Launching Prices for New Pharmaceuticals in Heavily Regulated and Subsidized Markets

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LAUNCHING PRICES FOR NEW PHARMACEUTICALS IN HEAVILY REGULATED AND SUBSIDIZED MARKETS

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ABSTRACT

This paper provides empirical evidence on the explanatory factors affecting introductory prices of new pharmaceuticals in a heavily regulated and highly subsidized market. We collect a data set consisting of all new chemical entities launched in Spain between 1997 and 2005, and model launching prices. We found that, unlike in the US and Sweden, therapeutically "innovative" products are not overpriced relative to "imitative" ones. Price setting is mainly used as a mechanism to adjust for inflation independently of the degree of innovation. The drugs that enter through the centralized EMA approval procedure are overpriced, which may be a consequence of market globalization and international price setting.

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1.   INTRODUCTION

Previous studies, detailed below, have documented price competition among patented pharmaceuticals in the US: introductory prices are higher for innovative pharmaceuticals which are priced higher than existing substitutes, and high introductory prices tend to fall over time as more competitors enter the therapeutic market. These results are consistent with Dean's (1969) optimal pricing strategies for new products.

Lu and Comanor (1998) modelled launch prices of 144 new pharmaceuticals introduced in the United States (US) between 1978 and 1987, relative to existing substitutes (LC model). They conclude that therapeutically "innovative" pharmaceuticals are introduced under a skimming strategy (high introductory prices, quality-based competition), while "imitative" pharmaceuticals are introduced under a penetration strategy (low introductory prices, price competition). The number of branded substitutes has a negative effect on actual launch prices and on subsequent price increases in the US.

Similar results, observing some degree of therapeutic price competition, have been reported by other studies (Reekie, 1978; Philipson and Dai, 2003; Wiggins and Maness, 2004).

Despite the high prevalence of different forms of price/reimbursement regulation and public financing in most industrialized countries (only the United Kingdom, the US and Germany do not require centralized price approval) (OFT, 2007), the bulk of the empirical evidence on the pricing of new pharmaceuticals mainly refers to the US, where market prices prevail.

The study by Ekelund and Persson (2003) compared pricing strategies for new pharmaceuticals in the price-regulated Swedish market and the US. Using identical explanatory variables as in the LC model for the regulated Swedish market, these authors conclude that launch price determinants of 218 new pharmaceuticals introduced in the Swedish (regulated) market between 1987 and 1997 are quite different. As in the US, Swedish introductory prices reflect the degree of therapeutic innovation, but all prices fall substantially over time for all products independently of their therapeutic gain (price increases are generally ruled out under the regulatory regime). That is, Swedish price regulation prevents penetration strategies for "imitative" pharmaceuticals. Also, unlike in the US market, in Sweden introductory and subsequent prices do not depend on the number of branded substitutes. These authors conclude that price regulation discourages price competition in this country.

In Canada, where pharmaceutical prices are regulated, Lexchin (2006) observed that new patented brand-name drugs introduced between 1994 and 2003 did not compete on price. Examining drugs competing for the treatment of hypertension – angiotensin converting enzyme inhibitors and angiotensin receptor blockers – in Canada from 1997 to 2003, Benda *et al* (2004) observed price decreases for new entrants in the same therapeutic class, but price increases when the new product is located in another therapeutic class.

Regulators in regulated systems may consider other factors than the degree of therapeutic innovation in their pricing/reimbursement negotiations, such as concern for budgetary impact (which depends on the expected number of prescriptions, and their co-payment rate), and other industrial policy goals (such as allowing higher prices for national firms, or attracting R&D investment), which need to be considered in the empirical model to explain introductory and subsequent prices. In addition to this, the authorization process for

new drugs has been progressively centralized in Europe. At present, some drugs are authorized by the European Medicines Agency (EMA) while others are authorized at national level. While the authorization process has been progressively centralized in Europe, the pricing process is still nationally based. Since 2004, most of biologics, as well as all new cancer drugs, HIV, diabetes and other conditions have to be centrally approved by EMA. The question is whether the centralized/decentralized pathways to the market are associated with higher or lower launching prices.

The purpose of this study is to identify and quantify the factors influencing the introduction of new pharmaceuticals in a heavily regulated and highly subsidized market, Spain, which represents the fifth European and the seventh world market according to the volume of pharmaceutical sales. We model the weighted average price of new pharmaceuticals in the period 1997-2005. Our hypothesis is that, as in the Swedish and US markets, the incremental efficacy or therapeutic value is a paramount determinant, but that price/reimbursement regulatory systems force a skimming pricing strategy for all products independently of their incremental efficacy. Furthermore, we hypothesize that government cost containment objectives and industrial policy goals are also key determinants of pricing strategies resulting from the price/reimbursement negotiation process.

