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Generic Entry into the Regulated Spanish Pharmaceutical Market

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Abstract This paper empirically analyses entry by generic firms into the strictly regulated Spanish pharmaceutical market. We estimate a fixed effects negative binomial entry model using a panel of 77 active ingredient markets during the period 1999–2005. The results show that generic entry depends positively on revenues, the age of the market, and the number of previous brand-name competitors, and negatively on the number of generic incumbents. We also find that regulation may drive out competition since, contrary to what policy makers might expect, the system of reference pricing restrains generic entry.

Keywords Generic entry · Pharmaceutical industry · Reference pricing

JEL Classification I11 · L11 · L65

1 Introduction

Since January 1997 Spain has allowed the introduction of generic drugs: drugs that are the bioequivalent of the original medicines and that enter the market when brand-

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name drugs are not protected by patents. The Spanish pharmaceutical market is highly regulated since it has a regulation that caps the price of each medicine individually, and since 2000 there has been a reference pricing system in which the National Health System (NHS) sets the reference price for reimbursement of drugs that have generic competition (López-Casasnovas and Puig-Junoy 2000).

The purpose of this paper is to identify the drivers of generic entry in a heavily regulated market; further, since the NHS funds most drug consumption, it is especially interesting to analyse how generic entry is affected by price regulations and reimbursement policies. We are interested in analysing to what extent entry depends on the market characteristics that have already been highlighted in the previous literature for less regulated markets, and how reference pricing affects generic entry.

Previous research, such as Rudholm (2001) and Ekelund (2001), have studied the drivers of generic entry, but no paper has yet been able to test robustly whether reference pricing has had an impact on entry dynamics. The Spanish case, with on-going and unexpected reforms on price regulations, offers a pseudo-experimental setting in which we can identify the impact of regulation on new generic entry.

The outline of the paper is as follows: The next section explains the main features of the Spanish pharmaceutical market. The third section reviews the literature briefly. The following section shows the empirical model of entry. The fifth section displays the data used in the estimations. The sixth section shows the estimation results. The next section discusses the results. The last section offers some concluding remarks.

2 The Spanish Pharmaceutical Market

Spain is the seventh largest market for pharmaceuticals in the world and the fifth largest in the European Union (EU) (IMS Health 2006a). The NHS in Spain is funded with taxes and provides health care services to all residents with small co-payments for prescribed pharmaceuticals. The usual co-payment rate is 40%, but the average co-payment is clearly smaller since prescription drugs for pensioners are provided free and the chronically ill pay only 10%, with a price cap. The prescription market dominates sales: the market share of prescription drugs is 85.50% of volume and 92% of total sales (Costa-Font and Puig-Junoy 2005).

There are a great number of different representations of drugs. This is due to the still considerable number of copies and the entry of new drugs, along with the introduction of generics, although the market share for generic medicines is only 14.60% in units and 7.90% in value (IMS Health 2006b). Spain did not grant product patent rights until October 1992. Before that time there were only process patents. As a result, there are four types of prescription drugs in Spain: original brand-name drugs, which are marketed by the patent holder; branded licensed products, which are marketed by a licensee under an agreement with the pioneering firm; copy brand-name drugs, which were obtained using a different process and are marketed without a licensing agreement with the patent holder; and generics.

Generics were only introduced in Spain in 1997. Generics are approved when one of the two following conditions is fulfilled: a generic has already been authorised in a

member state of the EU in which the original drug enjoyed product patent protection; or 10 years have passed since the original brand-name drug was launched in the Spanish market (the "ten-year rule"). As Segura (1997) highlights, for many new chemical entities the 10-year registration exclusivity expired before their first patents. This gave rise to systematic legal action for patent infringement by innovator companies in Spain against competing generic applicants.

Although Spain is a relatively low-price country with limited generic penetration, in December 2000 a reference pricing system was introduced. Reference pricing has gradually been extended to active ingredients (molecules) that have approved generic versions in the market. All versions of off-patent drugs, branded and generics, were included in their respective group of bioequivalent drugs once there was at least one generic version of the respective active ingredient. For each group a reference price was calculated as the weighted average selling price of the cheapest drugs accounting for at least 20% of the prescriptions. Therefore, only medicines with the same molecule were in a specific group and shared a reference price. This system established the maximum price that could be reimbursed by the NHS for any version of the same drug. Whenever the price of any prescribed drug was higher than the reference price, patients could opt for the prescribed drug by paying the difference between its price and the reference price.

