Delisting of Pharmaceuticals from Insurance Coverage: Effects on Consumption, Pricing and Expenditures in France

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Abstract

This work structurally estimates the impact on demand and supply of public insurance coverage of pharmaceuticals and its removal (so-called delisting). The analysis focuses on the 2008 delisting of oral phlebotonics (drugs to treat venous circulation disorders) in France, where insurance coverage is tied to price regulation: when a drug is delisted, its price becomes unregulated and the manufacturer can set it freely. This regulatory change and the fact that some drugs were never covered before 2008 provide the variation needed to identify price-cost margins and simulate the counterfactual pricing equilibrium without coverage and price regulation. Results suggest that insurance coverage with price regulation stabilizes prices and guarantees demand for some drugs, like generics, which would sell much less in the absence of coverage. Without insurance coverage and price regulation, increased competition and higher price elasticity would result in lower average prices and reduce demand for most drugs on the market, in line with what is observed after 2008 at the delisting of oral phlebotonics.

Keywords: empirical IO, regulation, pharmaceuticals, copayment, insurance coverage.

JEL Codes: L10, L5, I13, I18, C18

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1 Introduction

With ageing population and the diffusion of chronic diseases, the urge to control public expenditures in health has become a priority in many countries. The policy debate has centered on the identification of methods to reduce those expenditures and make the financing of public health systems sustainable both in the short- and in the long-run. The increase in copayment for health products is often one of the solutions proposed to control those expenditures, in order to shift the burden of costs towards patients, hence freeing public resources.

In the US, expenditures for prescription drugs account for 12% of total health care spending, roughly 2% of GDP: 37% of this amount is tax-financed (Berndt and Newhouse, 2010), as around 60% of all prescriptions are filled for beneficiaries of Medicare, Medicaid and other government programs (Duggan and Scott Morton, 2010). In this context, insurance coverage is based on formularies, which gather therapeutically similar treatments, and copayment differs by tier, with cheaper alternatives in lower tiers benefiting from lower copayments (Gibson, Ozminkowski and Goetzel, 2005; Berndt and Newhouse, 2010). Usually, when cheaper generic versions become available, brand-name drugs shift from being "preferred" to "non-preferred" and are moved to higher tiers subject to higher copayments. In Europe, where pharmaceutical expenditures have reached 1.5% of GDP, most of which is born by national health systems (WHO, 2014), prescription drugs meeting the requirements for public insurance coverage are included in lists similar to US formularies, which are revised regularly to remove those drugs considered obsolete or whose therapeutic value is no longer high enough to justify their coverage.

Given the widespread use of increasing copayment to control public expenditures in health, the question arises of which effects it produces on welfare, including the health of the patients, the level and distribution of profits in the industry, firms' incentives to further invest in research.

This work investigates the impact on demand and supply of the removal of drugs from public insurance coverage (so-called delisting), which is akin to an increase in copayment to 100% and entails the simultaneous removal of price regulation in the case under study. To do so, it carries out a structural analysis allowing to simulate the counterfactual equilibrium in the absence of insurance coverage and price regulation, to verify whether firms and patients would have behaved differently and thus infer the role that such regulation plays in the industry.

The role of copayment is to make the tradeoff between incentives for optimal consumption and risk bearing by the patient (Goldman and Philipson, 2007; Berndt, McGuire and Newhouse, 2011; Fiorio and Siciliani, 2010). On the one hand, while lower copayments tend to result in higher utilization (for example, Duggan and Scott Morton, 2010, on the effects of Medicare Part D), increased copayments translate into fewer doctor visits and prescriptions written and filled (Gibson et al., 2005; Fiorio and Siciliani, 2010; Pichetti, Sorasith and Sermet, 2011), automatically generating savings for health insurance (Ryan and Yule, 1990). On the other hand, substitution effects across drugs might occur, outweighing partially or fully the savings from lower coverage (Gaynor, Li and Vogt, 2006; Pichetti et al., 2011; Gur Ali and Topaler, 2011). In addition, the effects of increased out-of-pocket payments on health outcomes are not obvious, as worse adherence among existing users and discontinuation of therapy are frequent (Goldman, Joyce and Zheng, 2007; Cutler et al., 2010). In turn, these consequences may affect the health of patients and result in higher expenditures, such as those from increased hospitalization (Allegra, 2003; Atella et al., 2006).

Understanding the interplay between all of these factors is not easy and requires knowledge of the counterfactual situation where coverage never occurred in the first place (or was never removed). Yet, the evidence available so far documents mostly the reduced-form consequences of increased copayment, therefore not allowing to claim whether the effects observed on prescriptions, purchase and expenditures are due to the change in the coverage status of the drugs or to other unobserved factors, such as changes in demand or costs[1]. In addition, it mainly focuses on demand, while little attention is paid to the strategic reaction of firms to the regulatory change. Indeed, in many countries being removed from the list of drugs covered by public insurance implies that prices become free and firms can adjust price competition accordingly.

This work investigates the effects of delisting of pharmaceuticals from public insurance coverage with a structural approach, thus overcoming the drawbacks outlined in the existing literature. The method proposed allows to evaluate to which extent the effects observed at the regulatory change are due to the response of demand or to the pricing reactions of firms and is able to relate these effects to the regulatory status, by simulating what would have occurred in the absence of coverage regulation. The focus of the current study is on delisting of oral phlebotonics occurred

[1] A notable exception is the work by Duggan and Scott Morton (2010), though the focus is different.

in France in 2008, which represents the perfect setting to carry out such analysis. Pharmaceutical regulation in France is such that the regulator decides both on the coverage level and on the price of reimbursable drugs. Both must be consistent with the level of medical benefit of the drug, which is assessed at entry of the drug and re-assessed regularly, implying a revision of both at regular intervals. Phlebotonics, drugs to treat venous circulation disorders, in France were approved in the list of pharmaceuticals not requiring a mandatory prescription and could be purchased at the pharmacy without first consulting with a doctor. However, within the same class, two groups of drugs coexisted: those that never met the requirements for coverage, due to insufficient or lacking medical benefit (non covered/pure over-the-counter (OTC) drugs) and those with a medical benefit justifying coverage, but only if prescribed by a doctor (covered drugs). This latter group was the one subject to the 2008 delisting.

The fact that in France coverage is linked to price regulation adds an extra layer of effects of delisting on the supply side: when a drug is delisted, its price becomes free from regulation and the manufacturer can set it freely. Usually, an increase in the retail price is observed, both from higher taxes on OTC than covered drugs and from increased wholesale price. When expectorants and mucolytics were delisted in March 2006, sold packages halved, but revenues dropped only by 41%, suggesting an adjustment of prices (Mutualité Française, 2007). However, the price reaction was very heterogeneous, with drugs decreasing their price up to a fourth, while others increasing it by more than 200% (Pichetti and Sermet, 2011). Similarly, reduced-form evidence on the market of oral phlebotonics shows that the average wholesale price increased when delisting occurred in 2008, but this price reaction varied significantly across drugs: delisted drugs, which were sold at prices already lower than average when covered, experienced a significant price reduction, whereas their competitors, producers of drugs never covered by public insurance (pure OTC), increased prices significantly. At the same time, a dramatic drop in sales was observed.

These results are suggestive of the fact that regulation and its removal may pose constraints on firms not directly subject to regulation and thus have spillover effects across competitors due to substitution effects (Dubois and Lasio, 2014). From this perspective, it would be tempting to claim that price and coverage regulation succeeded in keeping average market price under control. However, these results do not account for the potential changes in demand conditions that might have occurred and thus attribute the strong decrease in sales and increase in prices solely to

delisting. In order to verify that these effects are truly due to the removal of regulation and understand the channels through which this happens, a structural model is needed, to simulate the price equilibrium that would have arisen in the absence of regulation. Indeed, though price setting is based on negotiations between the firm and the regulator, the extent to which this rule prevents firms to set their preferred price is not evident: on the one hand, it is the manufacturer in the first place to propose a price that needs to be approved (*depôt de prix* in French) and often this price is accepted by the regulator and changes little over time (Grandfils and Sermet, 2006); on the other hand, the firm may propose a price that differs from the one it would set absent regulation and potentially set a higher price if free to do so. That is, regulation *may* pose constraints on the behavior of firms, which are at best only partially observed by the econometrician.

Previous studies have emphasized how price and coverage regulation affects strategic incentives and behavior in the pharmaceutical industry. Reference pricing regulation, for instance, has been shown to drive prices and margins down (Pavcnik, 2002; Brekke, Holmås and Straume, 2011; Dubois and Lasio, 2014), but its effects on savings of public money may be outweighed by substitution between drugs subject to different regulatory rules (Dubois and Lasio, 2014). More generally, price controls may not be enough to compensate for the welfare losses originated from global patent protection (Chaudhuri, Goldberg and Jia, 2006) or lead to counterproductive consequences. Strict price regulation may hinder the effectiveness of generic competition (Danzon and Chao, 2000), delay or prevent launches both in the home and in foreign markets (Kyle, 2007; Danzon and Epstein, 2008) and even discourage the development of new drugs if unable to compensate firms for the introduction of high-quality products (Filson, 2012).

The reliability of the analysis proposed here hinges on the precise identification of the demand shape and of substitution patterns across differentiated products, which represent the first step of the method. The use of aggregate wholesale-level data makes the ability to accommodate demand heterogeneity especially crucial, as the different preferences of all segments of demand (physicians, patients subject to different copayments, pharmacists, hospitals) for drug characteristics and price disutility are confounded in the aggregate sales data. The empirical IO literature has addressed this need using random coefficient logit models (Berry, 1994; Berry, Levinsohn and Pakes (BLP), 1995; Nevo, 2000 and 2001), which have proved able to provide rich and plausible substitution patterns in diverse applications, from cars (BLP, 1995), to food (ready-to-eat cereals in Nevo, 2000 and 2001;

mineral water in Bonnet and Dubois, 2010), to pharmaceuticals (Dunn, 2011 on anti-cholesterol drugs; Yin, 2012, on antidepressants; Dubois and Lasio, 2014, on anti-ulcer drugs).

Once demand is identified, the supply side is modeled accounting for the potential constraints that regulation *may* impose and that *may* prevent firms from freely choosing the prices to maximize profits as in standard oligopolistic models. Such constraints stem from both explicit and implicit rules and result in a price cap unobserved to the econometrician, which may be binding or not for manufacturers. By using the method developed by Dubois and Lasio (2014) on IMS data on sales and prices for the period 1997-2013, unobserved constraints can be identified thanks to assumptions about the competition game played by firms and the variation across drugs that are not price constrained (drugs that are never covered and covered drugs after delisting) and those that may be (covered drugs before delisting). Adding restrictions on the marginal costs of drugs across time (markets), the method allows to infer whether constraints are binding and to identify price-cost margins. The counterfactual situation of free pricing during the coverage period can then be simulated to compare the price that was set by the regulator to the one firms would have chosen in the absence of price regulation and how demand would have been affected. These counterfactuals are then used to interpret the observed effects at delisting in light of the model predictions.