The Spanish pharmaceutical market offers a prime example of a heavily regulated and publicly subsidized market. As in many industrialized countries, the market in Spain is centrally price-regulated (price-cap regulation, generic reference pricing, prices not inflation adjusted over time, and price updates rarely allowed) (Antoñanzas *et al*, 2007). A public agency of the Ministry of Health is responsible for price setting and for funding conditions of public insurance coverage. The agency negotiates prices with the firm. Effective patient co-payment for pharmaceuticals is very low (user

rates account for less than 7% of the total expenditure in ambulatory health care system prescription pharmaceuticals). Previously to price setting, new drugs are approved. There are three different approval mechanisms: the only-for-Spain one; the mutual recognition mechanism (the drug is authorized in a particular country, and other European countries will recognize it automatically unless an objection is raised in 90 days); and the centralized approval mechanism through the EMA. As the Spanish National Health Service (NHS) is the main payer of ambulatory prescription pharmaceuticals (around 80% of sales are financed by the NHS), budgetary impact of new pharmaceuticals has been an increasing concern for the financial sustainability of the public health service. Cost containment policies have put great emphasis on maintaining traditional low prices, higher prices for new products being placed under increasing scrutiny, despite the fact that the increase in consumption is the main driver of the rise in expenditure (Puig-Junoy, 2004). Low regulated prices for old products have converted the Spanish market into an important source of parallel trade in the European Union.

The main contribution of this paper is to model the launching prices of new pharmaceuticals included in the NHS prescription drugs list, in a heavily regulated and highly subsidized market, considering that pricing any new pharmaceutical is the result of a negotiation between firm representatives and government representatives (regulatory agencies and public health service payers)[1], so that the regulatory agency, which is also in charge of the rating by therapeutic value, may use that rating to force prices downwards, particularly for those new drugs that have large potential markets. Of course the firm could in turn strategically select indications (market size) to maximize its objectives (Zaric, 2008).

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[1] The strategic wish of the innovative firm would be to launch new pharmaceuticals with high introductory prices, but the public regulator and the payers will try to force the price downwards if budgetary impact is a concern. Budgetary pressure will increase with the number of patients that are expected to receive subsidized prescriptions of that new pharmaceutical, and will decrease with higher co-payment rates.

This paper is structured as follows. We first discuss the economic framework and hypotheses. Equations and variables, data, and results are presented in the next two sections of the paper. The paper concludes with a section summarizing the main conclusions and policy implications.

2. ECONOMIC FRAMEWORK AND HYPOTHESES

In the price/reimbursement negotiation in any given country, Danzon *et al* (2005) hypothesized that launch of a new chemical entity (NCE) occurs when the government's maximum introductory offer price for it is equal to or higher than the firm's ask price (or reservation price).

In a country where prices of NCEs are regulated by a price-cap, price increases are not usually allowed over time, and prices are highly subsidized by public health care insurance (the main pharmaceutical buyer), our hypothesis is that the government's introductory offer price may be determined by the incremental health impact of the innovation and its impact on the incremental use of resources (incremental degree of innovation over existing close substitutes), the price of existing close therapeutic substitutes, the buyer's willingness to pay for incremental units of health outcomes, the budgetary impact of the new product for the buyer, and the contribution to other industrial policy goals of interest to the government. The firm's choice of ask price in the price/reimbursement process may be determined by the degree of innovation over close substitutes, indication for acute or chronic conditions, and the number of competitors (brands and generics), but also by the potential spillover effects of the price in that particular country when its prices are used as an external reference by other countries (Garcia Mariñoso *et al*, 2010).

The maximum relative introductory price of an NCE i, in a given price-regulated country, over that of its close substitutes c offered by the government (P^{max}_{ic}) may be higher if the new product has demonstrated superior health outcomes (efficacy, safety, side-effects, etc.) and if it reduces patient consumption of other health services (inpatient stays, physician visits, etc.). That is, P^{max}_{ic} will be higher for higher differences in efficacy ($E_i - E_c$); however, the premium price over that of close substitutes will be dependent on willingness to pay (WTP_i) for these incremental health outcomes. WTP_i may be time dependent (i.e., increasing over time as income and health value improve), and it may also be different for different types of conditions or illnesses (Becker *et al*, 2007). Changes in the use of other health service resources (i.e., hospital stays, medical visits, etc.) associated with the use of the NCE may be of importance to the government: the maximum relative price offered by the government may be higher when differences in cost offsets ($C_c - C_i$) are larger (Danzon *et al*, 2005). In countries where pricing/reimbursement decisions are based on the economic evaluation of NCEs, for a given price, differences in efficacy and in resource consumption result in an incremental cost-effectiveness ratio value. This has to be compared to the cap on the maximum incremental cost-effectiveness ratio[2]. This ratio represents the willingness to pay.

However, the government, acting also as the main payer for the use of the NCE, is highly concerned by the expected budgetary impact of the innovation. The cost-conscious government (public insurance agency) will offer an introductory price P^{max}_{ic} that will generate an expected maximum expenditure on the treatment of the illnesses for which the NCE i is indicated equal to or lower than its target pharmaceutical budget in the launch year. In the price/reimbursement negotiation, the government's concern for

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[2] The existence of incremental cost-effectiveness ratio thresholds would represent a particular case in the context of this hypothesis.

budgetary impact will be the result of the potential volume (Q_i) and the rate of co-payment in the insurance system for the pharmaceutical in the same therapeutic class (CO_i). That is, under the prevailing silo mentality in the cost containment policies of the country, the product of the dispensed quantity of the NCE i by its incremental price and by its co-payment rate should be less than or equal to the maximum budget increase considered acceptable by the government.

Notwithstanding, aside from health care policy goals, the government's maximum introductory price offer for the NCE may also be influenced by other industrial policy objectives of interest related to the production of product i (IP_i). In most industrialized countries, the price regulation mechanism for NCEs is used to provide non-market incentives through higher price premiums to firms that commit themselves to maintaining or increasing employment, and locating production and R&D investment in the country, or to those firms launching in their home country (OFT, 2007).