However, since January 2004 the reference price has come to be a system for setting a maximum reimbursement price for branded and generic drugs. The reference price has been calculated as the average of the three lowest costs per day of treatment for each form of administration of an active ingredient, according to its defined daily dose. With this new system, if prescriptions specify brand-name drugs that are priced higher than the reference price, pharmacists are mandated to substitute the cheapest generic version. When the prescription has been written using the name of the active ingredient, the pharmacist has to dispense the lowest-priced generic drug.

Finally, it should be taken into account that for all drugs (branded and generics) maximum ex-factory prices are set during the process of obtaining market approval, and usually the introduction price remains as the maximum price for most of the product life (Borrell 2003). The government uses a form of cost-based price regulation for branded drugs in which manufacturing, marketing, and research costs are allocated to new drugs. Wholesalers' and retailers' mark-ups are also regulated.

3 The Drivers of Generic Entry

Grabowski and Vernon (1992), in a seminal paper on generics, were the first to analyse explicitly the dynamics of entry. They found that generic entry depended on expected profits. This finding has been supported in the subsequent literature: Frank and Salkever (1997) reported that the number of generic entrants depended positively on market size in terms of drug sales before the patent expiration; Bae (1997), using a duration model, found that generic drug entry was faster on average in larger markets; Scott Morton (1999, 2000) found that brand-name product revenues affected generic entry positively; Reiffen and Ward (2005) concluded that there were more and faster entries in markets with larger expected profits and that the number of firms in each

market segment depended on the expected market size; and Saha et al. (2006) found that on average there were more entries in the largest markets in terms of sales.

Bae (1997) also showed that entries were faster for drugs that mainly treat chronic diseases, and Scott Morton (1999, 2000) found that this factor made entry more likely. The latter author also showed in both papers that generic entry was positively related to hospital sales. And both Bae (1997) and Scott Morton (2000) found that markets where there were more brand-name products competing were less attractive to potential entrants. Scott Morton (1999) found also that firms tended to enter therapeutic markets similar to those in which firms were already established, and Saha et al. (2006) showed that on average the number of new generic entrants was lower when the number of generic incumbents that were already in the market was greater.

Hudson (2000) studied the relationship between patent expiration and the introduction of generics not only in the US, as in the previous studies, but also in the UK, Germany, and Japan. He concluded that the major determinant of generic entry was the size of the market at patent expiry and that increases in sales reduced the lag between patent expiry and generic entry.

Magazzini et al. (2004) also studied generic entry in a multi-country dataset including France, Germany, the UK, and the US. They did not analyse the number of generic firms but instead their market share, and they found that in larger markets generic products gained larger market shares. Contrary to Bae (1997) and Scott Morton (2000), they found that the existence of different brand names in the market had a positive effect on generic entry as the original brand was not able to create strong loyalty before patent expiration. Also, contrary to Scott Morton (1999, 2000), they reported that the size of hospital sales had a negative impact on generic market shares.

As far as we know, Rudholm (2001) and Ekelund (2001) are the only studies to date to have analysed entry in a heavily regulated market: Sweden. Iizuka (2009) has also studied generic entry in the regulated Japanese pharmaceutical market, but the kinds of regulations in that country are quite different from those applied generally in Europe. Rudholm's main finding was that expected profits affected positively the number of generic entries and that a longer the exclusivity period for the brand-name product was associated with a lower the likelihood of generic entry. However, Rudholm (2001) was not able to identify clearly the impact of reference pricing on generic entry, since its implementation coincided with other structural changes in the market. Ekelund (2001) has also attempted to estimate the impact of reference pricing on generic entry. He found that the probability of one or more generics' being launched was on average lower when a reference price system was established, but the author offers only weak evidence of these effects.

4 Empirical Strategy

Starting from the aforementioned work by Rudholm (2001) on the Swedish pharmaceutical market and the contribution by Daunfeldt et al. (2006), we estimate an empirical count data model of entry.