Results suggest that demand for oral phlebotonics was elastic during the whole period, but elasticity increased for delisted drugs after 2008, as well as heterogeneity in the disutility of price. Despite strong differentiation, captured by small cross-price elasticities, the combination of substitution effects and price regulation affected the ability of firms to charge their preferred price both during the coverage phase and after delisting. Counterfactuals show that insurance coverage with price regulation stabilizes prices of covered drugs and ensures sales for generics. Its removal results in lower average prices and in lost sales for most drugs, except high-price/high-quality products, in line with what is observed at delisting in 2008. This effect originates from increased demand elasticity and lower perceived differentiation among the two groups of drugs (covered and pure OTC) once regulation is removed, suggesting that coverage was perceived as a high-quality certification by patients and doctors. As a result, manufacturers of most delisted phlebotonics respond by significantly decreasing their prices, while producers of pure OTC drugs increase them.

The remainder of the paper is organized as follows. Section 2 describes the regulatory framework in France, the market of oral phlebotonics, the data used and provides reduced-form evidence on

the effects of delisting on prices of drugs. Section 3 explains the model used for demand and supply. Section 4 reports the details of estimation and identification. Results are extensively presented in Section 5. Section 6 concludes.

2 Context

2.1 The regulatory framework

In France, public health insurance covers, at least partially, the expenditures on pharmaceuticals. In order to be covered, drugs need to belong to a specific list and their level of coverage (which currently ranges from 15% to 100%) depends on the medical benefit of the drug and the severity of the disease[2]. The medical benefit, both absolute and relative, is summarized by two indices, SMR and ASMR (*Service Médical Rendu* and *Amélioration de Service Médical Rendu*), which are assigned to each pharmaceutical product entering the French market and re-evaluated over time. The values of SMR and ASMR determine, respectively, the level of coverage and the price, which is regulated for all covered drugs, while non-covered drugs benefit from free pricing.

The process of SMR reassessment started in 1999 and continued for several years, leading to a recommendation by the so-called "Transparency Commission" to remove a large number of drugs from the list of reimbursable drugs, due to insufficient medical benefit. The first wave of delisting, in September 2003, concerned a composite group of 72 old drugs not subject to doctor prescription; the second, in March 2006, included 403 drugs subject to optional prescription but covered with a prescription, mainly expectorants, bronchodilators, homeopathic products, oligo-elements and drugs for digestive tract disorder; the third wave occurred in 2007 for 283 prescription drugs, mostly vasodilators and intestinal antiinfective agents. For some of these drugs, delisting occurred immediately, while for others it was postponed or implemented gradually, with a first step of reimbursement level reduction (i.e. an increase in copayment). This happened to phlebotonics, whose level of coverage was reduced to 15% (that is, 85% copayment) and their price cut on average by 12% until 2008, then delisted. Although the attribution of an insufficient SMR by the Transparency Commission should automatically lead to delisting, the Ministry of Health decided to maintain these drugs temporarily on the list due to the absence of substitutes, so as to leave some

[2]The level of coverage is (100%-copayment).

months to doctors and patients to find suitable alternative therapeutic strategies before delisting. Interestingly, the complementary health insurance association opposed the introduction of the 15% level of coverage and decided not to cover the 85% copayment.

After the second wave of delisting, the prescription of drugs decreased significantly, as well as total sales. At the same time, the final price increased, but on the whole revenues decreased, as the increase in price did not compensate for the lower demand (Mutualité Française, 2007; Pichetti et al., 2011). There also seemed to be a substitution effect towards drugs that are still covered but that were not considered as substitutes before delisting. In the case of expectorants and mucolytics, prescriptions and sales of antitussives and bronchodilators increased (Pichetti et al., 2011).

When a drug is removed from public insurance coverage, its price is no longer regulated: the manufacturer can freely set the price and the pharmacist and wholesaler can choose their margin; at the same time, the VAT rate applied is higher. As a result, the final price tends to be higher than the regulated price when covered. A study by DREES (Legal, Marbot and Pilorge, 2012) on delisted expectorants documents a significant and immediate increase in their price when they became OTC (+40% after one year and more after three years), with pharmacists setting similar prices for a long period. Manufacturers often try to avoid price dispersion and its negative effects on sales: when phlebotonics were delisted, they cut the wholesale price, engaged in a strategy of suggested price and set up a system of rebates for pharmacists (Noel and Magnien, 2008).

2.2 The French market of oral phlebotonics

The analysis focuses on oral phlebotonics, defined as those drugs approved by the French Agency for the Safety of Health Products (*Agence Française de Sécurité Sanitaire des Produits de Santé*, AFSSAPS) for at least one of the indications related to venous circulation disorders, namely chronic venous insufficiency (CVI), haemorrhoidal disease, vision impairment and capillary fragility. Additional indications include treatment of varicose veins, ecchymoses, and other conditions associated with perivascular inflammation and oedema (swollen legs, pain, restless legs)[3].

Prevalence of chronic venous disease may reach 40% in women and 17% in men, while annual incidence ranges from 1.9% in men and 2.6% in women. In France CVI affects around 20% of the population, entailing a cost to society (including direct and indirect costs) of up to 1 billion

[3]Homeopathic drugs as well as topical products (creams, gels) are excluded from the analysis.

US dollars, a size comparable to other countries like Germany, Italy and UK (Flota Cervera et al., 2008) and around a third of what estimated for the US (McDonagh, King and Guptan, 2007). Venous disease manifests not only with varicose veins but also with painful ulcers, achy and heavy legs, tingling sensations, cramps, skin pigmentation, itchy and hot feet. If not treated promptly, it may lead to complications such as venous leg ulcer and lymphoedema, which require surgical treatment.

Phlebotonics are a heterogenous class of drugs consisting of plant extracts (i.e. flavonoids) and synthetic compounds (i.e. calcium dobesilate). Although their precise mechanism of action has not been fully established and their effectiveness is controversial (Martinez et al., 2005), they have been found to improve venous tone, stabilize capillary permeability and increase lymphatic drainage. Tolerance of phlebotonics is usually high and the most common adverse effects are routine gastric disorders and skin reactions. They are widely used in mild to moderate CVI. In severe cases, alternative or complementary treatment includes compression therapy (compression stockings and bandages) or surgery (sclerotherapy, vein stripping).

In Europe and Latin America, the use of these drugs in the treatment of CVI is common (Ramelet et al., 2005). France seems, however, to be consuming more than comparable countries, mainly driven by high prescription rates. Given the high tolerability of these drugs, the regulator allowed them to be available at the pharmacy without prescription. On the basis of their medical benefit (SMR), some were included in the list of covered drugs until 2008, while others were always OTC medications. However, in order to be covered, they had to be prescribed. This explains the high rates of prescription and the low levels of self-medication, which never took off until delisting (5% in 2006, but high increase since 2006 when reimbursement rate decreased to 15% and complementary health insurances refused to cover copayment).

2.3 Data and Descriptive Statistics

The data used is provided by IMS Health and gathers all wholesale transactions annually for the period 1997-2008 and monthly from January 2009 until April 2013. In the dataset one observation (drug-period pair) is uniquely identified by the name of the medicine, the manufacturing firm, the active ingredient, the therapeutic form and the brand type (originator, licensed or generic drug). For the analysis, the unit of observation is a combination of the name of the drug and its therapeutic

form in a given period (year until 2008, month after). IMS quantities are reported in standard units to allow comparison across different drug dosages and strengths. A standard unit is defined as the unit containing the smallest common dose of the product, based on its therapeutic form: for oral solid form it corresponds to one capsule or tablet of the smallest dosage, while for syrups it is one 5 ml-teaspoon. This implies that brands sold in different strengths are subsumed into the same observation in each period and their respective contribution to the final sales is proportional to their dosage. Similarly, no information is reported at the package size level. From data on sales and revenues, the average wholesale price in US dollars per standard unit can be found.

Additional data used for the analysis include drug characteristics such as indications and side effects, as well as on price levels and their evolution until 2008. The website *www.theriaque.org* (approved by the regulatory agency HAS) and the database *Ameli* (managed by the public health insurance system) were used to collect this information.

Finally, data on exchange rates, Producer Price Index (PPI) and wages in the pharmaceutical industry (used as instruments in demand estimation) were retrieved from OECD and INSEE (the National French Institute of Statistics).

The market for oral phlebotonics between 1997 and 2013 comprises 134 drugs (113 brand names), based on around 40 active ingredients. Most of the drugs are based on synthetic compounds (only 42 are phytotherapic products) and branded and generic versions are almost equally represented (70 and 64, respectively). The vast majority of phlebotonics (110) belongs to the ATC class of capillary stabilizing agents (C05C), while the remaining ones are in class V03A (all other therapeutic products). Despite the large number of specialties, 3/4 of sales are generated by 10 drugs, which have been mainly the same all along the sample period (with Daflon, Endotelon, Ginkor and Esberiven ranking always in the top 4). The majority of these drugs were subject to delisting, i.e. were approved for coverage until 2008 only. The most important molecules are synthetic compounds derived from flavonoids (diosmin, troxerutine), which are also present as generics. Most drugs are sold under a single therapeutic form, with solid forms being the most common (capsules and tablets), followed by powders and syrups. A total of 63 firms are active in the market, often with several competing products. Major manufacturers of brand-name phlebotonics include Sanofi, Pfizer, Merck, Servier, Bayer, J&J and Pierre Fabre, while generic versions are mainly produced by Teva, Sandoz, Mylan, Biogaran, Arrow and Ranbaxy. 127 drugs have an indication for

venous insufficiency and 113 for haemorrhoidal disease. Most products are approved for at least two different indications (116) and report gastric disorders as adverse effects (101).

Table 1: The market: yearly

Year	Quantity in 1000 standard units	Revenue in 1000 US $	Average Price in US $ per standard unit	Nb. of Molecules includes combinations	Covered Drugs delisted in 2008
1997	2,853,576	763,085	0.24	20	26
1998	2,653,826	630,575	0.25	19	25
1999	2,494,596	607,762	0.25	19	24
2000	2,744,056	692,230	0.23	40	48
2001	2,804,718	671,053	0.21	41	53
2002	2,784,107	641,929	0.22	41	61
2003	2,840,384	621,088	0.24	42	72
2004	2,746,014	596,398	0.25	41	72
2005	2,776,915	600,947	0.23	39	74
2006	2,307,882	427,088	0.24	38	78
2007	2,109,165	377,726	0.23	36	78
2008	1,636,122	175,972	0.17	35	67
2009	1,498,631	168,480	0.18	32	58
2010	1,386,861	162,650	0.19	31	55
2011	1,227,209	156,298	0.20	29	50
2012	1,119,926	150,813	0.19	29	48

Notes: A standard unit is a commonly defined dose unit such as a pill, vial, spoon.

