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DISCUSSION PAPER

Originally published by Ipea in October 2010 as number 1511a of the series Texto para Discussão.

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Brasília, January 2015

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Eduardo P. S. Fiuza²
Barbara Caballero³

1. We thank Carla Marigo, Leticia Klotz, Guilherme Lima, Felipe Ruperti and Fernando Moura for valuable help, and Anvisa's staff, Brazilian Ministries of Finance and Justice, Leandro Safatle and his team, Grupemef, and ABCFarma for data and advice. Financial and material supports were provided by CNPq (Grants PQ 311766/2006-4 and IC 503122/2007-6), Ciee, Ipea's Program for Development Studies (PNPD) and Ministry of Justice (Convenio MJ 01/2006), all of them gratefully acknowledged. We thank attendants at the EARIE Conference and seminars at PUC-Rio and EPGE-FGV for useful comments. The usual disclaimer applies.

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DISCUSSION PAPER

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Discussion paper / Institute for Applied Economic

Research.- Brasília : Rio de Janeiro : Ipea, 1990-

ISSN 1415-4765

1. Brazil. 2. Economic Aspects. 3. Social Aspects.
I. Institute for Applied Economic Research.

CDD 330.908

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JEL: L65, C25, L13.

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SINOPSE

Duas grandes mudanças na legislação brasileira durante os anos 1990 remodelaram a indústria farmacêutica local: a ratificação do acordo TRIPS em 1996, incluindo uma provisão para a concessão de patentes a inventos em *pipeline*; e a Lei dos Genéricos, de 1999, que introduziu o teste de bioequivalência e facilitou a substituição de medicamentos pioneiros por genéricos na dispensação. Foram gradualmente retomados controles de preços na virada do século. O presente artigo estima a entrada de versões genéricas de medicamentos fora de patente nas várias classes terapêuticas, usando tanto modelos de dados de contagem como multinomiais ordenados. Os resultados indicam que um modelo simples de Poisson tem um pior ajuste, embora as variáveis explicativas exibam o mesmo padrão de significância e sinais. A maioria das variáveis explicativas utilizadas é significativa, em particular *proxies* para o tamanho do mercado potencial (valores defasados dos faturamentos dos medicamentos), concentração de mercado e idade do medicamento de referência. Múltiplas marcas (e não simplesmente genéricos próprios) e estratégias de *evergreening* parecem ser efetivas em deter entradas.

ABSTRACTⁱ

Two major changes in Brazilian legislation during the 1990s reshaped the local pharmaceutical industry: the ratification of the TRIPS agreement including a provision for pipeline inventions in 1996, and a Generic Drug Act in 1999, which introduced bioequivalence tests and facilitated generic drugs' substitution for the pioneer drugs at dispensing. Genuine generic drug entry may be dated back to 2000, when the first applications were approved. Price controls were gradually resumed in the turn of the century. The present article estimates entry of generic versions of off-patent drugs into various therapeutic classes using both count data and ordered multinomial models. Results point out that a simple Poisson model fits the data poorly, calling for further modelling of overdispersion or of excess zeros by applying Negative Binomial and zero-inflated count models. Ordered models seem to provide a worse fit, even though the explaining variables display the same pattern of significance and signs. Most of the

i. The versions in English of the abstracts of this series have not been edited by Ipea's editorial department.
As versões em língua inglesa das sinopses (abstracts) desta coleção não são objeto de revisão Editorial do Ipea.

explaining variables utilized are significant, in particular a proxy for potential market (lagged revenues of the drug), market concentration, and age of the pioneer drug. Multiple brands (rather than simply own-generics) and evergreening strategies seem to be effective in deterring entry.

1 INTRODUCTION

The present work is the first estimation of generic drug entry models in Brazil. The Brazilian market is of interest because of its size (tenth largest in the world) and because of two major changes in Brazilian legislation during the 1990s that reshaped the local pharmaceutical industry. The first one was the ratification of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement passed by the Congress in 1996, which included a provision for pipeline inventions. The second one was the Generic Drug Act in 1999, which introduced bioequivalence tests and facilitated generic drugs' substitution for the pioneer drugs at dispensing. Price controls were gradually resumed in the turn of the century following exchange rate steep depreciation. Genuine generic drug entry may therefore be dated back to 2000, when the first applications were approved.

The present article estimates entry of generic versions of off-patent drugs into the various therapeutic classes using both count data and ordered multinomial models. Results point out that a simple Poisson model fits the data poorly, calling for further modelling of overdispersion or of excess zeros by applying Negative Binomial and zero-inflated count models. Most of the explaining variables utilized are significant, in particular the lagged values of the revenues of the drug (proxy for potential market), of the number of own generics and other brands of the originator's group, and of the market concentration, and the age of the pioneer drug. In the ordered models significance and signs are similar to the count models. Marginal effects of the explaining variables are dampened as the number of entries increases.

The present article features four more sections. Next one brings a short description of the Brazilian pharmaceutical market and of its regulation. The following section surveys previous attempts to estimate empirically drug entry, with emphasis on generics, and introduces the model. The fourth section presents the results, performs diagnostic tests and discusses the results. The last section concludes.

2 THE BRAZILIAN MARKET

Brazil is at present the tenth largest market for pharmaceuticals in the world. Even though sales in units (1.8 billion in 2008) do not display a clear time trend—they are 2.5 percent below 1997 level, but twenty percent above 2003 level (Febrapharma/

Grupemef)—revenues in dollars (deflated by US and Brazilian price indexes) increased 2.35 percent a year during the same elapsed time. Revenues in local currency (deflated by Brazilian general price index) have also been steadily increasing: average 9.9 percent p.a. during 1997-2008 (Febrapharma/Grupemef), but the ratio sales/Total Brazilian GDP in nominal values has been oscillating in the percentual range [0.9, 1.11], an average 1.05 percent during the same period.

As in developed countries, sales in value increase more than units because of differences in the mix of drugs consumed. As more expensive drugs are launched, prices go up. On the other hand, two forces have kept prices down. For one, a severe price control was gradually resumed in the first years of the century, more ingenious and comprehensive than its counterpart adopted during the 1970s and 1980s. Second, a new strategy of promoting nonproprietary names has successfully been pursued since 2000. In fact, generic drugs achieved in 2008 a 13.8 percent market share in value, 16.9 percent in volume—Intercontinental Marketing Services (IMS Health apud Pro-Genérico). It is not a bad record if one takes into account generic drugs’ infancy in the country. Table 1 provides for comparison with other selected countries with tradition in generic drugs.

TABLE 1
Generic drug market share in selected countries
 (In %)

Country	Revenue	Volume
USA	13	60
Germany	26	60
United Kingdom	26	60
Canada	22	45
France	14	35
Spain	13	30
Brazil	13,8	16,9

Source: Associação Brasileira das Indústrias de Medicamentos Genéricos (Pró-Genéricos).