Then, the government's maximum offer price P^{max}_{ic} can be written as

$$P^{max}_{ic} = f \{(E_i - E_c),\ WTP_i,\ (C_c - C_i),\ Q_i,\ CO_i,\ IP_i\} \qquad (1)$$

The firm's ask price (or reservation introductory price) for an NCE i (P^{min}_{ic}) may be hypothesized to be adequately represented by the explanatory factors included in the unregulated Lu and Comanor model. In this model, the firm's choice of pricing strategy depends on the degree of innovation (incremental efficacy and changes in the use of resources; that is, $E_i - E_c$, and $C_c - C_i$), the anticipated number of repeated purchases (which are less likely for pharmaceuticals indicated for acute conditions, $ACUTE_i$), and the presence in the market of two types of rivals or competitors (branded substitutes and generic versions of substitutes) for product i ($COMP_i$), given that, assuming some buyers' price sensitivity, the indirect competition of substitutes sets limits to the monopoly power of the NCE. The

potential sales volume (Q_i) should also be an argument in the firm's asking price for a new NCE with an expected sign that is not determined a priori. On the one hand, the larger the potential market, the stronger the incentive of the firm to negotiate hard, pushing up prices; but on the other hand, the larger the potential market, the stronger the penalization imposed by the delay in terms of lost sales during the patent protection period.

Additionally, in the price/reimbursement negotiation process, P^{min}_{ic} may also be influenced by the potential spillover effects of the introductory price of i from parallel trade and external reference pricing (S_i). The European Union (EU) explicitly permits parallel trade between EU members. Regulated markets with low pharmaceutical prices are a source of parallel trade and a reference for those countries that increasingly use the lower prices in other countries to regulate prices in their own country (Kanavos and Costa-Font, 2005).

Then, the firm's ask price P^{min}_{ic} can be written as

$$P^{min}_{ic} = g \{(E_i - E_c), (C_c - C_i), ACUTE_i, COMP_i, S_i\} \qquad (2)$$

As we are interested in price determinants of effectively launched products, we assume that negotiation results in launch of the product at the introductory price P_{ic} over that of its close substitutes, which is equal to or higher than P^{min}_{ic} and equal to or lower than P^{max}_{ic}. Relative introductory prices as a result of the negotiating process will be influenced by the bargaining power of the firm launching the new product (B_i) when negotiating with the regulatory agency of the country (Bardey *et al*, 2010).

Then, the P_{ic} function can be written as

$$P_{ic} = h [P^{max}_{ic}\{(E_i - E_c), WTP_i, (C_c - C_i), Q_i, CO_i, IP_i\}; P^{min}_{ic}\{(E_i - E_c), (C_c - C_i), ACUTE_i, COMP_i, Q_i, S_i\}; B_i], \qquad (3)$$

with $P^{min}_{ic} <= P_{ic} <= P^{max}_{ic}$.

The reduced form for equation (3) can be written as

P_{ic} = h {(E_i − E_c), WTP_i, (C_c − C_i), Q_i, CO_i, IP_i, $ACUTE_i$, $COMP_i$, S_i, B_i}
(4)

The relative introductory price of NCE *i* over that of its close substitutes *c* is expected to be positively related to incremental efficacy, willingness to pay for health outcomes, cost offsets, co-payment rate, contribution to the achievement of industrial policy goals, treatment of acute conditions, potential spillovers, and bargaining power of the launching firm. We expect this price to be negatively correlated with the number of competitors in the market, and with potential volume of sales.

3. EMPIRICAL ANALYSIS

3.1 Equation and Variables

For equation (4), we specify the following regression equation:

LP_{ic} = a_0 + $a_1 RATEA_i$ + $a_2 RATEB_i$ + $a_3 t_{i0}$ + $a_4 NEO_i$ + $a_5 LAGE_{ic}$ + $a_6 LQC_{ic}$ + $a_7 HOME_i$ + $a_8 ACUTE_i$ + $a_9 LNUM_{i0}$ + $a_{10} DGEN_i$ + $a_{11} TOP_i$ + $a_{12} FDA\_NO_i$ + $a_{13} EMA$ + ε (5)

where

LP_{ic} = Natural logarithm of the relative introductory price of NCE *i* in relation to the price of its close therapeutic substitutes

$RATEA_i$ = Dummy variable that equals 1 if NCE *i* receives a rating of A (important therapeutic gain, defined in the next subsection)

$RATEB_i$ = Dummy variable that equals 1 if NCE *i* receives a rating of B (modest therapeutic gain, defined in the next subsection)

t_{i0} = Year of price authorization of NCE *i* (i=0, 1, 2,…,8)

NEO_i = Dummy variable that equals 1 if NCE i belongs to the therapeutic group L (antineoplastic and immunomodulating agents)

$LAGE_{ic}$ = Natural logarithm of the average number of years in the market for close therapeutic substitutes until price approval of NCE i, weighted by volume of sales

LQC_{ic} = Natural logarithm of the number of DDDs of the close therapeutic substitutes of NCE i sold the year before its approval, adjusted by its effective patient co-payment rate

$HOME_i$ = Dummy variable that equals 1 if NCE i has been launched in the originator or licensee firm's country

$ACUTE_i$ = Dummy variable that equals 1 if NCE i is indicated for an acute illness

$LNUM_{i0}$ = Natural logarithm of the number of branded close therapeutic substitutes for NCE i in the launching year

$DGEN_i$ = Dummy variable that equals 1 if a close brand-name substitute has a generic rival at the time of the new product's introduction