In terms of quantities, reported in standard units in Table 1, the market evolved very little until 2005, remaining fairly stable. A drop is observed in 2006, the year when the level of coverage of listed phlebotonics was decreased from 35% to 15%, and continues in following years, though with a tendency to stabilize. The trend of revenues and prices is instead downward, both before and after delisting, though the drop is much more relevant since 2008 and for revenues than prices. Sales of phlebotonics peak in summer (between April and July), as Table 11 in Appendix 1 shows, consistent with the seasonality of venous disorders (which worsen when temperature is high).

2.4 Reduced Form Evidence

The drop in average market price observed in 2008 deserves investigation. Unlike other drugs previously delisted (namely mucolytics and expectorants in 2006), which experienced a significant and immediate increase in price at delisting (Pichetti et al., 2011; Legal et al., 2012), the average wholesale price of phlebotonics drops significantly in 2008 and then stabilizes, never reaching again

the level attained during the coverage period. The average effect is the result of a large drop in prices of delisted products and an increase in the price of their OTC competitors (Table 2). Until 2008 regulated prices had been higher than OTC prices and much more stable, with little change over time.

Table 2: Average prices by covered and OTC drugs

Year	Average Price	Covered Drugs (delisted in 2008)	OTC Drugs (never covered)
1997	0.24	0.25	0.16
1998	0.25	0.26	0.10
1999	0.25	0.26	0.14
2000	0.23	0.26	0.20
2001	0.21	0.25	0.15
2002	0.22	0.26	0.15
2003	0.24	0.26	0.20
2004	0.25	0.27	0.22
2005	0.23	0.27	0.16
2006	0.24	0.27	0.17
2007	0.23	0.27	0.14
2008	0.17	0.17	0.17
2009	0.18	0.19	0.19
2010	0.19	0.18	0.21
2011	0.20	0.20	0.21
2012	0.19	0.19	0.20

Notes: Prices in US $ per standard unit.

In order to verify if covered drugs were indeed more expensive than pure OTCs between 1997 and 2007, Table 3 reports the results of a reduced-form regression of prices on drug characteristics (including molecule fixed effects), on the drug group dummy "Covered", on the dummy "After 2008", which takes value 1 for each period after delisting (2008-2013), and on their interaction.

As expected, the price level is affected by drug characteristics that proxy for quality, such as indications for usage in specific conditions and the absence of main side effects (gastric disorder). Drugs based on plant extracts tend to be cheaper, consistent with their perception of being of lower quality than synthetic compounds. Interestingly, when controlling for such drug characteristics, regulated prices of covered drugs do not appear to be as high as aggregate figures seem to suggest. The negative sign of the coefficient of the dummy "Covered" indicates that the regulated price of covered drugs tends to be lower than that of unregulated OTC products, though the effect is

Table 3: Determinants of price

	(1) price	(2) log(price)	(3) price	(4) log(price)
Covered	-0.0368	-0.794*	-0.0218	-0.762
	(0.102)	(0.447)	(0.104)	(0.506)
Covered * After 2008	-0.107**	-0.508**	-0.125***	-0.549***
	(0.0413)	(0.211)	(0.0419)	(0.163)
After 2008	0.0415	0.126	0.0409	0.125
	(0.0390)	(0.120)	(0.0387)	(0.120)
Reimbursement Rate	0.0006	0.0012		
	(0.0008)	(0.0032)		
Reimbursement Rate * After 2008	-0.0021	-0.0072		
	(0.0016)	(0.0056)		
Branded	-0.0055	0.0466	-0.0055	0.0465
	(0.0409)	(0.178)	(0.0407)	(0.177)
Liquid	-0.0093	0.0941	-0.0091	0.0948
	(0.0306)	(0.166)	(0.0305)	(0.165)
Indication: Venous Insufficiency	0.454**	2.544***	0.459**	2.558***
	(0.214)	(0.609)	(0.213)	(0.597)
Indication: Haemorrhoidal Disease	1.041	4.238***	1.045	4.246***
	(0.736)	(1.543)	(0.735)	(1.537)
Indication: Capillary Fragility	0.712	3.328***	0.714	3.333***
	(0.438)	(1.095)	(0.437)	(1.082)
Indication: Vision Impairment	0.391**	2.455***	0.392**	2.458***
	(0.179)	(0.868)	(0.178)	(0.857)
Indication: Other	1.001*	4.597**	1.006*	4.613***
	(0.556)	(1.714)	(0.555)	(1.696)
Nb. of Indications	-0.734	-3.420***	-0.736	-3.425***
	(0.462)	(1.126)	(0.461)	(1.116)
Side effect: Gastric Disorders	-0.0341	-0.0294	-0.0347	-0.0311
	(0.0574)	(0.397)	(0.0574)	(0.396)
Nb. of Side Effects	0.0283	0.0449	0.0287	0.0458
	(0.0320)	(0.101)	(0.0320)	(0.101)
Phytotherapic drug	-0.161**	-1.238**	-0.157**	-1.225**
	(0.0736)	(0.494)	(0.0728)	(0.497)
Constant	0.249	-0.638	0.249	-0.639
	(0.166)	(1.052)	(0.165)	(1.046)
Observations	4,379	4,379	4,379	4,379
R-squared	0.760	0.793	0.760	0.793
Molecule FE	Yes	Yes	Yes	Yes
Date FE	Yes	Yes	Yes	Yes

Notes: Standard errors are clustered at the molecule level. Significance levels: *** : 0.01, ** : 0.05, * : 0.1

not significant, i.e. when observed quality is accounted for, the price difference between the two categories is unimportant. This is in line with the fact that covered drugs were allowed to be on the list due to their higher quality, at least until the medical benefit index (SMR) revision. The trend captured by the dummy "After 2008" suggests that the average price reaction at delisting was an increase in prices, though small and not statistically significant. Yet, delisted drugs experienced a strong drop in price: the aggregate figures reported in Table 2 show that this effect was stronger than the upward trend of OTC products, resulting in a significant reduction in the average wholesale price level.

What these results suggest is a strong heterogeneity across drugs, covered drugs (both before and after delisting) vs. never covered/pure OTCs, in their price level and reaction. While delisted products decreased the price at delisting, presumably to contain the loss in sales, manufacturers of pure OTCs reacted by raising it. It would be tempting to attribute the observed price evolution to the regulatory change, with price regulation succeeding in controlling the average level of market prices, either directly (through price setting) or indirectly (through spillovers and substitution effects). However, the reduced-form approach does not allow to exclude that the observed effects are due to changes in demand and consumer preferences or cost shocks that drove prices down after 2008, differently for delisted and pure OTC drugs. Furthermore, it is not possible to draw a conclusion on the true impact of price regulation on prices, as the counterfactual scenario of free-pricing between 1997 and 2007 is unobserved. The structural method proposed in the following sections aims at explaining these results.

3 The model

3.1 Demand

The first stage of the analysis consists in the estimation of demand: this step is crucial for the identification of substitution patterns, which must be precise in order to correctly estimate price cost margins.

The demand model for this analysis must be flexible enough to accommodate heterogeneous tastes for drug characteristics and disutility of price. This is especially important as estimation is based on aggregate data where preferences of different segments of demand are subsumed, but

cannot be disentangled in wholesale data. Aggregate sales reflect, first, preferences of pharmacists, who respond to incentives to sell and substitute drugs on the basis of the different margins they might obtain on each, as well as to non-financial considerations. Preferences of consumers are heterogeneous due to demographic characteristics, health condition and different copayments, depending on the decision to buy the drug under prescription (thus being covered by the public system and potentially by complementary insurance), or freely at the pharmacy. Preferences of the physician may affect the decision to prescribe a specific drug or alternative treatments such as bandages or compression stockings.

Flexibility and focus on heterogeneity are guaranteed by the random coefficient logit demand model, which allows to identify precise substitution patterns using only aggregate data on market shares and drug characteristics, including prices (Berry et. al, 1995; Nevo, 2000).

The model specifies that the utility of using drug $j \in \{1, .., J_t\}$ for patient i in period t is

$$u_{ijt} = \sum\nolimits_k \alpha_i^k x_{jt}^k - \beta_i p_{jt} + \zeta_{jt} + \varepsilon_{ijt} \tag{1}$$

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 consumer i's deviation from the mean utility of taking drug j at period t. Preference parameters α_i^k, β_i are allowed to vary across users i (random coefficient). The model is completed by the inclusion of an outside good, which corresponds to not using any of the J_t products, with a normalized indirect utility $u_{i0t} = \varepsilon_{i0t}$[4].

Each user chooses an element in the choice set $\{0, 1, .., J_t\}$ according to the maximum utility (1). This modeling of choices can be seen as a reduced form of a more complex mechanism where patients, prescribers and pharmacists interact and where the final market share is a result of the combination of preferences of all those actors. It is thus important that the preference parameters be specific to each user i, because of the unobserved variation in price-sensitivity across users. 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.

[4]The outside option in the market for phlebotonics can be the use of bandages or compression stockings, or the decision not to take any treatment and increase physical activity, or surgery for the most serious conditions.

The random coefficients capturing such heterogeneity can be written as

$$\left(\alpha_i^k, \beta_i\right) = \left(\alpha^k + \sigma_{\alpha^k}\nu_i^k, \quad \beta + \sigma_\beta \nu_i^p\right)$$

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 $\mu_{ijt} = \sum_k x_{jt}^k \sigma_{\alpha^k}\nu_i^k - p_{jt}\sigma_\beta \nu_i^p$ 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

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

and the outside good choice probability is

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

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

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

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

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

3.2 Supply

The supply model considered for the analysis is a static oligopoly model with a given market structure, taking entry and exit decisions as exogenous. Within this general framework, two different models of price setting can be analyzed, accounting for the role that price regulation may play.

The first model assumes that the firm can freely set the price that maximizes profits. This is the case after delisting, when regulation of prices is no longer in place, as well as the case of drugs that were never covered (pure OTC) during the 1997-2007 period. However, this same model may apply to covered drugs even before delisting if manufacturers manage to choose prices that maximize profits in spite of price regulation. The presence of regulation does not necessarily affect firms' pricing decisions if bargaining between the regulator and the industry and lobbying are in favor of pharmaceutical manufacturers. The fact that price setting occurs through negotiations based on the price proposed by the manufacturer itself (*depôt de prix* in French) may go into this direction (Grandfils, 2008): the price approved by the regulator is often the initial one (Grandfils and Sermet, 2006), so that the final price equilibrium coincides with the profit maximizing one and the price remains a decision mainly under control of the firm. Nevertheless, the bargaining process itself may be restraining the final price, as it has been found in similar contexts[5]. Furthermore, the mere existence of price regulation may affect the initial pricing decision of firms, as they may anticipate the constraints imposed by the regulator and propose a price that may differ from the one chosen without regulation. This potential discrepancy between the profit-maximizing price and the one observed in practice is more likely in a setting, like the one of phlebotonics, where the same regulated price applies to patients with different price sensitivities and subject to different copayments, namely those benefiting from coverage (partially) for a prescription-based purchase and those buying without a prescription and thus paying the full price. In this case, a more appropriate model would allow firms to be *potentially* constrained by regulation in their price setting decisions, through unobserved constraints, without imposing that these constraints bind, but making such possibility the result of the analysis itself.