To better understand how the Brazilian market functions, a brief historical summary is useful. Price controls and absence of patent enforcement were the main strategies of the military government since the beginning of the 1970s. On the one hand, an import substitution attempt required that foreign patents were not recognized by Brazilian law. In fact, chemical-pharmaceutical product patents were not enforced

since 1945, and process patents were also revoked in 1969. On the other hand, macroeconomic policy in Brazil fostered inflation and led authorities to adopt price controls countervailing measures. Price controls, however, were in part circumvented by the pharmaceutical firms by introducing new packages, whose prices were not subject to scrutiny.

The 1990s were a time of major transformations in the Brazilian market. Price controls as a whole were replaced by a modern Antitrust legislation. A new Antitrust Act was passed in 1993, and subsequently reformed in 1994 (Lei nº8.884). Pharmaceutical drug price controls were phased out in 1992, and a series of price hikes followed. Antitrust investigations for “abusive price increases” were at that time filed at the Antitrust Tribunal (Cade)—a terrible public misunderstanding of the spirit of the new Antitrust legislation. As regards import substitution, the process was also reversed. Import tariffs had already been lowered, and non-tariff barriers dismantled, beginning in 1989. Local content in drugs marketed in Brazil consequently tumbled.

In 1996 a radical turn in intellectual property protection came out: the World Trade Organization (WTO)–TRIPS agreement from the Uruguay Round was finally ratified by the Congress (Lei nº9.279). This ratification brought back *patent enforcement* as from 1997. The maximum patent lifetime allowed was 20 years, but no extension was provisioned (in particular, none of the extensions provisioned by the US Patent Restoration Act of 1984). On the other hand, a controversial provision for *pipeline inventions* was introduced in the legislation: patents deposited under former rules (Lei nº5.772, from 1971) and not marketed yet were eligible to require convalidation by the Brazilian Patents’ Office–Instituto Nacional de Propriedade Industrial (Inpi); the patent lifetime was subject to the same expiration date of the first patent lifetime abroad, and not exceeding 20 years (upper limit of the Brazilian patent law). Other products already marketed or whose patents had already expired did not benefit from this.

The Brazilian legislation went much further than what was required by TRIPS and included a pipeline provision, where patents claims could be filed in the country between 1996 and 1997, allowing the protection of pharmaceutical patents that were already filed in at least one other country, without any national examination and even if the patent was prior to TRIPS signature, as long as the product was not yet commercialized anywhere or nobody had done efforts in the country for exploration at the time of the request (CHAVES; REIS, 2007).

Another feature of the Brazilian law worth mentioning is that pharmaceutical patents are granted only after registration at Agência Nacional de Vigilância Sanitária (Anvisa)—the Brazilian equivalent to United States Food and Drug Administration (FDA)—is cleared (Lei nº 10.196 from 2001; in force since 1999). As such, new drugs' patents are never scrutinized by Anvisa during registration for safety and effectiveness.

The other major transformation in the 1990s was the enactment of the first *Generic Drug Act* in 1999. The farthest the previous legislation had reached was requiring an outstanding disclosure of the Active Pharmaceutical Ingredient (API) description below the brand name in the package, so as to allow for comparison of brands. But prescribing doctors had reason to concern that drugs of same API were not substitutable for each other.

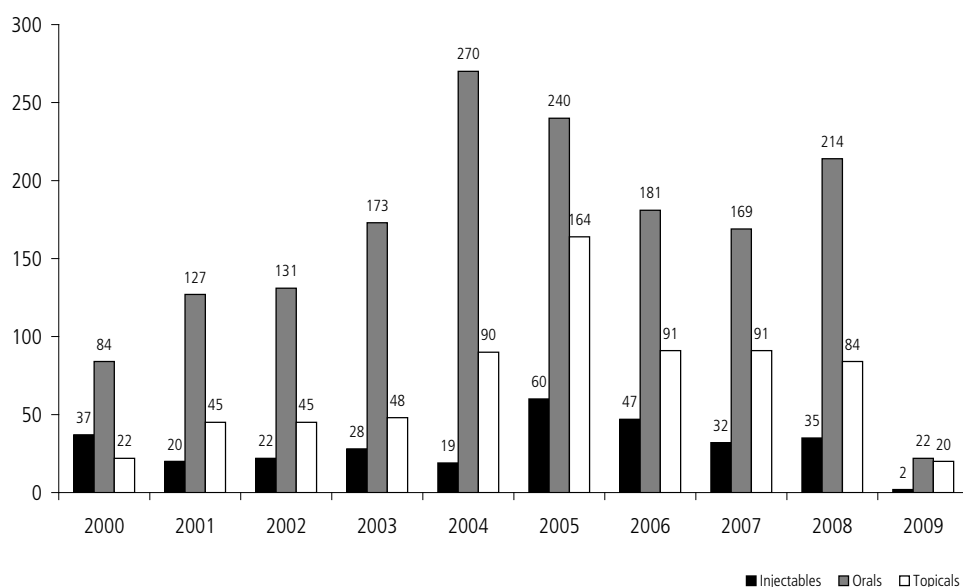
In fact, until 1999 the registration of new drugs only required safety tests, and absolute effectiveness; no comparisons were undertaken between drugs based on the same API. Generic names were utilized by pharmaceutical companies without demonstrating bioequivalence. They were actually *similar* drugs. In sum, Brazil had only pioneer (not necessarily originator's) and/or similar (branded or non-branded) versions of a same drug. The Generic Drug Act (Lei nº 9.787) introduced bioequivalence tests and the generic drug as bioequivalent. Similar drugs were then mandated to adopt brand if they had none. Generic names (either Brazilian or International Non-proprietary Names) have since then been allowed only to drugs bioequivalent to the pioneer. On the other hand, branded drugs may be pioneer (reference) or similar.²

Because of the TRIPS ratification, both similar and generic drugs are now only permitted if the original drug is off-patent (i.e. either the patent has already expired or it has never been enforced). But it is worth mentioning that no exclusiveness period is granted for the first generic, as it happens in the U.S.

The first generic drugs were launched in 2000. Figure 1 shows the evolution of generic drug registrations. Table 2 displays the evolution of drugs, firms and package versions.

2. Homedes, Linares and Ugalde (2005) report that in most Latin American countries (Bolivia, Chile, Colombia, Costa Rica, Ecuador, Nicaragua, Peru and Uruguay) pharmaceuticals are classified under two categories only: Branded (comprising branded originals, branded generics and branded similar) versus Generics (original or own generics, copy generics and unbranded similars). Argentina features three categories: innovative (branded original or copy), similar (non-bioequivalent), while generic applies to bioequivalent drugs, both branded and unbranded.

FIGURE 1
Number of generic drug registrations, by route of administration



Source: Anvisa/Núcleo de Assessoramento Jurídico em Regulação (Nurem), last update as of February 25, 2009.

TABLE 2
Evolution of generic drug presence in Brazilian market

	2000	2001	2002	2003	2004	2005	2006	2007
APIs	68	140	203	220	243	271	282	263
Firms	11	25	31	33	36	37	40	37
Drugs	118	295	503	619	818	1.040	1.169	1.099
Package versions	135	490	594	1.029	1.611	2.069	2.385	2.245

Source: Anvisa/Nurem.