TOP_i = Dummy variable that equals 1 if the firm selling NCE i is one of the top 15 selling pharmaceutical firms in the country the year before NCE introduction

FDA_NO_i = Dummy variable that equals 1 if the drug has never been approved by the FDA

EMA = Dummy variable that equals 1 if the drug has been centrally approved by the EMA (vs mutual recognition procedure)

In equation (5) the degree of innovation, comprising incremental efficacy and cost offsets, is measured by ratings of new pharmaceuticals in class A and class B, where the omitted category corresponds to products with little or no therapeutic gain, and to products for which there was not enough evidence to establish their

therapeutic advance at the introduction. We also include a dummy for NCEs that have never been approved in the US. This is an exogenous proxy for low therapeutic gain or innovative degree of the drug. Government willingness to pay is measured by three variables: the year of price authorization (t_{i0}), assuming an increasing willingness to pay over time; the therapeutic group L (antineoplastic and immunomodulating agents), assuming a higher willingness to pay for more life threatening conditions; and the weighted age of close substitutes ($LAGE_{ic}$), assuming a higher willingness to pay for NCEs indicated for conditions with older treatments. A higher willingness to pay positively related to the age of close substitutes would also be recognition of a more notable erosion of older prices of close substitutes by inflation given that these prices have not usually been inflation adjusted in Spain; but also, this regulatory feature may represent a clear incentive for the firm to rapidly introduce new products in substitution for older ones with declining real prices. Industrial policy objectives are represented in equation (8) by a variable ($HOME_i$) indicating that the NCE has been introduced in the market by a Spanish firm (this firm may be the originator or a licensee). Potential volume of sales is measured by the number of DDDs of the close therapeutic substitutes of NCE i sold the year before its approval, adjusted by its effective patient co-payment rate, which represents the budget impact concern of the government (expected negative price effect), but also the importance of potential spillovers as perceived by the firm (expected positive price effect). We assume the parallel trade risk to be higher for higher-volume NCEs than for smaller product volumes. Finally, bargaining power is represented in this equation by a dummy variable (TOP_i) which identifies the 15 top-selling firms in Spain the year before price authorization. The bargaining power is expected to be higher for larger firms. We include a dummy variable for the EMA centralized approval procedure. It has an expected positive sign because it

increases the bargaining power of the firm in Spain, as it tends to homogenize international prices, bringing Spain closer to the average of EU prices.

3.2 The Data

The data set consists of all pharmaceuticals approved by the Spanish Health Ministry between 1997 and 2005. In this period, 288 new pharmaceuticals were approved in Spain. We included new drugs for ambulatory therapies. Of these products, we excluded 174 from the present analysis for various reasons. First, 120 products were only used or dispensed in hospitals. They were excluded because the mechanism of price negotiation with health authorities is different than for ambulatory drugs. A second category of excluded products consists of 17 other products such as hormones, vaccines and diagnostic devices in order to keep the sample homogeneous. Thirteen products were excluded because they were not covered by the National Health Service (NHS) insurance system. Twenty-one topical agents (creams, lotions, and ophthalmic solutions) for which a recommended daily dose cannot be easily established were also excluded. Finally, three products did not show any sales to the NHS during the period and were also excluded. Our data set thus includes a total of 114 new chemical entities (NCEs).

In this study, we define the price of an NCE as the average weighted price (AWP) per defined daily dose (DDD). A DDD is defined as the average daily dose of an NCE used by an adult for treatment of the main indication of the pharmaceutical. The price of a new drug has been determined as the weighted average ex-factory price (WAP) without VAT[3] per defined daily dose (DDD) in the first quarter in the market. Discounts or rebates have not been reported for new

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[3] Ex-factory prices excluding VAT have been calculated from regulated consumer prices deducting VAT rates and time variant regulated margins set for wholesalers and pharmacies by the Spanish Health Ministry.

pharmaceuticals in Spain, so we may confirm that our price data do not overstate NCE consumer prices. Sales of each pack of NCE_i to the NHS have been used as the weighting structure. Pharmaceutical sales financed by the NHS represent most of the sales of prescription drugs in the Spanish market; therefore, we may consider NHS sales mix as an adequate proxy for the complete market.

We used the DDD system recommended by the World Health Organization (WHO, 1997) for studies of drug use in order to define comparable dosages. Official DDDs were available for most NCEs. For the remaining drugs, recommended daily doses were obtained from the files of the public Spanish Drug Agency.

We identified close substitutes of an NCE as those chemical entities that share the same indication, have the same or similar routes of administration, and that were the most commonly prescribed medicines among those with the same indication and route of administration in the year immediately preceding the introduction of the new drug. Usually, close substitutes belong to the same broadly defined chemical class, but this is not always the case; thus, in our study, being the most commonly prescribed pharmaceutical entity for the same indication the year before the introduction of the NCE was the main criterion to identify close substitutes in order to measure more accurately the pharmaceutical prices paid by the NHS for the same condition before NCE introduction.

In this study, close substitutes of each NCE were identified by taking advantage of the information about each new pharmaceutical approved in Spain that periodically appeared in the section titled "*New active ingredients*" of "*Información Terapéutica del Sistema Nacional de Salud*" (*Therapeutic Information of the NHS*), a regular publication of the Spanish Health Ministry[4], which covers all the years

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[4] The contents of this publication for all the years included in this study may be consulted at the web page: www.msps.es

included in the present study. We identified at least one close substitute for each of the 114 NCEs included in our study.