[5]Gowrisankaran, Nevo and Town (2014), on the bargaining between Managed Care Organizations and hospitals; Duggan and Scott Morton (2010), on the interplay between insurance, group purchase and formularies in Medicare Part D.

The role of the vertical structure of the pharmaceutical industry deserves some comment. The analysis is based on wholesale level data, i.e. sales and especially prices reflect what the pharmacist buys and pays. The price actually paid by the final consumer is not directly observed. Recovering this price (or at least a good approximation of it[6]) is possible during the coverage phase: the final price is the sum of the wholesale price observed in the data, the regulated margin of the pharmacist (which depends deterministically on the price level of the drug and its brand type) and some fixed taxes. When delisting occurs, not only is the wholesale price freely fixed, but also the pharmacist's margin. Without observing directly the final price at the pharmacy, it is no longer possible to predict its level. Unfortunately, with wholesale data only, some assumptions must be made on the behavior of pharmacists at delisting. In specific, for the analysis below to be correct, the pharmacist must behave similarly during the coverage phase and afterwards, i.e. setting a similar margin across drugs and periods. The structure of the industry may suggest that this is the case. Pharmacies in France are numerous (38 per 100 thousand inhabitants as compared to 10 in Sweden, 18 in UK, 26 in Germany and 29 in Italy (CNAMTS, 2007)) and their ownership is fragmented: there are no pharmacy chains as in other countries (for example in Sweden or the US), and by the law pharmacists are allowed to own at most one pharmacy. Thus, the bargaining power in the vertical chain should mainly lie on the manufacturer's side. In addition, three quarters of pharmacies' profits come from covered drugs and OTCs only represent a small share (14% in volume and 6.5% in value in 2009 (AFIPA, 2010; AESGP, 2012)). However, the evidence reported by Legal et al. (2012) may raise some doubts: they show that the retail price of a subset of drugs delisted in 2006 observed across 4700 French pharmacies increased rapidly and significantly mainly due to the increase in the margins set by pharmacists, rather than in the wholesale price. Luckily, there are reasons to think that such a reaction did not occur for phlebotonics. First, the large price increase of drugs delisted in 2006 entailed a strong negative reaction by consumer associations and politicians and was one of the arguments put forth by the Ministry of Health for maintaining phlebotonics covered until 2008 in exchange for a significant decrease in price (12% on average), rather than delisting them immediately in March 2006. In addition, the large price increase of drugs delisted previously prompted a more than proportional drop in sales, so that revenues and profits fell significantly. Fear that this would happen led manufacturers of delisted phlebotonics to

[6]Rebates of the manufacturers for wholesalers and pharmacists are not collected by IMS.

put in place a number of strategies to encourage pharmacists to set margins close to the margins they earned during the coverage period (Noel and Magnien, 2008), in line with what the union of pharmacists advised its members to do. These measures included rebates on direct sales (avoiding intermediaries as wholesalers) and suggested retail prices similar to RPM.

For all of the previous reasons, the supply model considered here only focuses on the manufacturer's problem of setting the wholesale price, assuming that the retail margin would be either regulated (coverage phase) or set homogeneously by the pharmacist after delisting to a level consistent with previous margins. Based on the evidence reported above, the model assumes that pharmacists mainly set the margin to cover distribution costs, which are non specific to drugs but mostly depend on storage space management costs and can therefore be proxied by time controls.

3.2.1 Free pricing

The first model describes the case in which the firm is free to choose the price that maximizes profits either in the absence of price regulation (after delisting) or despite regulation (before delisting, when the price proposed by the manufacturer is accepted by the regulator).

The (variable) profit of multiproduct firm m in period t (fixed costs and other R&D costs do not affect pricing decisions), denoted Π_{mt}, can be written as:

$$\Pi_{mt} = \sum\nolimits_{j \in S_m} (p_{jt} - c_{jt})\, s_{jt}(\mathbf{p}_t) \quad \forall j \in S_m$$

where p_{jt} is the price of drug j in period t, c_{jt} is the constant marginal cost of product j, $s_{jt}(\mathbf{p}_t)$ is the market share of drug j given the vector $\mathbf{p}_t$ of all drug prices in period t, and S_m is the set of drugs produced by firm m.

Assuming that firms maximize profits by choosing prices simultaneously after observing the demand factors, that technical conditions for the existence of a pure-strategy Bertrand-Nash equilibrium in prices are met and that equilibrium prices are strictly positive, the price of any product j sold by firm m must satisfy the first-order condition:

$$s_{jt} + \sum\nolimits_{k \in S_m} (p_{kt} - c_{kt}) \frac{\partial s_{kt}\left(\mathbf{p}_t\right)}{\partial p_{jt}} = 0, \quad \forall j, k \in S_m$$

Defining $\mathbf{s}_t$, $\mathbf{p}_t$ and $\mathbf{c}_t$ the vectors of market shares, prices and marginal costs for all products $j = 1, ..., J_t$ in period t, Ω_t the ownership matrix and D_{p_t} the matrix of derivatives of demand with respect to price,

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

$$\Omega_m = \begin{bmatrix} \mathbf{1}_{\{1 \in S_m\}} & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & \mathbf{1}_{\{J_t \in S_m\}} \end{bmatrix}, \quad D_{p_t} = \begin{bmatrix} \frac{\partial s_{1t}(\mathbf{p}_t)}{\partial p_{1t}} & ... & \frac{\partial s_{J_t t}(\mathbf{p}_t)}{\partial p_{1t}} \\ . & . & . \\ \frac{\partial s_{1t}(\mathbf{p}_t)}{\partial p_{J_t t}} & . & \frac{\partial s_{J_t t}(\mathbf{p}_t)}{\partial p_{J_t t}} \end{bmatrix}$$

first order conditions can be written more succinctly

$$\Omega_m \mathbf{s}_t + \Omega_m D_{p_t} \Omega_m \left(\mathbf{p}_t - \mathbf{c}_t \right) = 0$$

Given demand estimates and observed prices and market shares, price-cost margins per product and per period can be recovered by solving the system of equations, as expressed by the following equation (where products are componentwise multiplications), which is the multiproduct-firm oligopoly version of the usual condition linking price-cost margins to demand elasticity:

$$\Omega_m \mathbf{p}_t^{-1} \left(\mathbf{p}_t - \mathbf{c}_t \right) = - \left[\Omega_m D_{p_t} \Omega_m \right]^{-1} \Omega_m \mathbf{p}_t^{-1} \mathbf{s}_t \tag{2}$$

3.2.2 Constrained maximization

If price regulation is in place, the final pricing equilibrium may not correspond to the one implied by the maximization described in the previous section. In this case, the model must account for the fact that price regulation may pose constraints on firms that are not necessarily observed and act as an unobserved price cap. Ex post, manufacturer m cannot charge a higher price than the one approved by the regulator; ex ante, it proposes a price that *may* embed the subsequent negotiations with the regulator.

The model proposed in section 3.2.1 must then be modified accordingly, to allow that the price chosen by manufacturer m for its drugs on the coverage list (i.e. belonging to the set R_t of price regulated products) cannot be higher than $\overline{p}_{jt}$ (equivalently, must belong to a set R_{jt}):

$$\begin{aligned} \max_{\{p_{jt}\}_{j\in S_m}} \Pi_{mt} &= \sum\nolimits_{j\in S_m} (p_{jt} - c_{jt})\, s_{jt}(\mathbf{p}_t) \\ s.t. \quad p_{jt} &\leq \overline{p}_{jt} \qquad \forall j \in S_m \cap R_t \end{aligned}$$

The assumption that constraints are unobserved allows the identification method to work even if the price cap $\overline{p}_{jt}$ for all j in $S_m \cap R_t$ is endogenous, i.e. depends on quantities and prices chosen in equilibrium by all firms.

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

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

where λ_{jt} is the Lagrange multiplier of the price constraint $p_{jt} \leq \overline{p}_{jt}$ (or, equivalently, $p_{jt} \in R_{jt}$, as shown in Dubois and Lasio, 2014).

Using matrix notation, the first order conditions become:

$$\Omega_m (\mathbf{p}_t - \mathbf{c}_t) = -\left[\Omega_m D_{p_t} \Omega_m\right]^{-1} \Omega_m (\mathbf{s}_t - \lambda_t)$$

This equation is the counterpart of equation (2), where the right hand side now includes λ_t, a vector of size J_t (the number of drugs in period t) with as many unknown strictly positive elements as drugs on the coverage list (i.e. in the set R_t) and zeros for all other drugs. The positive elements in λ_t are the unknown binding constraints that regulation is posing on the price of each drug $j \in R_t$.

However, the fact that λ_t is unknown prevents price-cost margins from being identifiable even with demand estimates, prices and market shares. In addition, substitution across drugs (captured by own- and cross-price elasticities of demand) may have an impact on the whole price equilibrium, resulting in an ambiguous effect of regulation: a reduction or increase in the price of a covered drug may prompt strategic reactions of unregulated competitors (pure OTCs), as reduced-form evidence presented in section 2.4 suggests. Ideally, if marginal costs were observed, margins could

be recovered and identification of unobserved constraints could be easily achieved. In the absence of information on marginal costs, though, assumptions must be made to reduce the degree of underidentification. To see this, rewrite the marginal cost $c_{jt}(\lambda_t)$ for all drugs produced by manufacturer m as a known function of λ_t (depending on demand, prices and market shares):

$$\mathbf{c}_t^m(\lambda_t^m) = \mathbf{p}_t^m + D_p^m(\mathbf{p}_t)^{-1}(\mathbf{s}_t^m - \lambda_t^m) \tag{3}$$

The expression above shows that, if $D_p^m(\mathbf{p}_t)$ is invertible, for any marginal cost vector $\mathbf{c}_0$ it is always possible to find λ_t^m such that $c_t^m(\lambda_t^m) = c_0$, using $\lambda_t^m = D_p^m(\mathbf{p}_t)(\mathbf{p}_t^m - c_0) + \mathbf{q}_t^m$. Thus, assumptions on marginal costs of drugs across markets are needed for identification.

With unobserved marginal costs, identification becomes possible if the same product j is observed in market t where it belongs to the constrained set ($j \in R_t \Leftrightarrow \lambda_{jt} > 0$) and in market τ where it does not ($j \notin R_\tau \Leftrightarrow \lambda_{j\tau} = 0$) and some information is available on the cost difference between the two markets: $c_t - c_\tau = d$[7].