Price freedom, however, experienced a very short duration. In 1998 prices started being monitored by the Ministry of Finance. In 1999 the local currency's huge devaluation prompted a negotiation between government and manufacturers to delay the foreign cost passthrough (as most APIs in Brazil are now imported). Several agreements followed. In December 2000 the government resumed a price control based in cost spreadsheets, similarly to the system in force during the 1970s and 1980s. CAMED, a regulatory board assembling ministries of Health, Finance and Justice, and Anvisa, was then created. The same formula was applied in 2001 and 2002. In January 2003 three OTC (i.e., non-prescription) drug classes with low concentration levels – as measured by the Herfindahl-Hirschman Index (HHI) had their prices released from control. In June 2003 CAMED was replaced by Câmara de Regulação do Mercado de

Medicamentos da Anvisa (CMED) (assembling the same government bodies, plus the Secretariat of Government and the Ministry of Industry and Trade) and a unique price cap was introduced, based on the following formula:

$$\Delta p = IPCA - X + Y + Z$$

where CPI stands for the Consumer Price Index; X is a (prospective) productivity factor; Y is a credit for non-manageable (past) cost raises; and Z allows for different price raises according to competition level in each therapeutic class market (raise rate is equal for all drugs in the same class).

More importantly, generic prices had been following an unpublished rule of thumb that entrants should price 35% below the reference drug prices; this rule was then officially adopted in 2004 by CMED.

Since patents are not subject to so many extensions as in the United States³ and since generics are not granted exclusiveness, the main entry-deterrence strategies left in Brazil for the incumbents (reference drug sellers) are to launch follow-on drugs (life-cycle strategies, also known as *evergreening*), to launch own generics and/or to cross-license their generics. Additional strategies available are the ones already surveyed by the European Commission [EU]: strategic patenting (especially patent clustering); patent litigation; patent settlements; and questioning safety of generics. The first three strategies are more likely to occur and to be effective in the upcoming years, when a large wave of patents—in particular, many blockbusters—will expire locally. As a matter of fact, the Inpi estimated that foreign firms had seventy patent extensions applied for in July 2009, and that the wave of patent extension applications was started in 2004 by firms benefited from pipelines (*DCI*, July 20, 2009). Many of them simply claimed to be validating locally patent extensions obtained in the countries of origin (*IstoÉ Dinheiro*, June 26, 2006). We will turn back to this issue when commenting the data utilized.

In our sample, follow on drugs are already of concern: we counted 93 single-API drugs containing at least one extended-release version, with a distribution ranging from 1 to 23 brands per drug. As the European Commission puts it:

3. The U.S. patent legislation, including the 1984 Hatch-Waxman Act, provided for several entry-deterrence strategies. A useful source about these strategies is the Federal Trade Commission 2002 special report (FTC, 2002).

“In a number of cases, originator companies tried to switch patients of their medicine facing imminent loss of exclusivity to a so-called second generation, or follow-on, medicine. (...) In some cases, the first medicine was withdrawn from the market some months after the launch of the second generation medicine. If originator companies succeed in switching patients by that point, the probability that generic companies will be able to gain a significant share of the market decreases significantly. If, on the other hand, generic companies enter the market before the patients are switched, originator companies have difficulties in convincing doctors to prescribe their second generation medicine and/or obtain a high price for it” (European Commission).

It is also worth noting that in Brazil the regulator has to elect a new reference drug when the original one is discontinued, and this may affect the bioequivalence status of existing generics.

Regarding own generics, we detected in our sample 37 generics belonging to their respective reference drug seller groups (in 34 single-API drugs, as some sellers market generics under different umbrella brands). Moreover, many unnotified co-marketing agreements have been discovered by antitrust authorities, but the registration department at Anvisa has not been able to keep track of them. This is an important antitrust issue, because firms may divide their markets among them. An attempt to measure market division should be undertaken in future extensions of this paper, by exploring in greater depth the data base with respect to concentration and diversification of the firms.

The use of lobbying before the regulatory and competition agencies, however, has not been an important practice in Brazil. On the contrary, the antitrust agencies investigated the reference drug makers’ association for coordinated pressure (agreed during a documented meeting) on wholesalers to prevent them from distributing generic drugs, for deceitful advertisement questioning generics’ safety, right after the enactment of the Generic Drug Act, and for distributing to doctors stickers labeled “I do not authorize the substitution of the prescription at dispensing” (without this order, any reference drug may be legally replaced by the pharmacist at dispensing). The attempt investigated was punished by the Brazilian antitrust tribunal (CADE) in 2005, when the firms taking part in the meeting were fined in one percent of their previous year’s revenues, except the agreement leader, Janssen-Cilag, whose fine was doubled.

3 LITERATURE ON PHARMACEUTICAL ENTRY: A SURVEY

To the best of our knowledge, only two econometric estimations have been applied to the pharmaceutical in Brazil, all of them trying to measure the impact of generic drug entry on prices. Fiuza and Lisboa (2003) pointed out that branded drug prices would go up in face of similar drugs' market power increase, a result similar to Frank and Salkever's (FRANK; SALKEVER, 1997), but the data base utilized was previous to the Generic Drug Act.

Nishijima (2008) used a different sample (covering both before and after the Generic Drug Act) and a different model from Fiuza and Lisboa's (difference-in-differences) and got different results, namely that reference drug prices would go down as they faced greater numbers of generic copies. Lopes (2009) recently replicated Fiuza and Lisboa's model with more drugs in a more recent period and reached the same conclusions as the latter.

A better understanding of the process that generates generic drug entry is therefore of extreme interest for Brazilian policymakers, for the industry and for the academia in general. A few models in the international literature may then become a starting point for our work.

As Reiffen and Ward (2005) point out, the generic drug industry is a useful field for studying empirically how competition evolves within a market: *i*) each chemical represents a distinct experiment; *ii*) information about the market for each drug is observable to researchers; e.g. date of opening of the market (the patent expiration date); *iii*) firms must sink significant costs to apply for the authorities' approval prior to knowing when, or how many, rivals will enter the market.

Papers by Danzon and Chao (2000) and Lanjouw (2005) indicate that price regulation undermines competition in off-patent markets because they discourage generic drug entry. In the same direction—even though looking for industrial policy, scale economies, and safety regulation explanations—Thomas (1996) also finds that the same countries with weaker or non-existent price control—and consequently higher prices (United States, United Kingdom, Germany and Switzerland)—have stronger competitive performance, and account for most of the global drugs launched (drugs sold in more countries, and with greater market shares), while other developed countries tend to launch more often local drugs.

The main empirical references in generic drug entry are Scott-Morton (1999, 2000) and Reiffen and Ward (2005). The three papers studied the US market.