The first assumption is that potential entrants enter a particular active ingredient market if they expect to make a non-negative profit and that they face some en-

try costs. As a consequence of patents, we also assume that these markets are not perfectly competitive. From these assumptions it is derived that a firm will enter a market until profits (including the entry cost) in each period are driven to zero:

$$E[\pi_{it}] = p_{it}(Q_{it})q_{it} - C_{it}(q_{it}) - F_{it} = 0, \tag{1}$$

where π_{it} is the profit of any potential entrant in market i in period t; $p_{it}(Q_{it})$ is the price of the generic medicine as a function of the total market sales of that drug; q_{it} is the sales of the generic product conditional on entry; $C_{it}(q_{it})$ is the production cost as a function of the sales volume of the generic pharmaceutical product (including both variable and fixed production costs); and the term F_{it} is the entry cost corresponding to the zero profit condition (i.e., when new entrants cannot make positive profits). Thus Eq. 1 determines the number of firms in the market each period.

We assume that the entry cost depends on the number of firms and on unobservable specificities of the market. Therefore, entry costs are different across active ingredient markets, even for a given firm. For instance, in some markets, patents expired when the "ten-year rule" of registration exclusivity ended. For these drugs (e.g., ciprofloxacin, enalapril, and omeprazole) many copies were usually on the market before generics were introduced. Generic entrants were very unlikely to face infringement litigation by innovator firms in such cases. By contrast, there were some active ingredient markets for which the "ten-year rule" of registration exclusivity ended before the patent expired (e.g., acyclovir and famotidine). In these cases, generic entrants faced legal action for patent infringement, taken by innovator firms either in good faith or simply to deter entry (Segura 1997). Since there is not available exhaustive information about these litigations, we will use the number of brand-name products in the market as a proxy.

In addition, the number of generic firms may increase the entry cost if new entries mean an increase in the number of generic firms that are competing in the same market, and the potential generic entrant may have to invest more in marketing. However, more generic firms can also reduce the cost of entry if new entrants behave as free-riders and benefit from others' marketing (Daunfeldt et al. 2006).

We assume that the profits from entry are decreasing with the number of entrants. The number of entrants will reduce the expected number of units sold by each entrant. In addition, the price depends negatively on the number of generic firms in the market. This result has been found in prior studies such as Frank and Salkever (1997). Reiffen and Ward (2005) found that, for markets of sufficient size, eight or more entries lead to near-competitive generic prices.

Even in a market with regulated prices, a price reduction is expected when the number of competitors increases. In Spain maximum drug prices are negotiated between the firm and the health authorities, and in the case of generic medicines it is systematically observed that new generic entrants have lower maximum regulated prices than do incumbent generic firms.[1] Accordingly, the price at which new entrants will sell their production is expected to be decreasing with an increasing number of generic

[1] Anecdotal evidence obtained in conversations with representatives of generic firms and health authorities support this assumption, but research showing these price patterns is still lacking.

incumbents. Additionally, when there are new generics in the market with lower prices and the reference price is recalculated, the new reference price is also lower.

Let us assume that the expected profit of a potential entrant has the following linear form:

$$E[\pi_{it}] = \gamma_0 + \gamma_i + \gamma_t + \delta_1 \Delta N_{it} + \delta_2 N_{it-1} + \delta_3 BN_{it} + X_{it}\rho + \varepsilon_{it}, \qquad (2)$$

where ΔN_{it} is the number of generic firm entries in period t, N_{it-1} is the number of generics firms already established in the previous period, BN_{it} is the number of brand-name firms in the market, and X_{it} is a vector of market-specific variables such as market size or regulatory changes. The term γ_0 is a constant, γ_i is a fixed effect for each market, γ_t is a fixed effect for each period, and δ_1, δ_2, δ_3 and the vector ρ are parameters. Finally, ε_{it} is an error term with zero mean and constant variance. We include the number of generic firms, differentiating between new entrants and laboratories already established in the previous period. Since profits are driven to zero, this allows us to express the number of current entries as a function of the incumbents and other variables:

$$\Delta N_{it} = \alpha_0 + \alpha_i + \alpha_t + \beta_1 N_{it-1} + \beta_2 BN_{it} + X_{it}\beta_3 + u_{it}. \qquad (3)$$

From this basic theoretical approach we build an empirical probability specification of the number of entries into each market in each period. Since there are a negligible number of net exits, we focus our analysis on the drivers of net entries.[2]

The dependent variable only takes non-negative integer values and is measured in natural units so count data regression seems to be the suitable method. The starting point is the Poisson regression model, for which the mean of the dependent variable should be equal to the variance of the dependent variable conditional on the explanatory variables (equidispersion property). In our case, the data displays overdispersion (the variance is greater than the mean). Similarly to Iizuka (2009), we use the negative binomial distribution, which is more flexible, and relax the equidispersion requirement.

