410 699	349 286	1 984 796
	Generics	29 552	66 228	42 881	129 158	267 819
Famotidine	All	-5 421	-4 014	-2 883	-1 906	-14 224
	Generics	-23	-155	-878	-1 351	-2 407
Omeprazole	All	-457 652	-333 309	-243 491	-259 493	-1 293 945
	Generics	-142 645	-212 444	-203 795	-269 026	-827 910
Lansoprazole	All	-247 164	-254 567	-244 641	-206 913	-953 285
	Generics				-834	-834

Notes: Negative numbers mean there would have been less spending under the free pricing equilibrium.

Empty cells when drug not present.

Results in table 15 indicate that for the active ingredients that have some potentially constrained prices (Cimetidine, Ranitidine, Famotidine, Omeprazole, Lansoprazole), savings are overall negative, except for Ranitidine. We also see that negative savings are mostly due to large increase in expenses of branded drugs of Lansoprazole or of generics of Omeprazole. Savings for Ranitidine drugs also come mostly from branded versions and not generic versions. This shows that the policy that constrained downward the price of branded drugs led for some molecules to substitution from generic to branded drugs, generating savings on generics but at the cost of much larger expenses on branded drugs. This negative effect of TFR on the sales of generics has been acknowledged by the CEPS (Rapport d'Activité, 2004) and more recently by the French Competition Commission (Autorité de la Concurrence, 2013). The price reduction of branded drugs thus had a negative effect on overall spending.

Finally, Table 16 shows the overall savings on all drugs: as we can see, substitution across drugs, including the ones not directly price constrained, affects the picture. On the whole, savings due to the policy are inexistent; on the contrary the policy seems to have increased total spending by more than US$ 200 million per year in 2004 and 2005 and even more than 500 millions per year in 2006 and 2007. The overall savings are negative with US$ 1.629 billion increased expenditures on anti-ulcer drugs over 2004-2007, totaling of US$ 6.768 billion expenses over 2004-2007 (see Table 2), i.e. 24% increased sales in this class. These increased expenses would be less striking if demand stayed identical in the counterfactual situation, with increased expenses of around 355 million US$

on the four years, i.e. approximately 5% increased expenditures over 2004-2007. However, it is unlikely that fixed demand is a correct assumption, since substitutions across drugs are very likely to happen, as it has been shown by our demand model. Hence, expenses are much more important: the post 2006 policy led to greater expenses on all drugs due to the large substitutions from generic to branded drugs driven by branded drugs price decreases. Even if increased expenditures are less important in 2007, there are also no savings in 2007. Without additional policy changes in the regulation of prices, a free pricing of drugs would allow to save on drug expenditures. Total aggregate quantities would have been higher under the free pricing policy in 2004 and 2005 but smaller in 2006 and 2007 and the market would not have witnessed the expansion observed on this period (see Table 2).

Table 16: Savings on All Drugs (in 1000 $US)

Year	Drugs	Savings		Consumer
		Fixed Demand	Estimated Demand	Surplus Change
2004	Branded	-184 476	-128 271	
	Generics	5 038	-117 900	
	All	-179 438	-246 171	+3%
2005	Branded	-138 323	-50 808	
	Generics	19 259	-150 274	
	All	-119 064	-201 082	+5%
2006	Branded	-67 117	-354 105	
	Generics	39 173	-165 325	
	All	-27 945	-519 430	+8%
2007	Branded	-82 939	-516 797	
	Generics	53 996	-145 584	
	All	-28 943	-662 381	+7%
2004-2007	Branded	-472 855	-1 049 981	
	Generics	117 466	-579 083	
	All	-355 390	-1 629 064	

Notes: Negative numbers mean less spending under the free pricing equilibrium.

Surplus change is in percentage of observed estimated surplus.

Yet, if one computes the consumer surplus change between the free pricing equilibrium and the constrained pricing one, consumer surplus is higher under the constrained price equilibrium. Table 16 shows that the consumer surplus increased by 3% in 2004, 5% in 2005, 8% in 2006 and 7% in 2007, mostly and unsurprisingly due to greater utilization of sometimes cheaper drugs and of preferred branded drugs.

7 Conclusion

Using IMS Health data, we have estimated differentiated products demand models for anti-ulcer drugs in France, US and Germany for the period 1997-2007. We have then proposed a method allowing to identify the effects exerted by the regulation of prices in France on margins, on total drug expenditures and on welfare. The estimation of the demand takes into account the product differentiation of drugs and allows to identify the major drivers of demand in the period under study and the significant amount of consumers heterogeneity. Interestingly, cross-price elasticities capture the perceived substitutability of generics: when the price of a drug increases, consumers rather switch to a branded competitor than to the generic version of their preferred drug. On the supply side, we assume firms may be constrained by regulation in their price setting decisions on some markets (in France after 2004 for some drugs subject to reference pricing and after 2006 for the price decreases imposed on some branded drugs after generic entry). The identification method relies on the fact that some markets are known to behave under free pricing and on some cost restrictions imposed on the same drugs across markets. Our results suggest that prices have indeed been constrained by those policies. We find that average margins however increased over time between 2004 and 2007. Overall, generics display higher markups along the whole period and for most active ingredients, showing 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 model allowing constrained profit maximization 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 that some drugs are truly affected by the constraints (branded versus generic) but not all of them, showing that regulatory rules have not always been effective compared to what companies would have otherwise chosen. We also show that the pricing of some drugs non directly targeted is affected in equilibrium: this fact raises concerns about the design of such price