Scott-Morton (1999) used individual data on Abbreviated New Drug Applications (ANDAs) from the FDA during the 1984-1994 period to estimate entry. Firm characteristics were combined with market characteristics to produce novel explaining variables. She explored all ANDAs of the period, totaling 1,233 unique combinations of applicant, drug, dosage form, and patent expiration, in 363 markets. The FDA provided the submission date, approval date, applicant name, API, dosage form, route, and strength. She merged these data with IMS revenue datas from hospital and drugstore audits, and classified them into therapeutic classes using a standard pharmaceutical reference. Her approach uses observations at firm and drug (API, route, strength) level. Following Berry (1992), she creates a set of potential entrants, who then decide to enter or not, a discrete choice (probit) decision. Thereby she is able to include as explaining variables a range of firm characteristics, such as proxies of firm's experience with the ingredient, form, therapy and/or drug family—(KYLE, 2006) also uses firm's experience proxies (including country-class experience) along with geographical proximity and cultural and regulatory likeness measures for estimating entry of New Chemical Entities (NCEs) into the G7 countries as from 1980. The main indications of the drugs are also classified into chronic or acute conditions.⁴

Scott-Morton (2000) adopted a Poisson count data modelling for testing whether pre-expiration brand advertising deters generic entry. Her sample covered drugs that lost patents from 1986 to 1991. She observed revenues and quantity from two years before patent expiration to one year after expiration, and advertising data from three years before to one year after the same event. She found characteristics of a drug market before patent expiration to be significant predictors of generic entry. Entry was more likely in markets featuring higher market revenues, high share of sales to hospitals, drugs in topical form and for treating chronic conditions. The author also got a very small estimate of the effect of advertising on entry, and noted that its sign varied with the type of advertising.

4. We shall pursue this approach in a near future extension, after learning with the present research, merging registration data from Anvisa (important for testing hypotheses about firms' behaviors following entry authorization), and constructing the relevant proxies.

Reiffen and Ward (2005) developed a system of equations to explain generic entry, generic post-entry market share, and entry price. For entry, an expected profit was assumed to be zero for the last entrant; from this condition, and assuming that entry decisions are taken independently and simultaneously; the resulting mixed strategy Nash equilibrium number of entrants followed a binomial distribution, approximated by a Poisson distribution, yielding in turn a hazard rate regression; an iterative procedure was undertaken to account for the endogeneity of the (unobserved) rent variable present in the three equations. The post-patent-expiration price when there are i generic drugs of type k , relative to the price of the pre-entry branded version of the same drug was regressed on cost and demand shifters and on dummies for each possible number of generics. The total log-revenue of the generic drugs was then regressed on the average pre-patent-expiration branded version revenue and on other explaining variables (some of them present in the previous regression equation). The results indicate that the flow of generic industry rents in the United States increases for the initial 5 to 10 months following patent expiration but then falls as more entrants compete away price-cost margins. For markets of sufficient size entry will ultimately lead to near-competitive levels, while prices remain above marginal cost in small markets without inducing entry. The authors used a data set covering 31 drugs that went off patent in the late 1980s and early 1990s in the United States.

Bae (1997) used a proportional hazard regression model to estimate time of delay (in days) to entry after patent expiration in the United States for a list of 77 single-API drugs that lost patent during the period 1987-1994. Again, entry is faster in markets of greater revenue, with fewer branded competitors, and for chronic-use drugs. The Medicaid Drug Rebate Program, which imposed mandatory rebates off the private sector wholesale prices for the Medicaid (public) purchases, had a positive impact on the entry delay.

Hudson (2000) studied entry in four developed countries: United States, United Kingdom, Germany and Japan. United States and Japan are the greatest pharmaceutical markets in the world, as measured by revenues. He analyzed: *i*) the determinants of generic drug entry; *ii*) determinants of entry delay when entry does occur; *iii*) impact of entry on the original brand's sales. His results also suggest that the greater the market, the more likely are entry and its impact on the original drug's sales. His estimations are based on a sample of the 50 best-selling APIs present in at least one of these countries.

Rudholm (2005) analyzed determinants of generic entry in Sweden, where a reference pricing system has been used for reimbursement purposes since 1993. Unfortunately his data (a panel of 22 APIs from 1972 to 1996) have a short overlap with the period after the introduction of this system. He ran an integer-valued autoregressive model by Non-Linear Least Squares, and found that expected profits affect positively the number of entries, but the longer the exclusivity period enjoyed by the branded pioneer drug, the lower the likelihood of generic entry.

Recent unpublished papers by Moreno-Torres and Borrell-Arqué (2007) and Iizuka (2008) analyze entry respectively in Spain and Japan, two heavily regulated markets, with tight price controls.

Spain is the 70th largest market in the world (50th in the EU), and price controls have been in force there since the 1920s. Reimbursement by the government has been subject to reference pricing since 2000. Following Berry (1992), and unlike Reiffen and Ward (2005), Moreno-Torres and Borrell-Arqué assume different entry costs and use a pure strategy equilibrium concept. Still they end up assuming a count data model: starting with a Poisson, and rejecting the hypothesis of equidispersion, they end up moving to a (zero-inflated) Fixed Effects Negative Binomial model. Their data set is an unbalanced panel covering 86 prescription drug APIs for a maximum number of 34 quarters, collected from the Spanish National Health System. They exclude OTCs, drugs for hospital consumption, non-oral drugs (thus excluding topicals and injectables), pediatric drug types, and drugs with more than one API. One singular feature of the Spanish price control system is that the drug maximum prices are fixed in a negotiation between the firm and the health authority and in particular new generic entrants have systematically been priced below the incumbent generic drugs. Moreover, as new generics enter, and due to the formula utilized, the reference price for reimbursement is recalculated downwards. Explaining variables include dummies for reference pricing and long duration treatment, age of the pioneer drug, number of generic firms in the market, and number of APIs in the therapeutic (ATC-4) subgroup. The first dummy and the last two variables are found significant and negatively signed, along with a (negatively signed) time trend and the (four-quarter) lagged market revenue level (found significantly negative). The results contrast with findings in the US market, but reinforce the thesis that regulations fostering generic substitution (the reference pricing system) deter entry.

Japan is the second largest market in the world, and is severely regulated. Curiously, as Thomas (1996) note, a great share of drugs launched in Japan are local, i.e., they are marketed only there. Retail prices are set by the government, while wholesale prices are free. Prices are updated every other year, following a formula that combines the wholesale and the retail average prices. Generic drug introductory prices are set 30% below the comparable brand-name drugs', and entry approvals are issued only once a year. Generic drugs' shares are quite low in Japan, for several reasons, according to Iizuka (2008): *i*) difficulty to substitute generics at pharmacies (only allowed when prescription used the nonproprietary name, a provision reversed in April 2008); *ii*) widely believed perception of low quality for generics; *iii*) uncertainty in supply side, due to sudden exits of generic firms. A new reimbursement premium was created in 2002 that incentives generic prescription. Iizuka uses prescription data instead of market level data for 97 API-form-strength combinations (57 APIs) from Japan Medical Data Center from 2002 to 2006 and also uses a count data model (a negative binomial regression on pooled data) to estimate generic drug entry. He obtains some very interesting findings: *i*) fewer generic firms enter if there is a large number of brand names already in the market; *ii*) entry differs across therapeutic classes (for instance, they are lower in classes that treat cancer and the nervous system, where entry costs are higher and expected revenues lower); *iii*) fewer generics enter a market with a high share of institutions where prescribing and dispensing are separated⁵—suggesting that integration take greater advantage of the generic drugs' higher markup; and *iv*) fewer generics enter markets mainly used in large hospitals, whose physicians are strongly connected to medical schools, where in turn professors are often involved with the development of branded drugs.