Since there are markets in which no entry is observed, there might be barriers that are not observed in our data set and that may prevent entry, causing a large quantity of zeros in the dependent variable. As a result of this large proportion of zeros we additionally use a zero-inflated negative binomial regression. We also include market and time fixed effects that allow us to control for unobservable heterogeneity among markets and periods.[3]

We then maximise a sample likelihood function to estimate the parameters of the (zero-inflated) negative binomial regression given the observed count of entries under the assumption that the conditional mean has the following specification:

[2] Our dependent variable is the net positive variation in the number of generic firms in each market between periods. We excluded from the sample the net exits that represented 2.34% of the observations.

[3] Allison and Waterman (2002) have shown the good performance of applying an unconditional negative binomial regression estimator with dummy variables to represent the fixed effects.

$$E(\Delta N_{it}|N_{it-1}, X_{it}) = \mu_{it} = \exp(\alpha_0 + \alpha_i + \alpha_t + \beta_1 N_{it-1} + \beta_2 B N_{it} + X_{it}\beta_3 + u_{it}), \quad (4)$$

where α_0, β_1, β_2, and the vector β_3 are the set of parameters to be estimated and α_i and α_t are the market and time fixed effects.

5 Data

We use an unbalanced panel with quarterly data from the first quarter of 1997 through the second quarter of 2005. It covers the 77 largest markets of prescription drugs for which generics could potentially be launched. All of the markets that are included in our dataset meet the "ten-year rule", and therefore there is no regulatory impediment to the entry of generic firms.

We analyse outpatient data for non-pediatric oral prescription drugs containing only one active ingredient; those active ingredient markets with consumption lower than €8 million during the year previous to meeting the "ten-year rule" or the first year available in our dataset are excluded.[4]

The unit of observation is the active ingredient market. Each is formed by medications that compete with other imperfect substitute medications. Defining the relevant market is not an easy task because medications are indicated for treatment of different conditions. Although it is an imperfect approach many authors (for instance, Rudholm 2001, 2003; Aronsson et al. 2001; Bergman and Rudholm 2003; Ekelund and Persson 2003; Borrell et al. 2005) usually use the therapeutic active ingredient level that is defined by the ATC (Anatomical Therapeutic Chemical classification) as a proxy for the relevant market.

Our dataset contains the out-patient pharmaceutical prescription consumption paid by the government and recorded by the Directorate-General of Pharmacy and Health Products of the Ministry of Health and Consumer Affairs. This information has been complemented with data from the 'Nomenclator Digitalis' of the NHS Health Information Institute and from the 'Base de Datos del Conocimiento Sanitario 2005—BOT PLUS' (Consejo General de Colegios Oficiales de Farmacéuticos).

Table 1 reports the definitions and the descriptive statistics of the variables. As was indicated above, the dependent variable is the net entry of generic firm entries in each active ingredient market for each quarter. We only consider a case as an entry when we observe a firm's sales for the first time. If the same firm enters the same active ingredient market with a new drug type (for example, different form, dose, etc.), it is not considered as an entry.[5]

[4] We excluded small markets in order to reduce the percentage of observations that are equal to zero for our dependent variable.

[5] Before the entry of official generic drugs in the Spanish market there were generic copies in some markets, which were authorised following the standard procedure for branded products. Segura (1997) holds that there were around 100 international non-proprietary named (INN) products making up around 1% of the Spanish market in 1997. Since from an economic point of view these generic copies are identical to real generics, they are considered as generics and compose our dependent variable together with the