regulations, which have equilibrium effects difficult to predict ex ante. We finally perform some counterfactual analysis, by simulating the price equilibrium under free pricing in order to estimate the potential savings made possible by these price constraints in France. We find that these policies have not been effective in reducing total drug expenditures: even though prices of constrained drugs have been lower, substitutions across drugs have led to greater consumption of more branded drugs, which are more expensive than generics. Total expenses for anti-ulcer drugs have thus increased dramatically. However, our analysis does not take into account other regulations that may also limit prices in addition to the one introduced in 2004 and 2006 (price controls through reference pricing - called TFR - and price decreases). We thus attribute the differences between the counterfactual free pricing equilibrium and the observed equilibrium to these policies while we cannot rule out that other simultaneous government decisions may have played a role. Moreover, we cannot simulate the counterfactual case where some price regulation would be in place but not others and that for example reference pricing would be absent but some price controls would still be implemented by the government policy, such as the end of year rebates and volume controls. Finally, this is a short term evaluation of the effects of the policy, as in the long run we should take into account its effects on research and development and entry of new drugs, something left for future research.

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A Appendix

A.1 Data

We use IMS Health data where one observation is defined as a drug-country-year triplet. As we use the same market for anti-ulcer drugs for several countries, a drug is identified by the match 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.

As part of the instrumental variable strategy needs using the price of each drug sold in one country with the price of that drug in other countries, we also used a proxy of a drug showing as

many characteristics as possible in common (the active ingredient, therapeutic form, brand type) when matching for a drug was not possible.

For generics, it was sometimes very difficult to identify the same drug in France and abroad. In this case, when one needs the price in other countries of a unbranded generic sold in France, we used and average of the price of all unbranded generics with the same molecule in the other countries.

A.2 Additional Tables

Table A1: Summary Statistics for the US

	Number of drugs			Quantity	Market Share		Price	Revenue
Year	All	Branded	Generics	(1000 std units)	Branded	Generics	($US/std unit)	(1000 $US)
1997	51	9	42	3 708 548	74%	26%	0.91	3 372 121
1998	57	10	47	4 283 389	64%	36%	0.94	4 013 463
1999	66	11	55	4 501 942	61%	39%	0.93	4 198 792
2000	64	12	52	4 916 472	61%	39%	1.00	4 917 849
2001	72	13	59	5 433 401	59%	41%	0.86	4 659 802
2002	77	12	65	5 676 571	59%	41%	0.92	5 245 686
2003	85	12	73	6 105 044	55%	45%	0.96	5 842 045
2004	93	14	79	5 720 193	55%	45%	1.01	5 780 266
2005	95	14	81	5 522 443	56%	44%	1.05	5 798 501
2006	94	14	80	5 910 214	54%	46%	1.00	5 924 137
2007	99	14	85	6 216 810	50%	50%	1.17	7 299 669

Notes: Price is the average price per standard unit in $US across all drugs. Revenue is total revenue of the class.

Table A2: Summary Statistics for Germany

	Number of drugs			Quantity	Market Share		Price	Revenue
Year	All	Branded	Generics	(1000 std units)	Branded	Generics	($US/std unit)	(1000 $US)
1997	74	18	56	574 198	54%	46%	0.53	300 966
1998	71	19	52	649 366	55%	45%	0.52	338 304
1999	75	19	56	728 723	44%	56%	0.65	471 503
2000	85	21	64	847 310	35%	65%	0.61	514 688
2001	85	21	64	952 650	36%	64%	0.61	576 877
2002	88	20	68	1 059 942	38%	62%	0.60	630 514
2003	84	16	68	1 172 958	39%	61%	0.60	706 382
2004	81	15	66	1 216 147	43%	57%	0.64	783 244
2005	86	14	72	1 389 010	48%	52%	0.60	825 608
2006	86	14	72	1 406 715	48%	52%	0.52	727 942
2007	85	14	71	1 598 651	39%	61%	0.43	687 354

Notes: Price is the average price per standard unit in $US across all drugs. Revenue is total revenue of the class.