4 THE MODEL

4.1 METHODOLOGY

Our observation is a count of entries of generic drugs for a single-API drug in a given route of administration and ATC-3 class, in a given year. There are three basic approaches for estimating regressions where the dependent variable is a non-negative integer: *i*) the usual linear regression, sometimes undertaking some monotonic transformation of the dependent variable to render it continuous; *ii*) a regression using a count data specification, from the Poisson family; *iii*) an ordered multinomial regression.

5. A unique feature of this industry in Japan is the integration of prescription and dispensation of drugs by doctors, especially the office-based.

Since linear regressions are more known, we attain ourselves to describe the other two model families. We then discuss the pros and cons of the three approaches, and in the next section their results are compared.

4.2 COUNT DATA MODELS

Poisson

The starting point for standard count data analysis is the *Poisson* regression model. In a cross-section, the basic model usually utilized for explaining an integer-valued variable y_i is:

$$f(y) = \frac{e^{-\mu} \mu^y}{y!}$$

such that:

$$E(y_i | x_i) = \text{Var}(y_i | x_i) = \mu_i = \exp(x_i' \beta)$$

The advantages of the Poisson regression, according to Hausman, Hall and Griliches (1984) are: *i*) it is analogous to the standard regressions in the sense that the one obtains a parametrized mean conditional on explaining variables, estimated by some weighted least squares (nowadays extended to the generalized method of moments) or maximum likelihood procedure, and thanks to its global concavity the optimization algorithms converge fast; *ii*) the zero problem $y_i = 0$ is a natural outcome of the distribution, and the integer property as a whole is handled directly, in contrast to the usual logarithmic regression specification, where a continuous distribution needs to be truncated; and *iii*) the Poisson specification “allows for convenient time aggregation so long as its basic assumption of time independence holds true”, such that the summation of a Poisson-distributed variable over time also follows a Poisson whose mean equals the summation of the period means. However, the authors also point out, “the time independence property is also a potential weakness (...), given the often noted serial correlation of residuals in econometric specifications” (p. 911).

The Poisson distribution arises in two studies of generic drug entry: Scott-Morton (2000) and Reiffen and Ward (2005). The former very plainly asserts that a reasonable specification for regressing the number of entrants on the proposed explanatory variables is an exponential, thus yielding the Poisson family. The latter elaborate more the microfoundations for using a Poisson-type regression: they assume that the firms are

homogeneous in regard to their ability to enter and produce a generic drug. They also assume that generic rents are sufficient to enable at least one entry, and that each firm's profits from producing a drug are decreasing in the number of rival producers of the drug. Based on stylized facts that firms decide entry at a point usually 2 to 3 years prior to patent expiration, each firm's choice in a given market is modeled as independent and simultaneous. A generic drug firm deciding whether to enter or not forms an expected market profit by considering issues of demand, supply (other entrants), and regulatory uncertainty. Then it enters if the expected markup (net of variable costs)–Scott-Morton (2000)–or the net present value–Reiffen and Ward (2000)–covers the fixed cost of entry (namely, the cost of filing the ANDA). Thus, the larger the expected profits, the greater the number of entrants, until expected profit is zero:

$$E[N_i] = f(E[\Pi_i]) \tag{1}$$

where N is the number of generic drug firms and Π_i is firm i 's profit.

In the symmetric (mixed strategy) Nash equilibrium that comes out, each firm i chooses to enter market k with the same probability μ_k –reflecting the aforementioned firms' homogeneity–, which depends on the expected rents in the market. The resulting equilibrium distribution of the number of entrants is a binomial, which is then approximated by a Poisson.

For the Poisson Maximum Likelihood Estimator, it can be shown that (see CAMERON; TRIVEDI, 1998): *i*) consistency requires a correct specification of the conditional mean, but not that the dependent variable is actually Poisson distributed; *ii*) valid statistical inference using computed ML standard errors and t -statistics requires correct specification of both the conditional mean and variance. That requires equidispersion (i.e. the distribution's property that the mean equals variance, or equation (1), but, again, not a Poisson distribution for y ; *iii*) valid statistical inference using appropriately modified ML output is still possible when data are not equidispersed, as long as the conditional mean is correctly specified; in this case, it is necessary to adjust the standard error estimates, what yields a Pseudo-MLE; and *iv*) more efficient estimators than Poisson can be obtained if data are not equidispersed.

In fact, equidispersion in the Poisson model is a very severe restriction, analogous to homoskedasticity in OLS, and is often rejected by the data. To address this issue, a

number of alternatives have been proposed, departing in various extents from the basic Poisson model. We describe next the models we explored for the present study.

- Negative binomial

A more flexible specification allows for the conditional variance to be:

$$\text{Var}(y_i | x_i) = \omega_i = \omega(\mu_i, \alpha)$$

The most utilized specification for this function is the family:

$$\omega_i = \mu_i + \alpha \cdot \mu_i^p$$

In particular, the default Negative Binomial specification assumes $p = 1$ (NB1 model), so that the conditional variance becomes a *constant* multiple of the conditional mean:

$$\text{Var}(y_i | x_i) = (1 + \alpha)\mu_i = \phi \exp(x'\beta)$$

One derivation of the negative binomial is that the individual units follow a Poisson regression model, but there is an omitted variable v_i :

$$\mu_i = \exp(x_i' \beta + v_i) \tag{2}$$

such that v_i follows a Gamma distribution:

$$e^{v_i} \sim \text{Gamma}(\mu_i / \alpha, \alpha)$$

Another specification (NB2) is obtained when v_i follows another Gamma distribution:

$$e^{v_i} \sim \text{Gamma}(1 / \alpha, \alpha)$$

and therefore,

$$\text{Var}(y_i | x_i) = \mu_i(1 + \alpha\mu_i)$$

The distribution obtained can be interpreted as a parametric mixture of two distributions, the Poisson and a conjugate Gamma:

$$h(y | \mu, \alpha) = \int f(y | \mu, v) g(v; \alpha) dv$$

where $f(y | \mu, v)$ is the Poisson distribution referring to the conditional mean – equation (2) –, and $g(v; \alpha)$ in turn is another mixing distribution. In the NB1 case:

$$g(v; \alpha) = \frac{(\alpha^{-1})^{\alpha^{-1}}}{\Gamma(\alpha^{-1})} v^{\alpha^{-1}-1} e^{-v\alpha^{-1}}, \quad \alpha > 0 \quad (3)$$