This situation is similar to the one observed for the delisting of phlebotonics. Covered drugs are observed both in markets where they belong to the constrained set R_t where their price is regulated, i.e. the coverage list, and in markets where they are no longer subject to regulation, due to delisting. In addition, in each market where regulation is active, a combination of constrained (covered phlebotonics) and unconstrained drugs (pure OTC phlebotonics) is observed. However, nothing is known about the cost of the same drug when covered and when delisted and additional restrictions must be added for identification to be possible. Therefore, the cost difference between any two constrained and unconstrained markets t and τ can be modeled to depend linearly on the observable difference $z_\tau - z_t$ of the vector of observed variables $\mathbf{z}$ and on unobserved market-specific additive shocks ω_τ:

$$\mathbf{c}_\tau - \mathbf{c}_t = (\mathbf{z}_\tau - \mathbf{z}_t)'\delta + \omega_\tau$$

with

$$E(\omega_\tau | \mathbf{z}_\tau - \mathbf{z}_t) = 0$$

[7] To see this, it suffices to express c_t and c_τ as in equation (3) to recover λ_{jt} from observables, given $\lambda_{j\tau} = 0$.

Then λ_t is identified using the moment condition across all unconstrained markets τ

$$E\left(\omega_\tau\left(\delta, \lambda_t\right)\right) = 0 \tag{4}$$

In the current analysis this will allow to exploit both the variation across regulated and unregulated drugs within regulated markets (covered and pure OTCs before 2008) and the variation across regulated and unregulated markets for the same drug (before and after delisting). The additional assumption posits that the marginal cost is the sum of time-invariant drug effects, time fixed effects and an additive uncorrelated deviation: $c_{jt} = \phi_j + \alpha_t + \omega_{jt}$. This cost structure should capture the main determinants of marginal costs: observed and unobserved drug quality is captured by drug fixed effects and other observable drug characteristics (active ingredient, therapeutic form, etc.); market-specific effects proxy for factors that make marginal costs fluctuate over time, due to changes in packaging and distribution costs that might differ between the coverage and the OTC phase (Noel and Magnien, 2008)[8].

4 Identification and Estimation

The first step of the analysis relies on the estimation of demand. Identification of random coefficient logit models on aggregate data is based on moment conditions between the structural demand error ζ_{jt} and some instrumental variables (BLP, 1995, and Nevo, 2000), which are needed to account for the endogeneity due to the fact that prices are correlated with unobserved demand factors ζ_{jt} (Berry, 1994; BLP, 1995). In the absence of data on costs, the instruments used for the analysis consist in variables that are likely to proxy for them, i.e. determining prices without being correlated with demand shocks (as in the usual identification condition). A first set of instruments include the predicted values from the regression of prices on exchange rates between US dollars, Euros and GB Pounds and firm dummies: these are likely to capture the expected costs from international delocalization of research and production, which is common in the pharmaceutical industry, but may be more important for some firms than for others. The wage in the pharmaceutical sector in France and the producer price index (interacted with drug characteristics) are used to proxy

[8]See Dubois and Lasio (2014) for a broader discussion and for proofs of less strict assumptions needed for identification in more general settings.

for some more aggregate supply shocks that are likely to affect drugs differentially. In line with the approach proposed by BLP (1995), IVs include measures of the degree of competition in the market: however, rather than the characteristics of competing products, excluding those produced by the same firm, the number of competing drugs sharing similar characteristics is used, namely the same active ingredient, indication and side effect (Stern, 1996)[9]. As a proxy for the unobserved quality of the drug, the level of coverage is used, since its level is based on the SMR, which indirectly determines prices.

This heterogeneous set of instruments predicts prices well and its validity is confirmed in first stage regressions and by standard tests of validity[10]. However, in order to improve precision, efficiency and robustness of the estimates, following BLP (1999) and Reynaert and Verboven (2014), approximations of optimal instrumental variables (Chamberlain, 1987) are used. As shown in Reynaert and Verboven (2014) these optimal instruments can be approximated 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 market-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).

Then, estimation can be performed on aggregate data with Generalized Method of Moments (GMM) using the moment condition

$$E\left[\zeta_{jt}\left(\theta\right)|\mathbf{x}_t, \mathbf{w}_t\right] \tag{5}$$

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 potentially jointly with the supply equation as in BLP (1995)[11].

When estimating demand, a crucial issue is the market definition. The market size used here is the number of standard units potentially consumed yearly by the population affected by venous insufficiency-related disorders. Venous insufficiency in France is estimated to affect around 15 million people, who represent the potential set of patients to be treated with phlebotonics. The

[9]BLP-type IVs were used but did not prove valid. Similarly, drug fixed effects (as suggested by Nevo, 2000 and 2001) explain well prices but their large number make them weak instruments, though the results obtained when using drug dummies were qualitatively very similar to those reported below.

[10]The Sargan test passes when these IVs are used in a simple Logit estimation.

[11]Reynaert and Verboven (2014) 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 for the computation of optimal instruments produces negligible bias in the demand estimates.

average treatment comprises 2 to 4 standard units per day, during a 3-month period. This leads to a market size of 4.5 billion standard units/year. The monthly figure is recovered by accounting for the seasonality of the condition and sales, i.e. allocating the annual quantity on the basis of the average share of sales in each month observed in the data.

The set of drug characteristics included in the demand specification (see Table 4) aims at capturing all observable measures of quality and includes the brand type (branded vs. generic), the therapeutic form (captured by the dummy for liquid), indications and side effects (four dummies of indication for venous insufficiency, haemorrhoidal disease, capillary fragility and vision impairment, a dummy for gastric disorder adverse effects, and the total number of distinct indications and side effects), a dummy for products based on plant extracts (phytotherapic drug) and molecule fixed effects. Date controls are also included.

Table 4: Variables: summary statistics

	Mean	St.Dev.	Min.	Max.
Market share	0.004	0.016	$2.2\text{x}10^{-7}$	0.294
Price Covered * After 2008	0.187	0.132	0.047	1
Price Other	0.217	0.174	0.030	2.5
Branded	0.645	0.479	0	1
Liquid	0.159	0.366	0	1
Indication: Venous Insufficiency	0.955	0.208	0	1
Indication: Haemorrhoidal Disease	0.819	0.385	0	1
Indication: Capillary Fragility	0.419	0.494	0	1
Indication: Vision Impairment	0.075	0.264	0	1
Nb. of Indications	2.394	0.796	1	4
Side Effect: Gastric Disorders	0.814	0.389	0	1
Nb. of Side Effects	1.509	1.330	0	6
Phytotherapic drug	0.262	0.439	0	1

Once demand is estimated and substitution patterns are identified, price-cost margins by market can be computed. Under the first model, identification of price-cost margins directly stems from the inversion of the matrix of derivatives of demand and assumptions on the price competition game played by firms. Identification under the constrained maximization model requires, instead, more restrictions on the form and evolution of marginal costs. In specific, marginal costs are assumed to be drug-specific and to change over time only according to an aggregate trend captured by date dummies. Identification is then possible thanks to variation across drugs, covered or pure OTCs,

and within drugs, observing the same drug when its price is regulated and when it is delisted (before-after). These two forms of variation allow the model to estimate marginal costs, retrieve price-cost margins at each date and infer if the constraints posed by regulation actually bind and for which products.

5 Results

5.1 Demand and Elasticities

Estimates reported in Table 5 are the result of a specification search that included many controls as a starting point (mainly dummies for specific indications and side effects), to arrive to the more parsimonious specification chosen, which should capture the most important determinants of demand and proved to be robust to perturbations in the set of regressors, market size and estimation details. Estimation is based on simulated method of moments, using 100 normalized Halton draws (Train, 2003), tight tolerance levels for the nested fixed point algorithm and up to 50 starting values (Knittel and Metaxoglou, 2012).

The price variable is split: the variable "Price * Covered * After Delisting" refers to covered drugs after delisting, while the variable "Price * (1-Covered)" refers to pure OTC all through the period and covered drugs before 2008. The use of two different price variables aims at controlling for the potential shift in tastes (i.e. slope of the demand curve) for delisted phlebotonics and allows to estimate more precise substitution patterns[12]. Heterogeneity is controlled for with a normally distributed random coefficient on the price variables and on the brand type: preferences over other drug characteristics have been estimated as fairly homogeneous across the population in preliminary estimations and thus excluded from the final specification.

The results reported in Table 5 are in line with expectations. Brand-name drugs are preferred over generic versions (Dubois and Lasio, 2014, find the same for anti-ulcer drugs in France, while previous literature has documented it in several countries and therapeutic markets), and products in solid form (tablets, capsules, powders) over syrups. Being approved for several indications at the

[12] An alternative specification reported in Table 12 in Appendix uses four price coefficients for covered or OTC drugs, before and after delisting. The magnitude of the coefficients differs, but the relative size of the three coefficients grouped in the variable "Price * (1-Covered)" (price of covered products before delisting and of OTCs during the whole period) is comparable, thus making the current aggregation into a single price coefficient a good approximation for a more parsimonious specification.

same time seems to matter more than having specific indications, while for side effects the opposite is true, as the sign on the coefficient for gastric disorders and the number of side effects suggest. Some molecules are perceived as being of higher quality, as indicated by the sign and magnitude of the (unreported) molecule fixed effects; in general, synthetic compounds are deemed superior to plants extracts (negative sign of the phytotherapic dummy). The coefficient associated to both prices is negative and highly significant, suggesting that price sensitivity is high and demand is elastic. Unsurprisingly, demand is more elastic for covered drugs after they are delisted in 2008, but heterogeneity in the disutility of price also increases (captured by the random coefficient denoted sigma in Table 5).

These demand estimates produce an average own-price elasticity across all products and periods of -5.9, though some dispersion is observed: the 25th percentile is -6.5 and the 75th -2.9. Own-price elasticities tend to increase over time, consistent with the increase in copayment to 100% in 2008. The increase is larger for delisted drugs (from -4 in 1997 to -7 in 2013) than pure OTC (from -2.7 to -3.7). Demand for generics is on average more elastic than demand for branded (-7.3 compared to -5.1), though median values are very close (-4.2 versus -4.3).

Tables 13, 14 and 15, reported in Appendix, display own- and cross-price elasticities for the top-selling drugs in 2004, 2006 and 2008. The figures are to be read as the percentage increase in quantity that the drug in row benefits from if the drug in column raises its price by 1%. Substitution patterns suggest that drugs are highly differentiated and consumers are brand loyal. As expected, the highest cross elasticities for all drugs are towards drugs with the highest market shares (Daflon, Endotelon and Ginkor). Also, substitution is based on molecule, but it is stronger across brand-name drugs (Veinamitol and Rheoflux are two brand names for molecule troxerutine, which has many generic versions available) than toward generics and molecules are heterogeneous (the substitution between branded and generic versions of diosmin is much lower, as the figures for Diovenor and Diosmin BGA indicate). On average, cross-price elasticities decrease over time and remain high only toward top-selling drugs after delisting. Interestingly, they increase between covered and pure OTC drugs after delisting, indicating an increased substitution between the two groups of drugs: this suggests that insurance coverage was perceived by patients and doctors as a signal of the higher quality of covered drugs; when it was removed, the two groups were perceived as more similar and hence closer substitutes.