Table A3: Own-price elasticities (sample branded drugs, US)

Drug	subclass	1997	2000	2004	2007
Losec	PPI	-3.03	-3.27	-8.95	-13.47
Nexium	PPI			-5.00	-4.64
Ogastro	PPI	-6.78	-6.92	-8.48	-9.73
Tagamet	H2	-2.19	-4.42	-5.62	-9.67
Zantac	H2	-3.68	-5.60	-7.66	-8.32
Cytotec	Prost.	-1.64	-1.76	-3.38	-4.36

Notes: Empty cell when drug has not entered. Ogastro is how Lanzor is called in US (lansoprazole). The other lansoprazole-based drug, Takepron, is not present. Similarly, there is no Raniplex.

Table A4: Own-price elasticities (sample branded drugs, Germany)

Drug	subclass	1997	2000	2004	2007
Losec	PPI	-6.83	-8.80	-12.81	-8.62
Nexium	PPI		-14.35	-9.21	-5.17
Lanzor	PPI		-12.84	-11.72	-7.48
Takepron	PPI	-12.36	-12.31	-13.41	-8.69
Tagamet	H2	-3.45	-3.68	-3.63	-7.52
Zantac	H2	-7.46	-6.91	-4.34	-2.84
Ranidil	H2	-6.40	-7.19	-2.09	-3.24
Cytotec	Prost.	-2.93	-3.37	-4.02	-4.30

Notes: Empty cell when drug has not entered. Ranidil is how Raniplex is called in Germany.

Table A5: Own and Cross Price elasticities (sample of drugs, US 2004)

Sub-Class	H2	H2	PPI	PPI	PPI	H2	H2	PPI
Branded/Generic	Branded	Branded	Branded	Branded	Branded	Branded	Generic	Generic
Company	Glaxo	Glaxo	AstraZ	AstraZ	Takeda	Pfizer	Sandoz	Sandoz
Molecule	Cimet.	Rani.	Ome.	Esom.	Lanso.	Miso.	Rani.	Ome.
Drug Name	Tagamet	Zantac	Losec	Nexium	Ogastro	Cytotec	Generic	Generic
Tagamet	-5.62	0.53	0.17	0.66	0.81	0.05	0.02	0.01
Zantac	0.01	-7.66	0.22	1.09	0.12	0.03	0.01	0.01
Losec	0.001	0.07	-8.95	4.44	1.00	0.003	0.003	0.03
Nexium	0.001	0.05	0.59	-5.00	1.05	0.001	0.002	0.02
Ogastro	0.002	0.09	0.25	2.02	-8.48	0.002	0.01	0.01
Cytotec	0.03	0.64	0.24	0.83	0.53	-3.38	0.01	0.02
Rani. Novt	0.002	0.05	0.03	0.16	0.29	0.002	-0.78	0.05
Ome. Novt	0.000	0.02	0.11	0.60	0.18	0.001	0.02	-5.51

Notes: Each column is the price elasticity of demand for the drug in first row with respect to the drug named in first column.

Company names: Glaxo is GlaxoSmithKline. AstraZ is Astra Zeneca.

Molecules: Rani. is Ranitidine, Ome. is Omeprazole, Esom. is Esomeprazole, Lanso. is Lansoprazole. Miso. is Misoprostol.

Table A6: Own and Cross Price elasticities for a sample of drugs, Germany 2004

Sub-Class	H2	H2	PPI	PPI	PPI	H2	H2	PPI
Branded/Generic	Branded	Branded	Branded	Branded	Branded	Branded	Generic	Generic
Company	Euph.	Glaxo	AstraZ	AstraZ	Berag.	Pfizer	Sandoz	Sandoz
Molecule	Cimet.	Rani.	Ome.	Esom.	Lanso.	Miso.	Rani.	Ome.
Drug Name	Tagamet	Zantac	Losec	Nexium	Lanzor	Cytotec	Generic	Generic
Tagamet	-3.63	0.02	0.002	0.29	0.003	0.01	0.03	0.12
Zantac	0.003	-4.34	0.002	0.72	0.01	0.002	0.04	0.20
Losec	0.000	0.000	-12.81	4.74	0.001	0.000	0.000	0.17
Nexium	0.000	0.01	0.75	-9.21	0.003	0.000	0.01	0.42
Lanzor	0.001	0.02	0.06	1.11	-11.72	0.000	0.01	0.20
Cytotec	0.004	0.01	0.000	0.07	0.000	-4.02	0.01	0.06
Rani. Novt	0.002	0.02	0.000	0.28	0.002	0.002	-2.34	0.15
Ome. Novt	0.001	0.01	0.17	0.78	0.003	0.001	0.02	-10.19

Notes: Each column is the price elasticity of demand for the drug in first row with respect to the drug named in first column.

Company names: Glaxo is GlaxoSmithKline. AstraZ is Astra Zeneca. Euph. is Eupharma. Berag. is Beragena.

Molecules: Rani. is Ranitidine, Ome. is Omeprazole, Esom. is Esomeprazole, Lanso. is Lansoprazole. Miso. is Misoprostol.