Table 1 Variables and descriptive statistics

Variable	Definition	Obs.	Mean	SD	Min.	Max.
Entries	Number of generic firm entries	1,963	0.26	0.75	0	13
Revenues	Market revenues (€1,000,000)	1,963	6.85	8.73	0.12	66.63
Reference price I	Dummy variable equal to 1 when the market is regulated by reference pricing until 2003	1,963	0.15	0.35	0	1
Reference price II	Dummy variable equal to 1 when the market is regulated by reference pricing from 2004 onward	1,963	0.13	0.33	0	1
Generic firms	Number of generic firms in the market	1,963	3.24	5.36	0	32
Brand-name competitors	Number of brand-name firms in the market additional to the pioneer	1,963	5.00	6.17	0	34
Active ingredients per ATC-4	Number of active ingredients in the therapeutic subgroup	1,963	4.96	3.50	0	14
Age	Number of quarters since the first authorised drug in each market	1,963	77.71	30.91	40	181

The explanatory variables are the market and drug characteristics. In order to take into consideration the approval time lag between the generic firm entry decision and the actual launch of the generic drug on the market, all explanatory variables are lagged four quarters. Lagging these variables corresponds directly to the decision problem of the potential entrant, since firms observe the drug and market characteristics long before taking the decision to enter the active ingredient market. Also, this lag allows us to avoid possible endogeneity problems since previous values of the variables are assumed to be predetermined.

The variable REVENUES is the market size measured in terms of sales revenues.[6] The dummy variable REFERENCE PRICE I is equal to 1 when the reference price system is implemented in the market until the last quarter of 2003 and 0 otherwise, and REFERENCE PRICE II is equal to 1 when the reference price system is implemented from the first quarter of 2004 on. We incorporate these variables in order to evaluate the effect of the two types of reference price systems on the number of entries. The number of GENERIC FIRMS already established in the market is included to explain how the number of incumbents affects the potential generic entrant decision. The NUMBER OF BRAND-NAME COMPETITORS in the market in addition to the

Footnote 5 continued
official ones. Most of the generics approved prior to 1997 were recognised officially as generics under the new 1997 regulation.

[6] The unit is €1,000,000 to avoid numerical problems in the estimation of the model. Revenues are adjusted for inflation with the CPI for medicines and pharmaceutical products from the Instituto Nacional de Estadística (INE). Using revenues as a proxy for profits may bias our estimates, as Daunfeldt and Rudholm (2009) highlight. However, this is the only data that are available in our case. Therefore, our results should be interpreted with caution.

Table 2 Structure of the data sample in 1997 and 2005

Number of generic firms	Active ingredient markets		Markets with reference pricing		Percentage of markets with reference pricing	
	1997	2005	1997	2005	1997	2005
0	26	19	–	–	–	–
1–5	14	27	0	17	0	62.96
6–10	1	13	0	9	0	69.23
11–35	0	18	0	18	0	100
Total	41	77	0	44	0	75.86

original firm is included in order to take into consideration the considerable number of copies and licensee medicines in the Spanish market. The variable ACTIVE INGREDIENTS PER ATC-4 is the number of molecules that compete in the same (four-digit ATC) therapeutic subgroup. This variable is the best available approach to therapeutic substitution but is subject to measurement error since substitutability differs between active ingredients in the same therapeutic subgroup, and drugs in other subgroups may also be substitutes (Danzon and Chao 2000). The last variable is AGE and is defined as the number of quarters since the first drug was authorised. This variable seeks to capture the maturity of the market.

Table 2 shows some descriptive statistics about the structure of our data sample in the first quarter of 1997 and the second quarter of 2005. In 1997, most markets had either no generics or five generics at most. In 2005, there were still many markets with no generics, but most markets had from 1 to 5 generics, many had 6 to 10, and a handful had 11 or more. On the other hand, in the second quarter of 2005 reference pricing had been applied in 44 of the 77 markets analysed (57.14%); interestingly, this was not the case in all of the active ingredient markets with generics but only in 75.86% of them.

Figure 1 shows the number of generic entries per quarter aggregated for all the active ingredient markets. We see a strong increasing trend in the number of entries until the first quarter of 2002, when the Spanish generic market reached 31 entries, although with major oscillations between quarters. A large number of original drugs were reaching the threshold of ten years since first authorisation (the "ten-year rule") during this period. From that quarter onward, there was a reduction in the number of entries until it reached eight entries per quarter in the fourth quarter of 2003. After that there was a slight recovery in the number of entries.

6 Results

Table 3 reports the estimates of the negative binomial and zero-inflated negative binomial regressions. In both cases we control for unobserved market and time heterogeneity with fixed effects.