Table 5: Demand for phlebotonics, 1997-2013

	mean	sigma
Price * Covered * After Delisting	-39.48***	14.62***
	(5.36)	(1.67)
Price * (1-Covered)	-16.73**	6.23**
	(7.15)	(1.97)
Branded	1.00***	1.05
	(0.13)	(1.36)
Liquid	-1.07***	
	(0.19)	
Indication: Venous Insufficiency	-2.37**	
	(1.00)	
Indication: Haemorrhoidal Disease	-4.83***	
	(0.31)	
Indication: Capillary Fragility	-2.87***	
	(0.56)	
Indication: Vision Impairment	1.23**	
	(0.60)	
Nb. of Indications	3.12***	
	(0.22)	
Side Effect: Gastric Disorders	-0.85***	
	(0.20)	
Nb. of Side Effects	0.36***	
	(0.06)	
Phytotherapic Drug	-4.93***	
	(0.28)	
Obj. function value	0.000	
Observations	4,379	
Molecule FE	Yes	
Date FE	Yes	

Notes: Standard error in parentheses. Significance levels: *** : 0.01, ** : 0.05. Optimal IVs are used, based on the first stage instruments described in section 4 "Identification and Estimation". The column "sigma" reports the normally distributed random coefficient capturing heterogeneity in the taste for the variable it refers to.

5.2 Price-cost margins and marginal costs

Once substitution patterns are identified, price-cost margins can be computed under assumptions on the game played by firms described in the models in section 3.2.1 and 3.2.2. The free-pricing model is suitable for all drugs after delisting (2008-2013), when price regulation is removed. At the same time, it might be appropriate even before delisting if price regulation does not affect the behavior of firms. The constrained model applies to covered drugs between 1997 and 2007, when price regulation might have constrained the pricing decisions of manufacturers of covered phlebotonics. Identification of margins under the constrained model requires restrictions on marginal costs, as well as knowledge of unconstrained and potentially constrained markets and drugs.

All markets (periods) after delisting occurred on January 1st 2008 can be considered as unconstrained. Ideally, all covered drugs might be constrained between 1997 and 2007, accounting for more than half of the drugs present on the market in each year (see Table 1). However, it is economically more reasonable to think that some drugs rather than others might be more affected by regulation. Expensive drugs with a high market share should be more constrained, especially if subject to competitive pressure by substitute drugs, where substitution is mainly driven by sharing the same or a similar molecule (as cross-price elasticities suggest). Indeed, highly-priced drugs are likely to be of high quality and thus have high costs and are those which would set an even higher price in the absence of regulation to gain more margin. Following this criterion, generics can be excluded and 7 brand-name drugs remain. They include branded versions of molecules subject to generic competition (Diovenor tablets and Veinamitol powder), drugs based on combinations of such molecules (Daflon tablets, Ginkor capsules and Cyclo 3 capsules), phytotherapic drugs based on plant extracts with many pure OTC substitutes (Endotelon tablets and Esberiven vials). In addition, these drugs are more likely to have been constrained in years when revision of prices or level of coverage took place. This excludes years before 2000. The final set of potentially constrained drugs is listed in Table 6, while the dates of price revisions and the specific constraints are reported in Table 16 in Appendix.

The marginal cost is modeled to be linear in a drug fixed effect, which captures the observed and unobserved time-invariant quality of each product, a form effect, which controls for different costs in the production of solid or liquid forms of drugs sold under different formats (tablets, powders,

Table 6: Potentially constrained drugs

Drug		Molecule	Average Price	Average Share	Main Unconstrained Substitutes
Cyclo 3	capsules	Ruscus, Hesperidin, Ascorbic Acid	0.22	0.02	Bicirkan Veinobiase
Daflon	tablets	Diosmin, Hesperidin	0.23	0.15	Diosmin generic Cemaflavone
Diovenor	tablets	Diosmin	0.35	0.01	Diosmin generic
Endotelon	tablets	Vitis Vinifera	0.24	0.08	Opo-Veinogene Elusanes Vigne Rouge
Esberiven	tablets	Melilotus, Rutoside	0.20	0.03	Veliten Vincarutine
Ginkor	capsules	Ginkgo, Troxerutine, Heptaminol	0.25	0.06	Rheoflux Troxerutine generic
Veinamitol	powder	Troxerutine	0.62	0.01	Rheoflux Troxerutine generic

capsules and vials), a date effect, to account for aggregate fluctuations in marginal costs common across firms and products, and an uncorrelated additive deviation: $c_{jt} = \phi_j + \alpha_t + \omega_{jt}$.

Table 7: Price-cost margins by year

Year	Covered		Pure OTC
	free	constr.	free
2000	35%	34%	45%
2001	34%	33%	53%
2002	32%	32%	54%
2003	34%	32%	52%
2004	32%	31%	48%
2005	33%	32%	48%
2006	31%	30%	49%
2007	32%	30%	51%
2008	21%		45%
2009	20%		41%
2010	20%		40%
2011	19%		41%
2012	20%		44%
2013	20%		41%

Notes: free: free pricing equilibrium, constr.: constrained pricing equilibrium. Margins as a percentage of price.

Estimated margins under free-pricing and constrained maximization are reported in Table 7 (column "free" and "constr.", respectively). On the whole, average price-cost margins for years when regulation is in place and active (as of the price revision dates reported in Table 16 in Appendix) are lower than margins estimated using the free-pricing method that disregards the

presence of regulation. The aggregate effect is not large, but it is actually driven by a small subset of drugs (5-7 drugs by year, out of 90-100 drugs present on the market). On average, pure OTC drugs are able to charge twice the margin as covered drugs, both before and after delisting and regardless of the model used (44% versus 22%), but dispersion is also higher across pure OTCs. In 2008, at delisting, all margins drop but more for delisted than pure OTCs. As expected, the price cuts associated to the revision of the level of coverage to 15% in March 2006 (increase in copayment to 85%) affect strongly all drugs subject to the constraints, and more than price revisions occurred in previous years. As Table 8 displays, the magnitude of the effect, though, varies across drugs, as well as the speed to which the price cuts translate into lower margins: most drugs are immediately affected in 2006 and see their margins drop dramatically (Daflon) or even halved in both years (Cyclo 3, Diovenor, Esberiven, Ginkor and Veinamitol), while others are constrained in 2007 only (Endotelon). Concerning price cuts occurred earlier, it is interesting to notice that, despite the price revisions, in some years some drugs do not seem to be constrained, confirming that price regulation might not necessarily bite. It is the case of Cyclo 3 in 2001, and to a lesser extent Daflon, Endotelon and Ginkor in 2000. Most times lower margins estimated by the constrained model can be explained by drops in prices. Other times, however, constrained margins do not differ too much from free margins even in the presence of such drops or, conversely, constrained margins are lower despite negligible changes in prices. In these cases, substitution effects across drugs may explain how firms could gain higher or lower margins as a response to higher or lower prices of competitors. This seems to be the case of Cyclo 3, Endotelon and Ginkor in 2001 that, despite their drop in price, managed to exploit the even higher decrease in the price of their closest competitor Daflon to gain high margins.

Marginal Costs of pure OTCs are on average lower than marginal costs of covered drugs, both before and after delisting, confirming their lower quality. This is true regardless of the model used (free pricing or constrained maximization), though the constrained model provides higher estimates of marginal costs for covered drugs. Dispersion is higher for pure OTCs, both across markets and across drugs: they tend to fluctuate more across the years and range from nearly zero for some drugs in some periods to values above 2 US $ per standard units; conversely, marginal costs of covered drugs are never above 1. On the whole, marginal costs of pure OTC drugs increase since 2008, while the opposite is true for covered phlebotonics when they are delisted, consistent with the

Table 8: Price-cost margins of constrained drugs

Drug		2000	2001	2002	2003	2004	2005	2006	2007
Cyclo 3	*free*	28%	29%	30%	29%	29%	29%	33%	35%
	constr.	23%	28%	-	-	15%	27%	17%	18%
Daflon	*free*	27%	29%	32%	33%	34%	34%	38%	40%
	constr.	23%	18%	27%	17%	24%	17%	25%	26%
Diovenor	*free*	14%	14%	15%	15%	14%	15%	17%	18%
	constr.	7%	10%	9%	8%	7%	8%	9%	9%
Endotelon	*free*	26%	28%	30%	32%	32%	33%	37%	38%
	constr.	23%	24%	-	16%	32%	32%	36%	31%
Esberiven	*free*	28%	30%	32%	34%	34%	34%	38%	40%
	constr.	15%	20%	9%	18%	8%	17%	20%	21%
Ginkor	*free*	26%	27%	28%	28%	28%	29%	32%	34%
	constr.	22%	24%	20%	14%	27%	22%	13%	19%
Veinamitol	*free*	11%	11%	11%	13%	9%	11%	11%	12%
	constr.	6%	6%	-	7%	5%	6%	7%	6%

Notes: free: free pricing equilibrium, constr.: constrained pricing equilibrium. Missing figure under the constrained model when no constraint is assumed for that drug in that year.

downward trend in their prices at delisting. These results seem to suggest that coverage and price regulation tends to stabilize prices and costs, shielding covered drugs from demand fluctuations and competitive pressure on prices, while OTC drugs are more exposed to such uncertainty, reflected in the pattern of their prices and costs. On the other hand, the drop in prices for delisted drugs after 2008, which translates into lower marginal costs, points to the fact that this advantage of coverage and price regulation may not be innocuous and entails higher marginal costs: regulation may impose strict requirements to guarantee coverage, such as high and constant levels of quality, specific rules for packaging, continuous provision of information to the regulator. Meeting all of these requirements may be costly for the manufacturer.

5.3 Counterfactual equilibrium: prices, welfare and expenditures

The fact that during the coverage period margins estimated under the constrained model are often lower than margins computed under free pricing suggests that coverage and price regulation had some grip on influencing firms' behavior. Similarly, the pattern in prices and margins at delisting, especially for delisted phlebotonics, indicates that removing this regulation is inducing a reaction by all drugs on the market in a way that was not predicted ex-ante, i.e. with a significant drop in price especially for delisted drugs.