where:

$$\Gamma(a) = \int_0^{\infty} e^{-t} t^{a-1} dt, \quad a > 0$$

Substituting the Poisson and the mixed Gamma – equation (3) – back into $h(y | \mu, \alpha)$, we obtain:

$$h(y | \mu, \alpha) = \frac{\Gamma(\alpha^{-1} + y)}{\Gamma(\alpha^{-1})\Gamma(y+1)} \left(\frac{\alpha^{-1}}{\alpha^{-1} + \mu} \right)^{\alpha^{-1}} \left(\frac{\mu}{\alpha^{-1} + \mu} \right)^y$$

and the log-likelihood to be maximized in the NB1 case is:

$$\ln L(\alpha, \beta) = \sum_{i=1}^n \left\{ \sum_{j=0}^{y_i-1} \ln(j + \alpha^{-1}) - \ln y_i! - (y_i + \alpha^{-1}) \ln(1 + \alpha \exp(x_i' \beta)) + y_i \ln \alpha + y_i x_i' \beta \right\}$$

- Zero-inflated models

Lambert (1992) introduced the Zero-Inflated Poisson in order to account for the excess number of zeros usually found in count regressions, which imply overdispersion. It can be interpreted as a mixture of the Poisson distribution $f_2(\bullet)$ with a degenerate distribution whose mass is concentrated at zero. A binary process with density $f_1(\bullet)$ sorts

the outcomes between the two distributions. Thus, a zero can be an outcome either of the degenerate distribution or of the Poisson distribution, and the resulting probabilities are:

$$\Pr[y_i = 0] = f_1(0) + (1 - f_1(0))f_2(0)$$

$$\Pr[y_i = r] = (1 - f_1(0))f_2(r), \quad r = 1, 2, \dots$$

The binary distribution is ordinarily specified as a logit with regressors z_i and parameters γ . The log-likelihood then becomes:

$$\begin{aligned} \ln L(\beta) = & \sum_{i=1}^n 1(y_i = 0) \ln(\exp(z_i' \gamma) + \exp(-\exp(x_i' \beta))) + \\ & + \sum_{i=1}^n (1 - 1(y_i = 0)) (y_i x_i' \beta - \exp(-\exp(x_i' \beta))) - \sum_{i=1}^n \ln(1 + \exp(z_i' \gamma)) \end{aligned}$$

The zero-inflated negative binomial follows the same reasoning, just substituting the negative binomial for $f_2(\bullet)$.

4.3 ORDERED MULTINOMIAL MODELS

In such models a fixed number of outcomes, say m , can be obtained, which can be then ordered into integer categories. Let the latent variable be:

$$y_i^* = x_i' \beta + u_i$$

Then define the observed outcome

$$y_i = j \quad \text{if} \quad \alpha_{j-1} < y_i^* \leq \alpha_j$$

where the α_j are the thresholds, or cutoff points, to be estimated along with the β parameters by MLE. It is conventioned that $\alpha_0 = -\infty$ and $\alpha_m = +\infty$. Then

$$\Pr[y_i = j] = \Pr(\alpha_{j-1} < y_i^* \leq \alpha_j) = F(\alpha_j - x_i' \beta) - F(\alpha_{j-1} - x_i' \beta)$$

where $F(\bullet)$ is the cdf of u_i . An ordered logit is such model where the cdf is a logistic distribution, and an ordered probit where the cdf is a Normal. In the former case,

there are $K + m - 1$ parameters to be estimated, where K is the dimension of β , while in the latter case, there are $(m - 1)(K + 1)$ parameters. These models have been applied to count data that take very few values. In some cases, as in our present study, the frequency of higher values is low enough so that an upper censoring is undertaken (namely, entries above five are censored at that level).

5 DATA AND RESULTS

Our estimations are based on retail level market data. IMS Health is the main market audit company of the pharmaceutical industry worldwide. Pharmaceutical Market Brazil (PMB) surveys sales only through retail channel, so we are not able to include hospital sales as explaining variable. Only recently have hospital sales started being collected. We use then PMB data but exclude drugs sold typically or exclusively to hospitals, such as anesthesia, parenteral solutions, diagnostic agents, and blood derivatives. The data base had also to be cleaned up with the exclusion of functional food, shampoos, soaps and other cosmetics. But phytotherapics have not been excluded.

PMB records extracted comprised monthly sales in volume and value (local currency). Units are packages. Strength (amount of API content in the drug) is not available for all drugs in a separate field, but packaging description is not standardized; as a consequence, the field for equivalent dosages is also incomplete. We observe sales per brand and packaging. Descriptive variables include: seller's name; API; type of drug (reference, similar or generic); launching date of the packaging; launch date of the brand or generic; form and route of administration (e.g., tablets, sprays, ampoles, etc.). Following Scott-Morton (1999, 2000) and advice from the industry,⁶ we grouped forms into: *i*) oral solids; *ii*) oral liquids; *iii*) semi-solids (topics and suppositories); *iv*) injectables; and *v*) sprays. Scott-Morton's original papers groups orals together, and semi-solids and sprays into "topics". We define then a drug as the triple API-class-form.

We have no reliable data on advertisement and promotion (*detailing*). Prescription data have not been explored yet.

6. We are extremely grateful to Mr. Jair Calixto, manager of good manufacturing practices and pharmaceutical audits of the Pharmaceutical Industry Syndicate of São Paulo for graciously providing advice on the classification of production processes.

PMB has an unfortunate feature worldwide: the seller's name is not tracked along the months; when a brand is transferred because of divestiture, licensing, partial or total merger or acquisition, the whole sales series are relabeled to the new seller. Depending on the date of the extraction, the whole series will be completely assigned to the current seller. We overcame this obstacle with an external data base, from ABCFarma, a monthly magazine containing all drug price lists. By consolidating all price lists throughout the period, we were able to identify each drug's seller in each month. As the drug labels of IMS and ABCFarma were not completely comparable, we summarized the transition pairs of sellers and doublechecked them with merger dates from the Brazilian antitrust agencies and by searching the Web. Parent companies were also checked this way, and additionally by checking the addresses of the companies registered at CMED/Anvisa. The heavy workload at this stage of our research process could never be overstated. To the best of our knowledge, this is the first work in the international literature that complements IMS data with other pieces of information to overcome such a classical data limitation problem.

5.1 DESCRIPTIVE STATISTICS

We found 686 single-API drugs that were not under patent at least one year of our sampled period; in fact, 20 drugs had their patent expired during our sample; only three of them had generics launched. One of them was letrozole, expired in 2007, but with an (own-) generic launched in 2006. This was the only case of own-generic launched before expiration in our sample. We then obtained 1,023 drugs (triples API-class-form).