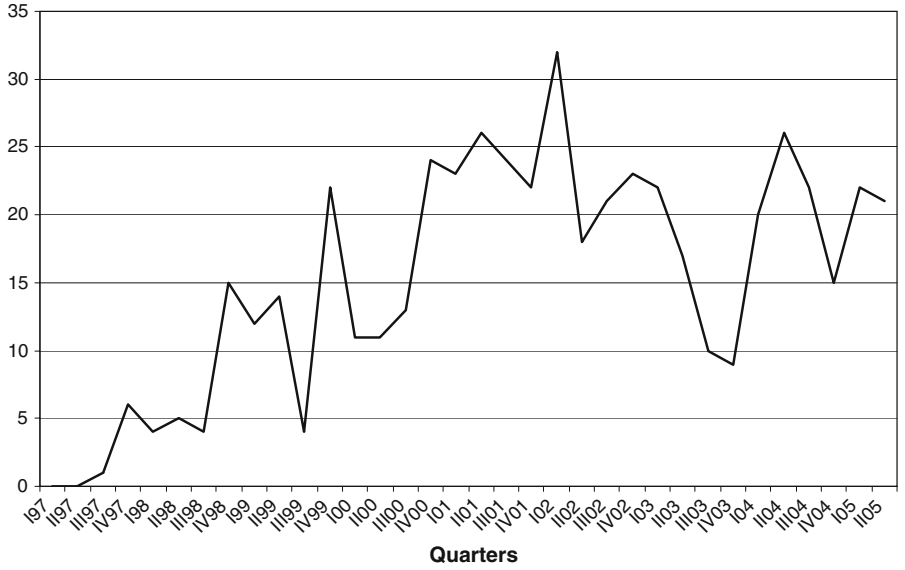

Fig. 1 Generic entries per quarter (flow)

The coefficients estimated in both models are similar and robust to the specification. The Vuong test does not provide evidence in favour of one of the two estimated models, and the likelihood-ratio tests reject the null hypothesis of no overdispersion, indicating evidence in favour of the negative binomial model in comparison with the Poisson option. For the sake of brevity we do not show the market and time fixed effects.[7]

In both models, estimates for the coefficients of revenues, reference pricing systems, number of generic firms, brand-name competitors, and age are significant. The signs of the estimated coefficients are as expected. The most counterintuitive case is the positive coefficient of the number of brand-name competitors. Only the number of molecules in the therapeutic subgroup does not seem to have a significant impact on the flow of generic entries.

In line with the previous literature, the revenues have a positive parameter, showing that there are more entries in larger markets. If revenues increase by € 1 million, the number of entries increases by 3.60%.[8] The reference price system has a negative effect. When the first system was implemented, the expected number of entries

[7] We calculate the test of serial correlation suggested by Cameron and Trivedi (1998), and it does not reject the null hypothesis of no serial correlation. This was the expected result since as Cameron and Trivedi (1998) stated, when the number of firms in an industry is modelled, "serial correlation is much less for the net change in the number of firms (entry minus exit) than for the total number of firms in the industry (cumulative entry minus exit)".

[8] Since the model has an exponential conditional mean, the coefficient of this continuous variable can be interpreted as a semi-elasticity (calculus method), whereas the remaining marginal effects are interpreted as percentage variations of the expected number of entries when there is a unit change in the integer-valued regressor (finite-difference method) (Cameron and Trivedi 2005).

Table 3 Entry model estimation results

	Negative binomial	Zero-inflated negative binomial
Revenues	0.0360*	0.0348*
	(0.0155)	(0.0143)
Reference price I	−0.6589*	−0.6703*
	(0.2785)	(0.2752)
Reference price II	−1.3055**	−1.3642**
	(0.4643)	(0.4690)
Generic firms	−0.0582**	−0.0697**
	(0.0161)	(0.0171)
Brand-name competitors	0.0950*	0.0864*
	(0.0383)	(0.0352)
Active ingredients per ATC-4	0.0883	0.1210
	(0.1065)	(0.1044)
Age	0.1831**	0.1726**
	(0.0161)	(0.0156)
Constant	−26.4132**	−24.9050**
	(1.6581)	(1.6599)
Number of observations	1,963	1,963
Log pseudo-likelihood	−885.0300	−882.4300
LR test (p-value)	45.1000 (0.0000)	14.2400 (0.0000)
Vuong test (p-value)	1.0000 (0.1600)	