With such evidence at hand, it would be interesting to simulate the counterfactual equilibrium if coverage and price regulation were maintained after 2008, to test if the lower prices are due to change in the regulatory setting or are a consequence of the observed drop in demand. Unfortunately, simulating this counterfactual equilibrium requires strong assumptions on the prices that the regulator would set for the covered drugs: inferring the actual level chosen for each of them entails too much speculation. Also, it is not clear whether these prices would act as a binding price cap, as the entire equilibrium depends on the substitution of demand across drugs.

An alternative way to interpret the 2008 post-delisting situation is to simulate the counterfactual equilibrium before 2008 assuming that no drug at all in the class of phlebotonics was subject to price regulation and hence all prices were set freely. Indeed, the question arises of whether the constraints identified by the model translate into a price equilibrium different from the one that would have been observed without regulation and how demand would have reacted; eventually this scenario can be compared to the one observed after 2008.

To simulate the counterfactual price equilibrium in the absence of regulation, the method illustrated in section 3.2.2 combines estimates of demand, marginal costs and first-order conditions. The results are reported in Table 9 for the years in which the constraints imposed by regulation were estimated to be binding for manufacturers.

On average, the prices set by firms when free to do so would be slightly lower than those actually observed, but this average aggregates some major differences. Covered drugs would set a higher price than the average, but anyway lower than the regulated price, fairly stable over time; pure OTC drugs would set a higher price than the one observed in the data for the same periods, but significantly lower than drugs on the coverage list. This prediction is in line with the price pattern observed after 2008, with delisted drugs dropping their prices and pure OTCs increasing it. Also, it suggests that manufacturers strategically react to the behavior of competitors when they can, but competitive pressure affects the final price equilibrium. All in all, the price level is consistent with the actual and perceived quality of drugs: the higher price of phlebotonics on the coverage list, which were approved for coverage on the basis of their medical benefit, reflects their higher quality (and higher marginal costs) with respect to drugs that were never covered. The same pattern would be observed in the absence of regulation, with high price signaling high quality.

Table 9: Observed and counterfactual prices for constrained drugs

		2000	2001	2002	2003	2004	2005	2006	2007
Cyclo 3	*observed*	0.23	0.22	0.22	0.22	0.22	0.22	0.19	0.19
	counterf.	0.25	0.26	0.16	0.13	0.13	0.12	0.11	0.07
Daflon	*observed*	0.25	0.23	0.22	0.21	0.21	0.21	0.18	0.18
	counterf.	0.25	0.21	0.27	0.26	0.13	0.10	0.19	0.29
Diovenor	*observed*	0.44	0.41	0.40	0.39	0.39	0.39	0.34	0.33
	counterf.	0.43	0.10	0.21	0.17	0.33	0.32	0.12	0.17
Endotelon	*observed*	0.27	0.21	0.20	0.19	0.22	0.22	0.17	0.16
	counterf.	0.14	0.16	0.13	0.12	0.13	0.11	0.33	0.23
Esberiven	*observed*	0.23	0.21	0.20	0.19	0.19	0.19	0.17	0.16
	counterf.	0.15	0.16	0.13	0.12	0.13	0.12	0.33	0.23
Ginkor	*observed*	0.26	0.25	0.24	0.24	0.24	0.24	0.20	0.20
	counterf.	0.24	0.21	0.24	0.30	0.13	0.13	0.24	0.17
Veinamitol	*observed*	0.64	0.60	0.60	0.58	0.58	0.58	0.51	0.50
	counterf.	0.65	0.61	0.64	0.59	0.49	0.48	0.49	0.55
Covered drugs	*observed*	0.26	0.25	0.26	0.26	0.26	0.26	0.27	0.26
	counterfactual	0.25	0.23	0.24	0.24	0.20	0.17	0.25	0.25
Pure OTC drugs	*observed*	0.19	0.15	0.15	0.20	0.22	0.16	0.17	0.14
	counterfactual	0.20	0.18	0.18	0.21	0.27	0.24	0.19	0.16

Notes: Prices in US $ per standard unit.

Turning to counterfactual prices of constrained drugs, a closer inspection sheds some light on the heterogeneity of their price setting decisions. Variation is high both across drugs and across periods, confirming the role of price regulation in stabilizing and reducing dispersion of prices. Table 9 shows how several of these drugs would set a higher price in some periods, though sometimes the price would be lower or close to the one set by the regulator: this is especially true for years when constraints are not binding (in line with the evidence reported in Table 8) or close substitute drugs are especially constrained (for example, Ginkor in 2001 and Endotelon in 2006). However, without the protective role of regulation, some of these drugs would be forced to set a significantly lower price than the regulated one (Endotelon in all periods, Cyclo 3 since 2002, Esberiven before 2006). These are the drugs that would suffer the fiercer competition of several cheaper OTC substitutes (drugs based on similar molecules that were never covered), which pose less competitive pressure with coverage and price regulation.

The drop in prices for most drugs reflects the higher elasticity of demand in the counterfactual scenario without coverage and price regulation. Counterfactual demand drops substantially for most drugs, both covered and pure OTCs, with generics losing most of their market share. Consistent

with the findings in demand estimates (Table 5), consumers have a preference for brand-name drugs and in the absence of coverage regulation switch to branded versions: the counterfactual price of generics, though lower than the observed one on average, is not low enough to guarantee sales. However, a handful of drugs manage to keep their sales and even sell more than with coverage and price regulation. These are high-quality/high-price drugs, covered until 2008, which would sell even more in the absence of coverage and price regulation and despite sometimes setting a higher price than the regulated one. Eventually, the counterfactual total quantity does not differ much from the observed one due to the sales of these drugs.

Total expenditures under the counterfactual scenario are lower in some years, in others higher than total expenditures in drugs under coverage and price regulation (Table 10), depending on the sales of expensive drugs relative to cheaper ones. The effect on welfare of coverage and price regulation is reported in Table 10. With the data used, only the sum of the consumer surplus and the surplus of the public health insurer can be recovered: the effect on this measure of welfare is negative (in all years except 2003 and 2004). This is due to lower prices under the counterfactual scenario, with consumers buying cheaper branded drugs at the detriment of generics. However, this aggregate measure does not capture the distribution of this welfare between the user and the payer. When drugs are covered, the user and the payer may not coincide perfectly: for covered drugs bought with a prescription, users only partially pay for the drugs they consume. This would translate into higher consumer surplus relative to the surplus of the insurer. Without coverage, the whole price, though lower, is paid out of pocket by the consumer, implying a potentially lower consumer surplus as compared to the case with insurance coverage.

Table 10: Expenditures and change in surplus

Year	Total expenditures		Change in surplus
	observed	counterfactual	from regulation
2000	37073	34461	-0.5%
2001	28800	30183	-0.5%
2002	26366	29696	-0.5%
2003	77443	43158	+0.2%
2004	100000	64544	+0.2%
2005	23118	20009	-0.1%
2006	40011	38401	-0.5%
2007	19772	24627	-0.5%

Notes: Total expenditures in thousand US $. Surplus is the sum of the surplus of consumers and public insurance.

The counterfactual demand and prices uncover interesting features of the role that coverage and price regulation is playing. It stabilizes prices, though at the expense of imposing higher costs on regulated drugs; it guarantees some level of sales for certain types of drugs, like generics; it increases the perceived quality of covered drugs as compared to never covered pure OTCs. When coverage and price regulation is removed in the counterfactual scenario, these effects disappear and the observed fluctuating prices and redistribution of demand arise due to increased competition and demand elasticity.

These effects help explain the situation observed after the 2008 delisting. The model predicts well the observed price evolution, with a general price drop, driven by the reduction in prices of delisted drugs, which outweigh the increase in price of never covered drugs. Similarly, it explains how most drugs lose sales while few high-price/high-quality drugs manage to keep them. However, the model underestimates the general drop in prices and overestimates the sales of these drugs, eventually predicting a fairly stable total demand. Potentially, the true demand elasticity was much higher than the one estimated by the model and this might explain the underestimation of the drop in both prices and demand. In addition, despite lower estimated marginal costs of covered drugs at delisting, the model may be overestimating their level. For instance, when drugs are removed from insurance coverage, manufacturers stop or reduce substantially advertizing their products to doctors (so-called detailing): this may result both in lower costs and in lower sales, affecting both prices and demand. Without data on detailing, it is not possible to control for this effect and the counterfactual assumes detailing unchanged, which would also explain the imperfect prediction of the model[13].

6 Conclusion

This work focuses on the impact that health insurance coverage of pharmaceuticals and its removal generate on demand and prices. As previous literature has shown, the consequences of policies that increase copayment of drugs often go beyond the automatic effect of reducing sales and expenditures for the public system: switching by patients from drugs subject to high copayments towards drugs

[13]The instrumental variable approach used in demand estimation controls for the endogeneity of prices and is able to capture the effect of any omitted variable that may be correlated with the price, so the lack of data on detailing should not bias the estimated price coefficient.

with more generous coverage status sometimes dilute or completely wipe out any savings of public money; at the same time, the effects on consumption and health outcomes are not obvious.

This work explores the impact of delisting of drugs by carrying out a structural analysis allowing to simulate the counterfactual equilibrium without coverage and price regulation, in order to infer which role it plays and disentangle the effects due to demand shifting and the strategic reactions of firms. In doing so, it overcomes the limitations of previous reduced-form evidence, which attributes the entire effects observed on sales and expenditures to the regulatory change and cannot exclude that changes in demand or costs contribute to the final result. The role of regulation is accounted for in the model of the supply side by assuming that pricing decisions of firms *may* be affected by regulation, which *potentially* poses constraints on some drugs. The variation across drugs subject to different regulatory regimes and the change in these regimes across time, combined with assumptions on costs and on the game played by firms in the market, allow to identify how binding the constraints posed by regulation actually are.

The analysis for the delisting of oral phlebotonics, occurred in France in 2008, uncovers interesting effects. Regulation stabilizes prices of covered drugs and ensures sales for generics. Removing coverage and price regulation slightly decreases prices on average and reduces sales for most drugs. However, the variation is high, and redistribution of demand arises due to increased competition and demand elasticity. In specific, demand for delisted drugs becomes more elastic and cross-price elasticity between covered drugs and pure OTC drugs increases, indicating that the two groups become closer substitutes once delisting occurs. This suggests that insurance coverage was perceived as a certification of the higher quality of listed drugs and, when it was removed, the perceived quality difference between the two groups decreased, prompting the different price reaction observed after the 2008 delisting. The model predicts the general price drop, coming from a significant decrease in the price of delisted drugs and an increase in the price of pure OTC drugs. Also, it explains how top-selling phlebotonics (high-price/high-quality drugs) manage to keep their sales at the detriment of generics, though it underestimates the magnitude of the drop in both demand and prices observed at delisting.