During a revision of the article, a number of APIs were found to be erroneously excluded. At the same time, we had access to a compilation—made by the Brazilian patent office Inpi—of patent litigations initiated by patent holders regarding the so-called pipeline inventions. The patent holders went to court alleging that the patent lifetimes should expire later than what had been granted by Inpi. Some cases were won by the patent holders, other were won by Inpi. We found therefore many divergences between the expiry dates of our original source IMS Life Cycle and the dates eventually settled or resolved in court. We summarize in Table 3 the divergences of expiry dates and the eventual expiry dates that we settled for.

TABLE 3
Divergences in patent expiry dates across different sources

API name	Est. expiry date (IMS)	Expiry date according to Inpi	Market status	Reached conclusion	Starting year in our sample
ATORVASTATIN	30/5/2006	May/2006	No generic	-	2006
ATORVASTATIN	28/12/2010	May/2006	No generic	-	2006
BRINZOLAMIDE		-	No generic	-	2006
BRINZOLAMIDE	3/4/2006	-	No generic	-	2006
CEFUROXIME AXETIL	2/8/2016	-	Pioneer launched before 1995	No patent valid	All years included
CETRORELIX	17/7/2007	-	No generic	-	2008
CLOPIDOGREL	5/7/2003	Pending for decision	Generic in 2007	Jul./2002	2003
CLOPIDOGREL	5/7/2003	Pending for decision	Generic in 2007	Jul./2002	2003
CLOPIDOGREL	16/2/2007	Pending for decision	Generic in 2007	Jul./2002	2003
CLOPIDOGREL	16/2/2007	Pending for decision	Generic in 2007	Jul./2002	2003
EPOETIN BETA	11/1/2005	-	No generic	-	2005
EXEMESTANE	7/7/2006	-	No generic	-	2007
FULVESTRANT	2/10/2004	Oct./2003	No generic	Oct./2003 or Mar./2010	Not included
GANIRELIX	5/2/2007	-	No generic	-	2007
GATIFLOXACIN	18/9/2006	Pending for decision	No generic	Jan./2006	2007
IBANDRONIC ACID	9/7/2007	-	No generic	-	2008
LAMIVUDINE		-	Generic in 2001	No patent valid	All years included
LAMIVUDINE		-	Generic in 2001	No patent valid	All years included
LAMIVUDINE		-	Generic in 2001	No patent valid	All years included
LAMIVUDINE	20/2/2012	-	Generic in 2001	No patent valid	All years included
LETROZOLE	18/12/2007	-	Own generic in 2006	-	2008
MILNACIPRAN	22/6/2001	-	No generic	-	2001
NATEGLINIDE	19/3/2006	-	No generic	-	2006
NATEGLINIDE	29/7/2012	-	No generic	-	2006

(continua)

(continued)

API name	Est. expiry date (IMS)	Expiry date according to INPI	Market status	Reached conclusion	Starting year in our sample
OLOPATADINE	15/8/2006	-	No generic	-	2007
OMEPRAZOLE		-	Pioneer launched before 1995	No patent valid	All years included
OMEPRAZOLE	11/6/2018	-	Pioneer launched before 1995	No patent valid	All years included
ORLISTAT	5/6/2004	June/2003	No generic	Jun./2003	2004
PIOGLITAZONE	9/1/2006	Pending for decision	No generic	Jan./2005 or Jun./2015	Not included
PRAMIPEXOLE	16/12/2005	Pending for decision	No generic	-	2006
QUETIAPINE	24/3/2007	Pending for decision	No generic	Mar./2006	2007
RALOXIFENE	3/4/2001	Apr./2001	No generic	Apr./2001	2001
RALOXIFENE	20/3/2017	Apr./2001	No generic	Apr./2001	2001
ROPINIROLE	7/12/2002	Application filed	No generic	Dec./2002	2003
SAQUINAVIR	10/12/2005	-	No generic	-	2006
SIBUTRAMINE	31/3/2002	Pending for decision	Generic in 2006	Apr./2001 or May/2006	2006
SIBUTRAMINE	31/3/2002	Pending for decision	Generic in 2006	Apr./2001 or May/2006	2006
TIMOLOL		-	Pioneer launched before 1995	No patent valid	All years included
TIMOLOL		-	Pioneer launched before 1995	No patent valid	All years included
TIMOLOL	23/6/2013	-	Pioneer launched before 1995	No patent valid	All years included
TOLCAPONE	11/3/2007	Mar./2006	No generic	Mar./2006	2007
VERTEPORFIN	24/4/2007	Jan./2007	No generic	Jan./2007	2007
VORICONAZOLE	3/8/2009	Application filed	No generic	Jan./2011 or Aug./2008	Not included
VORICONAZOLE	1/2/2006	Application filed	No generic	Jan./2011 or Aug./2008	Not included
VORICONAZOLE	24/1/2011	Application filed	No generic	Jan./2011 or Aug./2008	Not included
ZIPRASIDONE	2/3/2007	Mar./2007	No generic	Mar./2007	2007
ZOLMITRIPTAN		Application denied	No generic	No patent valid	All years included
ZOLMITRIPTAN	6/6/2011	Application denied	No generic	No patent valid	All years included

Sources: IMF LifeCycle and Inpi.

Authors' compilation.

Tables 4 and 5 summarize entry and generic penetration in the markets. Table 4 brings the shares of drugs containing generic versions in each year, both in number and in revenue. It also brings the shares of drugs where generic entry occurred in the same year, also in number and in revenue. One interesting feature to remark is that the revenue shares of drugs with entry and of drugs with generics moved in opposite directions. Table 5 counts drug market yearly observations according to the number of generic drug entrants recorded in the respective year.

TABLE 4
Drugs with entry and drugs with generics, versus total sample

Year	Share of drugs with entry along the year, in number	Share of drugs with generics, in number	Share of drugs with entry along the year, in revenue	Share of drugs with generics, in revenue
2000	11,35	12,24	81,31	4,40
2001	13,95	17,95	79,37	11,08
2002	15,52	23,59	78,41	16,35
2003	12,81	25,00	65,34	19,70
2004	15,60	28,20	68,52	21,85
2005	15,98	30,94	65,63	24,59
2006	13,14	32,85	50,91	29,28
2007	12,72	33,99	60,42	33,87

Source: IMS/PMB sample of single-API drugs.
Authors' compilation.