Note: Clustered robust standard errors are in brackets. ** and * indicate $p < 0.01$ and $p < 0.05$ statistical significance level respectively.

was approximately 48% smaller, and the application of the second reference pricing reduced the number of entries by 72.90%. An increase of one generic incumbent reduces the expected number of entries by 5.65%. When there are more generic firms, there is more competition, and the market becomes less attractive to potential entrants. Instead, the positive coefficient of the number of brand-name competitors indicates that when there is an additional brand-name competitor in the market the average number of generic entries increases by 9.97%. Lastly, each additional quarter since the first authorised drug in each market increases the expected number of entries by 20.10%.

7 Discussion

In general the results are consistent with the results in the prior literature. Our estimates show that some of the main drivers of generic entry in less regulated markets, such as market revenues and the number of incumbent generic firms, are also key drivers of entry in the Spanish market.

However, some of our estimates differ from the previous literature. We find a positive impact of the number of brand-name competitors on entry, contrary to what it has been estimated for the American market by Bae (1997) and Scott Morton (2000) and for the Japanese market by Iizuka (2009). Our result is similar to what was also found by Magazzini et al. (2004) for a set of countries that included France, Germany, the UK, and the US. They concluded that the explanation could be that patent holders were not able to create strong brand loyalty before patent expiration. Also, as we argued in section four, in some markets many brand-name copies were already on the market before generics were introduced. In those markets, generic entrants were unlikely to face infringement litigation by pioneering firms. This should reduce expected entry cost and increase the number of entries in those markets.

We find a positive impact of age on entries. By contrast, age was expected to have a negative effect on entries because mature markets and markets in which the brand-name products have been sold exclusively for a long time seem to be less attractive for generic entry. Rudholm (2001) found that the number of quarters in which the brand-name drug was sold under patent protection negatively affected the number of generic entries. Our result might be related to the relatively less strict exclusivity that is enjoyed in Spain by original brand-name products under the patent regime in force for old products.

We find that the number of active ingredient competitors per therapeutic subgroup is not a significant driver of entry. Scott Morton (2000) also reported that the number of substitutes in the same therapeutic group did not affect generic entry. It could be due to a lack of substitutability between molecules.

In relation to the impact of the reference price system, even though it was supposed to foster generics' take-off, on the contrary it seems to have constrained generic entry. A likely explanation may be that the main advantage of generic drugs with respect to brand-name drugs is their lower price. By contrast, brand-name drugs have the advantage of being known by both physicians and patients, who have previous experience prescribing and consuming them, and firms build up a brand image by informing doctors and patients about the clinical properties of their brand.

In Spain it has been observed that when the reference price system is implemented in any active ingredient market, brand-name firms quickly set their prices very close to the reference price. This observed result in Spain is consistent with the idea of price convergence toward the reference price that was suggested by Danzon and Ketcham (2004). In fact, since 2004 brand-name firms have been forced to reduce their prices to the reference price, so as to not be excluded from the list of publicly financed drugs. The implementation of this second reference price system has reduced the entry of generics more than did the previous system, which allowed brand-name products to have a price higher than the reference price. This convergence in prices has caused generic drugs to lose their main advantage because generic drug prices have become very similar to brand drug prices (Puig-Junoy 2004a,b, 2007). Since in the second reference pricing system the cluster of drugs is more extensive than in the first system, the results are also consistent with Brekke et al. (2007). From their theoretical model they argue that reference pricing, and in particular therapeutic reference pricing, might discourage generic entry.

Rudholm (2001) found that the reference price system had no effect on generic entry in the Swedish market although, as the author indicated, this result might be due to the fact that this variable combines the reference pricing implementation with other reforms that made it easier to register new generic drugs. Also for the Swedish market, Ekelund (2001) found that the reference price system reduced the likelihood of generic entry. Our estimates indicate that there is no need to implement the reference price system in order to achieve generic entries in those markets that are large enough for several generic firms to enter. It might even have adverse effects because it deters further generic entry. Such reference pricing might be good for achieving cost savings for consumers, but it does not encourage generic entry or the consumption of generics.

One limitation of our work is that we have restricted our analysis to those active ingredient markets with consumption greater than €8 million during the year previous to meeting the "ten-year rule" (or the first year available in our dataset). This fact could bias downwards the estimated coefficient of the variable REVENUES (i.e., market size) and could increase its standard error.