Some caveats anyway apply. First, for the analysis above to be correct, the use of wholesale data imposes that the behavior of the pharmacist must be constant across time and drugs and unaffected by regulation. The increase in the margin set by the pharmacists at delisting of other drugs before

2008 may suggest that pharmacists do react to the regulatory change. However, the involvement of the union of pharmacists to avoid dramatic increases in margins of delisted phlebotonics suggests that the current assumption should be a fair approximation of reality. Retail level data would be needed but are not available to date. Second, the static model used takes entry and exit decisions of firms as exogenous and cannot accommodate a situation where firms exit as a consequence of delisting. Some exits are indeed observed at delisting, though they are due to low-selling drugs, while major products are still on the market today. Future research will address these limitations.

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Appendix

Table 11: The market: monthly (2009-2013)

Year	Month	Quantity in 1000 SU	Revenue in 1000 US $	Average Price in US $ per SU
2009	January	140,296	15,161	0.19
2009	February	114,470	12,404	0.19
2009	March	118,322	12,890	0.18
2009	April	155,507	18,211	0.18
2009	May	115,037	12,573	0.18
2009	June	160,115	18,036	0.19
2009	July	155,056	17,597	0.18
2009	August	74,484	8,915	0.18
2009	September	143,606	14,906	0.20
2009	October	133,190	15,820	0.18
2009	November	81,502	9,265	0.18
2009	December	106,987	12,701	0.18
2010	January	115,787	13,484	0.19
2010	February	81,758	9,612	0.18
2010	March	115,914	14,758	0.19
2010	April	183,966	18,749	0.18
2010	May	104,310	11,847	0.19
2010	June	152,790	17,963	0.19
2010	July	165,947	19,661	0.19
2010	August	61,674	7,802	0.19
2010	September	143,370	16,102	0.19
2010	October	108,220	13,519	0.19
2010	November	66,754	8,303	0.20
2010	December	86,322	10,840	0.19
2011	January	99,041	12,795	0.20
2011	February	85,322	10,514	0.20
2011	March	113,460	14,437	0.20
2011	April	135,983	17,131	0.20
2011	May	122,953	15,207	0.20
2011	June	129,449	16,077	0.20
2011	July	122,291	15,675	0.19
2011	August	52,485	6,884	0.20
2011	September	110,694	13,458	0.20
2011	October	111,414	15,179	0.20
2011	November	64,041	8,290	0.19
2011	December	80,067	10,646	0.19
2012	January	100,287	13,869	0.19
2012	February	75,052	9,545	0.19
2012	March	109,684	14,194	0.19
2012	April	122,587	17,047	0.19
2012	May	95,574	11,723	0.19
2012	June	116,364	15,390	0.19
2012	July	122,077	16,822	0.19
2012	August	52,748	6,977	0.20
2012	September	123,357	17,396	0.19
2012	October	67,052	8,943	0.20
2012	November	84,855	11,993	0.20
2012	December	50,276	6,905	0.19
2013	January	87,767	12,504	0.20
2013	February	64,067	8,414	0.20
2013	March	136,006	20,254	0.20
2013	April	72,195	9,719	0.20

Table 12: Demand for phlebotonics, 1997-2013: alternative specification

	mean	sigma
Price * Covered * Before Delisting	-15.31***	5.15***
	(3.40)	(1.86)
Price * Pure OTC * Before Delisting	-8.51**	3.01**
	(3.62)	(1.33)
Price * Covered * After Delisting	-51.16***	18.79***
	(6.81)	(2.71)
Price * Pure OTC * After Delisting	-17.79***	6.09**
	(6.30)	(2.22)
Branded	1.10***	0.07
	(0.12)	(0.23)
Liquid	-1.41***	
	(0.12)	
Indication: Venous Insufficiency	-1.98***	
	(0.64)	
Indication: Haemorrhoidal Disease	-5.04***	
	(0.61)	
Indication: Capillary Fragility	2.80***	
	(0.33)	
Indication: Vision Impairment	-0.29	
	(0.23)	
Nb. of Indications	0.04	
	(0.08)	
Side Effect: Gastric Disorders	-6.05***	
	(0.55)	
Nb. of Side Effects	-1.49***	
	(0.58)	
Phytotherapic Drug	-1.41***	
	(0.58)	
Obj. function value		0.000
Observations		4,379
Molecule FE		Yes
Date FE		Yes

Notes: Standard errors in parentheses. Significance levels: *** : 0.01, ** : 0.05. Optimal IVs are used, based on the first stage instruments described in section 4 "Identification and Estimation", plus drug fixed effects. The column "sigma" reports the normally distributed random coefficient capturing heterogeneity in the taste for the variable it refers to.

Table 13: Elasticities for top-selling drugs: 2004

	CYCLO 3 capsule	DAFLON tablet	DIOVENOR tablet	DIOSMIN BGA tablet	ENDOTELON tablet	ESBERIVEN vial	GINKOR capsule	RHEOFLUX powder	VEINAMITOL powder	TROXER. MAZ powder
CYCLO 3 capsule	-3.585	0.509	0.074	0.048	0.549	0.144	0.399	0.024	0.097	0.058
DAFLON tablet	0.108	-2.962	0.069	0.046	0.538	0.142	0.390	0.021	0.086	0.053
DIOVENOR tablet	0.131	0.576	-7.097	0.074	0.656	0.148	0.499	0.101	0.408	0.211
DIOSMIN BIOGARAN tablet	0.102	0.457	0.088	-5.000	0.506	0.124	0.376	0.038	0.154	0.160
ENDOTELON tablet	0.111	0.510	0.074	0.048	-3.185	0.144	0.401	0.024	0.099	0.059
ESBERIVEN vial	0.104	0.484	0.060	0.042	0.516	-2.878	0.372	0.017	0.067	0.043
GINKOR capsule	0.113	0.517	0.079	0.050	0.560	0.145	-3.543	0.027	0.110	0.065
RHEOFLUX powder	0.125	0.522	0.297	0.094	0.633	0.121	0.505	-12.101	1.144	0.637
VEINAMITOL powder	0.125	0.522	0.297	0.094	0.633	0.121	0.505	0.283	-11.239	0.637
TROXERUTINE MAZAL powder	0.100	0.423	0.202	0.128	0.502	0.102	0.393	0.208	0.839	-9.318

Table 14: Elasticities for top-selling drugs: 2006

	CYCLO 3 capsule	DAFLON tablet	DIOVENOR tablet	DIOSMIN BGA tablet	ENDOTELON tablet	ESBERIVEN vial	GINKOR capsule	RHEOFLUX powder	VEINAMITOL powder	TROXER. MAZ powder
CYCLO 3 capsule	-3.098	0.394	0.035	0.039	0.436	0.110	0.302	0.011	0.052	0.041
DAFLON tablet	0.087	-2.636	0.034	0.038	0.431	0.109	0.297	0.011	0.049	0.039
DIOVENOR tablet	0.101	0.440	-5.865	0.073	0.502	0.116	0.357	0.026	0.116	0.110
DIOSMIN BIOGARAN tablet	0.084	0.366	0.055	-5.312	0.420	0.095	0.301	0.028	0.129	0.180
ENDOTELON tablet	0.088	0.395	0.036	0.040	-2.781	0.110	0.303	0.012	0.053	0.042
ESBERIVEN vial	0.084	0.378	0.031	0.034	0.416	-2.522	0.286	0.009	0.042	0.032
GINKOR capsule	0.089	0.399	0.037	0.041	0.444	0.111	-3.094	0.012	0.057	0.046
RHEOFLUX powder	0.104	0.445	0.082	0.120	0.522	0.111	0.380	-9.389	0.207	0.226
VEINAMITOL powder	0.104	0.445	0.082	0.119	0.522	0.111	0.380	0.045	-9.224	0.226
TROXERUTINE MAZAL powder	0.100	0.424	0.094	0.203	0.504	0.102	0.372	0.060	0.275	-10.386

Table 15: Elasticities for top-selling drugs: 2008

	CYCLO 3 capsule	DAFLON tablet	DIOVENOR tablet	DIOSMIN BGA tablet	ENDOTELON tablet	ESBERIVEN vial	GINKOR capsule	RHEOFLUX powder	VEINAMITOL powder	TROXER. MAZ powder
CYCLO 3 capsule	-4.477	0.784	0.044	0.025	0.265	0.181	0.557	0.005	0.070	0.033
DAFLON tablet	0.123	-4.289	0.046	0.027	0.256	0.190	0.599	0.006	0.083	0.041
DIOVENOR tablet	0.122	0.810	-4.912	0.026	0.259	0.188	0.587	0.006	0.079	0.038
DIOSMIN BIOGARAN tablet	0.077	0.516	0.029	-3.259	0.160	0.120	0.387	0.005	0.064	0.050
ENDOTELON tablet	0.089	0.548	0.031	0.018	-1.678	0.123	0.340	0.002	0.025	0.009
ESBERIVEN vial	0.125	0.836	0.046	0.027	0.252	-5.133	0.616	0.007	0.089	0.044
GINKOR capsule	0.130	0.886	0.049	0.030	0.235	0.208	-5.480	0.008	0.113	0.060
RHEOFLUX powder	0.134	1.004	0.054	0.040	0.144	0.244	0.916	-10.686	0.261	0.175
VEINAMITOL powder	0.134	1.006	0.054	0.040	0.142	0.245	0.922	0.019	-10.610	0.179
TROXERUTINE MAZAL powder	0.123	0.964	0.051	0.061	0.095	0.239	0.961	0.025	0.349	-13.526

Table 16: Regulatory revision dates

Date	Price revision details	Constraints
Oct 1999	Price decreased by a few French Francs per box: all drugs	2000: 7
Nov-Dec 2000	Price decreased by a few French Francs per box: all drugs	2001: 7
Mar 2001	Price revision for of Veinamitol (-0.8 French Francs/box)	
Oct-Nov 2001	Price revision for:	2002: 4
	Daflon (-2.2 French Francs/box)	
	Diovenor (-2.3 French Francs/box)	
	Esberiven (-1.4 French Francs/box)	
	Ginkor (-0.7 French Francs/box)	
Oct-Dec 2002	Price revision for:	2003: 6
	Daflon (-0.18 Euros/box)	
	Diovenor (-0.16 Euros/box)	
	Endotelon (-0.5 Euros/box)	
	Esberiven (-0.16 Euros/box)	
	Ginkor (-0.15 Euros/box)	
	Veinamitol (-0.08 Euros/box)	
Apr 2004	SMR reassessment of phlebotonics starts	2004: 7
Jun 2005	SMR reassessment of phlebotonics ends	2005: 7
Jan 2006	Reimbursement rate is reduced from 35% to 15%	2006: 7
Mar 2006	Price of all drugs decreased by 12% on average	

Notes: price refers to wholesale price per box

Drugs: Cyclo 3 capsules, Daflon tablets, Diovenor tablets, Endotelon tablets, Esberiven vials, Ginkor capsules, Veinamitol powder

1 French Franc corresponds to 0.19 US $ and 0.15 Euros

Revisions occurring at the end of the year are likely to produce effect during the following solar year