We defined an NCE as acute if it is intended for conditions lasting no more than three months. A pharmacy expert was consulted in this regard.

No official centrally established rating of therapeutic advance is available for pharmaceuticals in Spain. However, the cited publication of the Spanish Health Ministry *"Therapeutic Information of the National Health Service"* published an unofficial rating similar to that of the US Food and Drug Administration. We will call it the regulator rating (RR). It has two main limitations for this study: first, the lack of information for the last three years of the study (24 NCEs); and, second, its potentially endogenous nature as a central government rating that may be used by the government regulator as a tool in the price/reimbursement negotiation with the firm. There is also an insurer rating (IR) for the therapeutic advance of NCEs in Spain which covers the whole period of our study. It has been issued by several regional governments, which are in charge of decentralized financing/buying of pharmaceuticals and management of health services[5]. Six NCEs were not evaluated in the IR. The IR could also be a biased proxy of the *true* innovation value of new drugs, because it is in the interest of regional governments to avoid paying for expensive medicines, therefore they could rate new drugs systematically below their true therapeutic value, and it could be endogenous because expensive drugs could be downgraded in an opportunistic behaviour. Nevertheless, the IR is less suspicious of endogeneity, because it is issued ex-post (after price negotiation) by regional governments, which are not directly involved in the

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[5] Several evaluation committees of new drugs have been set up by some Spanish regional governments (Andalusia, Aragon, Catalonia, and the Basque Country) and have been issuing common ratings of therapeutic advance for new pharmaceuticals since January 2004. The rating publicly issued by the government of Navarre is the only one covering all new pharmaceuticals since January 1997. Thus, in this paper we use the rating of Navarre from January 1997 to December 2003, and the common ratings issued by the five regional governments after that date.

pricing/reimbursement negotiation process, and as such, it represents a broader, more official, and potentially more evidence-based consensus than the RR.

The therapeutic advance associated with an NCE is measured, in both the RR and the IR, by the following ratings: A = important therapeutic gain; B = moderate therapeutic gain; C = little or no therapeutic gain; D = not enough clinical information or experience to establish therapeutic advance at launch. It is worth noting here that evaluating therapeutic gain is especially difficult when relying on premarket clinical trials that are universally sponsored by the company requesting reimbursement. Company sponsored clinical trials have been repeatedly shown to have a positive bias. We include in the model dummy regressors for rates A and B. An alternative model combines the categories A and B in a A+B category. We also include a dummy variable equal to 1 if the FDA never approved the drug. We assume that it is exogenous to the price in Spain, and those drugs that were never approved in the US should probably have low therapeutic value. We expect, then, a negative sign.

Finally, we included a dummy variable (EMA) for the drugs centrally approved by the European Agency. The rest (EMA equals 0) were approved only in Spain, or through the mutual recognition procedure. We expect a positive sign.

4. RESULTS

4.1 Summary Statistics

Table 1 reports univariate statistics and bivariate associations with the relative launching prices for continuous variables (Table 1A) and categorical variables (Table 1B).

[Insert Table 1 about here]

All continuous variables have large variances. Relative launching prices are significantly correlated with the number of years of competitors in the market and with the number of competitors. Only one new drug defines the category A. It is indicated for some specific types of cancer, it was approved by the EMA in 2001 and it started to be marketed in Spain in 2002. Although relative launching prices by rating groups have average values that compare as expected (A higher than B, and B higher than the rest), the ANOVA test fails to find any significant differences in relative launching prices by therapeutic value. Figure 1 shows the scatter plot of relative launching prices and number of years of competitors in the market, with rates of innovation displayed. Oncological and life threatening condition drugs are priced significantly above the rest. Local companies have lower prices than foreign companies, but differences are not significant. Drugs for acute conditions are priced above drugs for chronic conditions. Top companies do not differ from the rest. Those drugs that have been approved by the EMA in a centralized process have significantly higher prices.

Comparing the two alternative ratings, IR and RR, notable disagreements are found. The IR is more demanding than the RR, as expected.

[Insert Figure 1 about here]

4.2 Regression Results

Table 2 reports the estimation results of the model (5). Therapeutic value does not influence the relative launching price significantly, although signs are as expected. Lack of significance does not seem to be due to collinearity because the Variance Inflation Factors (VIF) of

RATEA and RATEB are low (1.19 and 1.18 respectively). The alternative model which combined these two categories into a single (A or B) category gives similar results with a coefficient of the combined variable equal to 0.356 (p-value of 0.14), and the remaining coefficients do not almost change . The number of years of competitors in the market is highly significant, and its standardized coefficient is the largest one. Competitive pressure, measured through the number of competitors in the market, is significant and it has a large coefficient (-0.43). It is correlated with market size, because drugs with large sales in DDDs the year before launching had more competing firms (linear correlation = 0.62). This is why market size is not significant (and it has the wrong sign). In fact, the VIF of market size (LQC) is the highest (2.12). Neither is the presence of generic firms significant. The coefficient of centralized approval (EMA) is positive, large and significant. Cancer drugs have a significant premium after controlling for the rest of the covariates. Their coefficient (0.97) can be interpreted as follows: the relative launching price of an oncological drug is 2.6 times that of a non-oncological drug. On the other hand, acute indications are penalized in Spain, compared to drugs for chronic conditions. The coefficient (-0.38) shows that drugs for acute conditions are priced at a level that is only 68% of the relative price of a similar drug for a chronic condition. As in the bivariate analysis, neither top companies nor local companies differ significantly in launching price of their subsidized drugs.