Additionally, our model does not control for incumbent strategic behaviour such as entry-deterring strategies. Brand-name firms may have incentives to introduce their own "generics" (Mestre-Ferrándiz 1999; Hollis 2005; Reiffen and Ward 2007), to create product line extensions (Hong et al. 2005), to over-invest in advertising in order to deter generic entry (Königbauer 2006), etc. This is a topic for assessment in future research.

8 Conclusion

The evidence from drug markets subject to strict price regulations such as those implemented in Spain shows that the drivers of generic entry are similar to those found in other more market-friendly environments. However, the evidence also shows that the reference price system constrains the take-off of generic markets.

There are three key drivers for fostering generic entry: One is the number of brand-name firms in the market. When there are more copies or licensees in the market, there is less original brand loyalty and less risk of litigation for patent infringement, and the number of generic entries increases considerably. The second driver of entry is market size in terms of revenues. Finally, the age of the market also seems to spur generic entry.

Two main factors slow down generic entry: The first is the number of generic incumbents. When the number of generic firms already in the market is considerable, there are more direct competitors, and the number of generic entries decreases. The other is the setting up of a reference pricing system. From the moment the system is implemented, the number of entries is lower. This is the case especially when the reference price system forces brand-name drugs to reduce their prices to the reference price, since it deprives generic drugs of their main advantage vis-à-vis brand-name equivalents: a considerably lower price.

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9 Appendix

See Table 4

Table 4 List of active ingredient markets

ATC code	Active ingredient	ATC code	Active ingredient
A02AD02	Magaldrate	J01CA04	Amoxicillin
A02AD03	Almagate	J01DC02	Cefuroxime
A02BA02	Ranitidine	J01DC04	Cefaclor
A02BA03	Famotidine	J01DD08	Cefixime
A02BC01	Omeprazole	J01FA01	Erythromycin
A03FA02	Cisapride	J01FA06	Roxithromycin
A03FA91	Cinitapride	J01FA09	Clarithromycin
A06AD11	Lactulose	J01FA11	Miocamycin
A10BB01	Glibenclamide	J01MA02	Ciprofloxacin
B01AC05	Ticlopidine	J01MA06	Norfloxacin
B01AC18	Triflusal	J02AC01	Fluconazole
C01DA14	Isosorbide mononitrate	02AC02	Itraconazole
C01EB15	Trimetazidine	J05AB01	Acyclovir
C02CA04	Doxazosin	L02AB01	Megestrol
C03BA11	Indapamide	L02BA01	Tamoxifen
C03CA01	Furosemide	L02BB01	Flutamide
C04AD03	Pentoxifylline	L04AA01	Ciclosporin
C05BX01	Calcium dobesilate	M01AB05	Diclofenac
C05CA05	Hidrosmin	M01AB16	Aceclofenac
C07AB03	Atenolol	M01AC01	Piroxicam
C08CA01	Amlodipine	M01AE02	Naproxen
C08CA04	Nicardipine	M04AA01	Allopurinol
C08CA05	Nifedipine	N02AX02	Tramadol
C08CA06	Nimodipine	N02BB02	Metamizole sodium
C08CA08	Nitrendipine	N05BA05	Potassium clorazepate
C08DA01	Verapamil	N05BA06	Lorazepam
C08DB01	Diltiazem	N05BA12	Alprazolam

Table 4 continued

ATC code	Active ingredient	ATC code	Active ingredient
C09AA01	Captopril	N05CD06	Lormetazepam
C09AA02	Enalapril	N05CF02	Zolpidem
C09AA03	Lisinopril	N06AB03	Fluoxetine
C09AA05	Ramipril	N06AB05	Paroxetine
C09AA06	Quinapril	N06BX06	Citicoline
C09AA08	Cilazapril	R03DA04	Theophylline
C10AA01	Simvastatin	R05CB01	Acetylcysteine
C10AA02	Lovastatin	R05CB06	Ambroxol
C10AA03	Pravastatin	R05DB21	Cloperastine
C10AB02	Bezafibrate	R06AX13	Loratadine
C10AB04	Gemfibrozil	R06AX22	Ebastine
H02AB13	Deflazacort		

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