The Breusch-Pagan test does not reject the null hypothesis of homoscedasticity (BP=14.18, p=0.36).
There are four positive outliers with standardized residuals larger than 2, and two negative outliers with standardized residuals smaller than -2. Two of the positive outliers are drugs launched in 1999 by local companies, and the other two are drugs launched in 1997. The two negative outliers were launched in 2001 and 2002 respectively.

One is a non-oncological drug with NEO=1 for prevention of organ reject after transplant. All outliers have small market sizes.

[Insert Table 2 about here]

5. CONCLUSIONS AND POLICY IMPLICATIONS

Contrary to expectations and to the results published by Lu and Comanor (1998) for the US and by Ekelund *et al* (2003) for Sweden, in Spain the therapeutic value or degree of innovation does not seem to be a key factor in determining the launching price of new drugs. Price setting is mainly used as a mechanism to adjust for inflation erosion independently of the degree of innovation.

Notwithstanding, there are difficulties to measure the degree of innovation of new drugs objectively and exogenously. We have discussed some alternatives in our text. In Spain, ratings by the public regulator and by the public insurer are potentially endogenous, in opposite ways. The regulator could use his rating to justify the prices he has authorized. The insurer could opportunistically underqualify the most disruptive drugs in order to control expenditure. The alternative unofficial ranking provided by the pharmaceutical councils was not significant either. We used alternative proxies for innovation, such as the dummy for being first in class proposed by Grabowski *et al* (1992), but we did not get significant results for this either. A proxy for (lack of) therapeutic value that is clearly exogenous is the dummy of non-approval by the FDA. According to the model, these drugs have lower launch prices, although the difference is not statistically significant.

While none of the three explanatory variables describing the therapeutic value in our model is significant, their signs are as expected. Our finding that the price of new drugs is hardly influenced by their degree of innovation is robust to alternative measures, all

potentially problematic, of degree of innovation. The fact that in Spain, unlike in Sweden and other European countries, there is not a fourth threshold of cost-effectiveness for new drugs could help to explain our result that price does not depend on therapeutic value. In the price negotiation there is no need to justify prices with evidence on effectiveness or cost per QALY at different levels of price.

The main contributing factor to predict the relative launching price is the average age of competitors on the market. In Spain, once the price of a new drug is set, it will rarely never be reviewed. Therefore, in practice, the setting of prices for new drugs is also a mechanism of adjustment for inflation. Our model points clearly to this fact. Because we have selected only new molecules, our model is not sensitive to the plausible strategic behaviour of those firms that ask for authorization of old drugs by disguising them as new ones, for instance setting new combinations of old molecules, in order to update prices against inflation erosion.

Since 1995 there have been two alternative procedures in Europe for authorizing new drugs: the centralized one, by EMA, and the one based on mutual recognition. In the latter, the drug is authorized in a particular country, with the understanding that all the other European countries will recognize it automatically unless an objection is raised in 90 days. Also, a drug could be authorized only in a particular country. European regulation sets compulsory centralized approval for some types of drugs (monoclonal antibodies; orphan drugs) and medical conditions. After authorization, national authorities set prices and decide whether to include the drugs in the public insurance coverage list. Our data do not show a definite time trend in the frequency of centralized authorizations in Spain. About one third of the new drugs in our database have been authorized by the EMA using the centralized procedure, and that share ranges from 25% to

50% of the drugs authorized each year, except 1997, with only one centralized authorization.

An interesting new finding of this study is that drugs centrally authorized by the EMA are overpriced by 70% ($=e^{0.5327923}$). This effect is large, very significant and robust to changes in the model specification. A possible explanation of this result is that those drugs that were centrally approved have more homogeneous prices among countries because their markets are more globalized. As drug prices in Spain are on average lower than in most countries, and below the European average, centrally approved drugs are priced above the rest in Spain. In summary, the dummy variable for centralized approval could reflect the combined effect of market factors and regulation factors in a globalized context. There is no difference between the top 15 companies and the rest. There is no evidence that the more innovative drugs are centrally approved.

Companies try to speed up the introduction of new drugs in markets, particularly in the larger ones. The countdown to patent expiry is a key element in the profitability of the new drug throughout its lifetime. But in the negotiation game, the company could possibly prefer to delay the launching in order to avoid suffering spillover effects of lowering international reference prices. We introduced into the model the time elapsed from the first authorization of the drug to its launching in Spain. We expected a negative effect, because large delays could reflect harder negotiations in Spain, finishing up with prices less favourable to the company. However, we did not find any significant effect.

Competition influences prices, as expected. The more competitors, the lower the relative launching price, as in the US. Market concentration is also responsible for higher prices for antimalarial drugs in developing countries (Goodman, 2009). But in Spain the presence of substitutive generic drugs does not influence the price.

The volume of the market, measured through the number of DDDs sold the year before the launching by competitor drugs, apparently does not influence the launching price either. This lack of significance of the market volume could be due to the positive correlation with the number of competitors, which is a significant regressor in the model. Perhaps it would be more relevant to include the potential expected market ceiling – instead of real sales – which could be approximated with data on morbidity. Some medical conditions, such as Alzheimer's disease or obesity, have a large market potential, in terms of unmet demand, because of the lack of effective drugs. In fact, in the past, the appearance of new disruptive drugs for certain conditions increased the number of patients treated for such conditions. For instance, the new antidepressants launched since the 1980s increased consumption of antidepressants in the US from 5 to 460 million DDDs between 1988 and 1997 (Berndt *et al*, 2002). Unfortunately there are no available data on the potential market for each drug in our study.

Drug characteristics are important determinants of prices. In Spain, where drug prices are traditionally low, the treatment of life threatening conditions, including cancer, is overpriced. According to the model, all other factors being equal, the relative launching price of a drug against a life threatening disease is 2.65 times (e $^{0.9545}$) higher than that of other drugs. There is abundant literature, more often theoretical or based on social values than empirical, on the social willingness to pay for these kinds of treatments (Becker *et al*, 2007). In our study we found that overpricing is more specific to cancer than to generic immunomodulating drugs, because two out of the three non-oncological drugs, which prevent organ rejection after transplant, have negative residuals. One of the three is even an outlier.

Unlike in the US and Sweden, in Spain acute treatments have a price penalty. This result is the opposite of what we expected because in Spain acute treatments generally have higher co-payments than drugs for chronic conditions. Therefore it would be plausible that the regulator would be ready to accept higher prices without affecting public expenditure. The result for acute drugs is robust to alternative specifications, but it is sensitive to the precise definition of acute treatment. It would be useful to dig deeper into the causes, as it may be that our finding cannot be generalized. In our database, acute treatments are not associated with a better or worse therapeutic value, and neither are they associated with the number of years the competing drugs have been on the market.

After taking into account the rest of the covariables, there is no definite temporal trend in the dynamics of the relative launching prices authorized in Spain. A linear time trend is not significant, and annual dummies are not significant either. Outliers are concentrated in specific years: overpricing in 1997 and 1999 and negative outliers in 2000. We expected a positive sign of the linear trend, indicating that the willingness to pay for a drug in the country goes up over time. But on the other hand, launch timing also reflects other contextual factors, not accounted for in the model, which may vary over time. In practice, the composite resultant of these forces is not significant.

Two limitations of the study are the sample size (n=114) and the problems of collinearity. Both are responsible for the lack of robustness of the model results to small changes in the definition of therapeutic innovation. However, this sample of 114 drugs is in fact the population of new drugs launched on the Spanish market during the period of study. The implied challenge in this context is to know whether our findings can be generalized to other years, and whether they describe stable phenomena of cause-effect relationships. Our

model fitting is good. The method used to determine close substitutes is not perfect, but it is the usual method in market studies of drug entries.

Another limitation is the omission of variables that are potentially explanatory, related to the European context. We included the dummy of centralized approval by the EMA but we omitted, due to lack of data, other international references of spillover effects and contagion effects (Kanavos and Costa-Font, 2005), which could change the bargaining power of the company. The average price previously approved in other countries (international reference price) and the number of European countries that previously approved both the drug price and its funding conditions would have been potentially useful regressors in our model. They were not included either in the Swedish model, which makes that comparison of results between Sweden and Spain easier.

In summary, in Spain innovation is not a key factor in determining the launching price of new drugs. Drugs centrally authorized, drugs for treating life threatening diseases, and drugs for chronic conditions (unlike the US) are overpriced. The more the number of competitors, the lower the launching relative price, but the presence of substitutive generic drugs does not influence the price. Price setting is mainly used as a mechanism to adjust for inflation erosion independently of the degree of innovation. These results cannot be generalized without empirical evidence to every single country with a highly regulated market. This a pending task for researchers.

REFERENCES

Antoñanzas F, Oliva J, Pinillos M, Juárez C. 2007. Economic aspects of the new Spanish laws on pharmaceutical preparations. *European Journal of Health Economics* 8(3): 297-300.

Bardey D, Bommier A, Jullien B. 2010. Retail price regulation and innovation: reference pricing in the pharmaceutical industry. *Journal of Health Economics* 29(2): 306-316.

Becker G, Murphy K, Philipson T. 2007. The value of life near its end and terminal care. *NBER Working Paper No. 13333*, National Bureau of Economic Research, Cambridge, MA.

Benda M-C, Mallory C, Lu H. 2004. An econometric estimation of pricing of brand-name drugs. *Applied Health Economics and Health Policy* 3(1 suppl): S12.

Berndt ER. 2002. Pharmaceuticals in U.S. health care: determinants of quantity and price. *Journal of Economic Perspectives* 16(4): 45-66.

Berndt ER, Bhattacharjya A, Mishol DN, Arcelus A, Lasky T. 2002. An analysis of the diffusion of new antidepressants: variety, quality, and marketing efforts. *Journal of Mental Health Policy and Economics* 5(1): 3-19.

Danzon PM, Wang YR, Wang LL. 2005. The impact of price regulation on the launch delay of new drugs—evidence from twenty-five major markets in the 1990s. *Health Economics* 14: 269-292.

Dean J. 1969. Pricing pioneering products. *Journal of Industrial Economics* 17(3): 165-179.

Ekelund M, Persson B. 2003. Pharmaceutical pricing in a regulated market. *The Review of Economics and Statistics* 85(2): 298-306.

Garcia Mariñoso B, Jelovac I, Olivella P. 2010. External referencing and pharmaceutical price negotiation. *Health Economics* doi: 10.1002/hec.1630.

Goodman C, Kachur SP, Abdulla S, Bloland P, Mills A. 2009. Concentration and drug prices in the retail market for malaria treatment in rural Tanzania. *Health Economics* 18: 727-742.

Grabowski HG, Vernon JM. 1992. Brand loyalty, entry and price competition in pharmaceuticals after the 1984 Drug Act. *Journal of Law and Economics* 35(2): 331-350.

Hong SH, Shepherd MD, Scoones D, Wan TTH. 2005. Product-line extensions and pricing strategies of brand-name drugs facing patent expiration. *Journal of Managed Care Pharmacy* 11(9): 746-754.

Kanavos P, Costa-Font J. 2005. Pharmaceutical parallel trade in Europe: stakeholder and competition effects. *Economic Policy* 20(44): 751-798.

Lexchin J. 2006. Do manufacturers of brand-name drugs engage in price competition? An analysis of introductory prices. *Canadian Medical Association Journal* 174(8): 1120-1121.

Lu ZJ, Comanor WS. 1998. Strategic pricing of new pharmaceuticals. *The Review of Economics and Statistics* 80(1): 108-118.

Office of Fair Trading (OFT). 2007. *The Pharmaceutical Price Regulation Scheme*. Office of Fair Trading, London, UK.

Philipson TJ, Dai C. 2003. Between- vs. within-patent competition. *Regulation* Fall: 42-48.

Puig-Junoy J. 2004. Incentives and pharmaceutical reimbursement in Spain. *Health Policy* 67: 149-165.

Reekie WD. 1978. Price and quality competition in the United States drug industry. *Journal of Industrial Economics* 26(March): 223-237.

Wiggins SN, Maness R. 2004. Price competition in pharmaceuticals: the case of anti-infectives. *Economic Inquiry* 42(2): 247-263.

Zaric GS. 2008. Optimal drug pricing, limited use conditions and stratified net benefits for Markov models of disease progression. *Health Economics* 17: 1277-1294.

Table 1. DESCRIPTIVE STATISTICS AND BIVARIATE ASSOCIATIONS WITH RELATIVE LAUNCHING PRICE

Table 1A. Continuous variables

Variable	Mean	Std. Dev.	Min	Max	Correlation With relative launching price (in log)(*)
Relative launching price (P_{ic})	4.8	6.1	.5	37.7	1
Launching price (P_{i0})	5.7	13.9	.2	82.3	0.39(*)
Competitors' average price (P_{c0})	1.6	2.7	.06	16.3	-0.14
Average number of years competitors in market (AGE_{ic})	13.9	8.3	1.1	49	0.42(*)
Market size (DDDs sold by competitors the previous year) (QC_{ic})	31.7	50.6	.001	229.5	-0.15
Number of competitors (NUM_{i0})	3.0	1.7	1	9	-0.30(*)

Table 1B. Bivariate associations

Categorical variable	Categories	n	%	Average relative launching price
Innovation rating (*)	A	1	0.9	7.8
	B	10	8.8	6.7
	NoA NoB	103	90.4	4.5
Oncological/life threatening indication (*)	Yes	10	8.8	9.6
	No	104	91.2	4.3
Year of launching	1997	17	14.9	6.7
	1998	19	16.8	2.6
	1999	12	19.5	4.6
	2000	9	7.9	4.5
	2001	12	10.5	7.4
	2002	14	12.3	5.7
	2003	12	10.5	2.0
	2004	12	10.5	3.8
	2005	7	6.1	6.6
Local company	Yes	36	31.6	3.9
	No	78	68.4	5.1
Acute	Yes	32	28.1	3.1
	No	82	71.9	5.4
Generic competitors	Yes	58	50.9	4.3
	No	56	49.1	4.4
Top company	Yes	74	64.9	4.9
	No	40	35.1	4.6
Non-FDA approved	Yes	23	20.1	2.9
	No	91	79.9	5.2
EMA centralized approval	Yes	37	32.5	6.6
	No	77	67.5	3.9

n=114
(*) Significant at 5%

Table 2. DETERMINANTS OF RELATIVE INTRODUCTORY PRICES

Variable	Coefficient	Std. Err.	t	P>t	[95% Conf.	Interval]
$RATEA_i$	.6012085	.7750288	0.78	0.440	-.9364266	2.138844
$RATEB_i$	.3302826	.2540725	1.30	0.197	-.17379	.8343553
FDA_NO_i	-.2452535	.2030331	-1.21	0.230	-.6480654	.1575584
EMA_i	.5327923	.1593886	3.34	0.001	.2165699	.8490146
$LAGE_{ic}$	.7146351	.1073921	6.65	0.000	.5015723	.9276979
$LNUM_i$	-.4327426	.151737	-2.85	0.005	-.7337846	-.1317007
LQC_{iC}	.0109941	.0383689	0.29	0.775	-.0651288	.087117
$DGEN_i$	.071764	.1632375	0.44	0.661	-.2520946	.3956225
$HOME_i$	.1559611	.1655685	0.94	0.348	-.1725221	.4844444
TOP_i	.102674	.1536355	0.67	0.505	-.2021345	.4074825
NEO_i	.9745416	.2799591	3.48	0.001	.4191106	1.529973
$ACUTE_i$	-.3825421	.1629164	-2.35	0.021	-.7057636	-.0593207
t_{i0}	-.0200322	.0277618	-0.72	0.472	-.0751107	.0350463
const	-.5176107	.3322843	-1.56	0.122	-1.176853	.1416318

n=114
R2=0.5156; adjusted R2=0.4526; F(13,100)=8.19

Figure 1

Launching prices and age of competitors in the market
by therapeutic gain (A=important therapeutic gain; B=moderate therapeutic gain)