TABLE 5
Yearly generic entry across ATC-1 classes

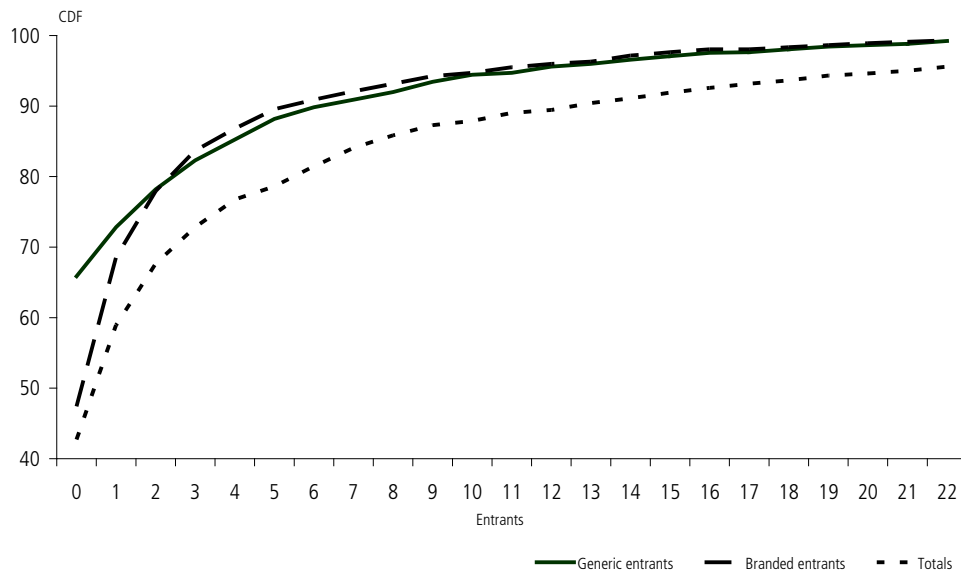
ATC-1 class	0	1	2	3	4	5+	Total
A	609	51	25	12	3	4	704
B	249	5	2	0	0	0	256
C	827	89	26	17	8	3	970
D	561	49	28	7	9	10	664
G	615	27	13	6	2	0	663
H	185	10	11	4	5	2	217
J	744	94	56	13	13	12	932
L	264	9	0	0	0	0	273
M	506	42	21	6	6	11	592
N	1.104	106	36	15	11	10	1.282
P	242	7	10	2	6	5	272
R	667	58	22	11	11	7	776
S	425	16	9	0	2	1	453
Total	6.998	563	259	93	76	65	8.054

Source: IMS/PMB sample of single-API drugs.
Authors' compilation.

We notice that the greatest share of our observations is of drugs without generic drug entry (appr. 86.8%). Shares of yearly observations of no entry in the class's total number of observations range from 79.30% (class J–Antiinfectives) to 97.27% (class B–Blood and Blood Forming Organs). Class J is therefore the class with the greatest rate of generic entry.

Accumulating generic drug entry changes a little the picture: the number of classes with no generic entry whatsoever during the period 2000-2007 goes down to 65.88% in number. The cumulative density of entries up to 6 is 90.91% (see figure 2).

FIGURE 2
Distribution of accumulated number of entrants across drug markets (CDF)



Source: Authors' compilation.

5.2 EXPLANATORY VARIABLES

Other than the year dummies, the explanatory variables utilized can be classified into three groups, and all of them are lagged.

1) Proxy for potential market (expected positive signs):

a) total revenues of the drug.

2) Variables concerning market structure (expected mixed signs):

- a) the log of the ratio of the total revenues of single-API drugs in the therapeutic class (ATC-3) to the total revenues of the drug (so as to measure the importance of other single-API drugs in the class; a negative sign would signify that the particular drug faces harsh competition of therapeutic substitutes);
- b) the log of the ratio of the total revenues of the therapeutic class (ATC-3) to the total revenues of single-API drugs in that class (so as to measure the importance of multi-API drugs in the class; a negative sign would signify that there are additional therapeutic substitutes, combining different APIs);
- c) share of the pioneer drug's seller (branded + generic) in the drug market;
- d) number of firm groups in the therapeutic class (ATC-3);
- e) Herfindahl-Hirschmann concentration index (HHI) of the drug;
- f) number of single-API drugs in the therapeutic class (ATC-3);
- g) number of single-API drugs in the therapeutic class (ATC-3) and with the same form;
- h) number of non-generic brands of the drug;
- i) share of phytotherapeutic drugs in the therapeutic class revenues.

3) Variables related to barriers to entry (expected negative signs):

- a) number of extended release brands;
- b) number of own-generics of the same drug;
- c) number of brands and generics of the pioneer drug's seller in the drug market;

- d) share of the own-generic revenues in the drug's total revenues; e
- e) age of pioneer drug.⁷

5.3 RESULTS

The reader should bear in mind that, unlike in the linear regressions, marginal effects in count data regressions are nonlinear. In particular, the derivative of the expected count w.r.t. a particular regressor x_j in the Poisson and Negative Binomial family has the following formula:

$$\frac{\partial E[y | x]}{\partial x_j} = \beta_j \exp(x'_i \beta)$$

The K-vector of derivatives in an ordered multinomial model is calculated for each value of the dependent variable's support:

$$\frac{\partial \Pr[y_i = j | x_i]}{\partial x_i} = [F'(\alpha_{j-1} - x'_i \beta) - F'(\alpha_j - x'_i \beta)]\beta$$

where $F'(\bullet)$ is the derivative of the respective cdf applying to the problem: in the logit case, $F'(\bullet) = \Lambda(\bullet)(1 - \Lambda(\bullet))$, where $\Lambda(\bullet)$ is the logistic cdf; in the probit case, $\phi(\bullet)$ is simply the Normal pdf $F'(\bullet)$.

Tables 6 and 8 display the marginal effects of the count data models and of the ordered probit, respectively. Ordered Probit and Ordered Logit's results are compared in Table 7. Results show that: as regards count models, we found that a simple Poisson regression provides a poor estimation of generic drug entry because of overdispersion; both the Negative Binomial family and the zero-inflated models improve considerably over Poisson. Most of the explaining variables utilized are significant throughout all or most of the regression specifications, in particular:

- 1) The proxy for potential market (the lagged revenues of the particular drug) has significant positive sign, as expected.

7. As a proxy for the drug's maturity, this variable is the only one expected to be positively related to entry.

- 2) Both the two log ratios (total ATC-3 class revenues to total revenues of single-API drugs, and the latter to revenues of the drug) have negative signs, thus indicating that competition from other drugs is quite important in the decision whether to enter.
- 3) The share of the pioneer drug's seller has an ambiguous sign; in some specifications, has a dissuading (negative) significant effect on entry for most specifications, but is positive and non-significant for the zero-inflated models.
- 4) A higher number of firms selling in the ATC-3 class apparently attracts prospective entrants.
- 5) A lower drug market concentration as measured by the HHI attracts entry.
- 6) The coefficients of the number of single-API drugs in the therapeutic class have mixed signs: the summation over the entire class has a positive sign (not significant in all specifications), while the summation within the same form in the class has a negative sign (also not significant everywhere).
- 7) The lagged number of non-generic brands is positively correlated with entry; apparently the rules for entry pricing favor entry of branded drugs before generics, so the number of brands seem to work as leading indicators of generic entry.
- 8) The lagged number of own generics surprisingly affects positively entry (although not always significant), but their share has a significant (positive) coefficient only when measured in the restricted drug's market, not in the whole single-API market (excluded from the regressions reported).
- 9) The number of extended release brands (except in the negative binomial specification, where it is non-significant) and the number of brands belonging to the reference drug's seller (barely, and not always significant) mostly seem to affect negatively entry, as expected (market preemption).
- 10) The share of phytherapeutic revenues is not significant for explaining entry.
- 11) The significant coefficient for the age of the pioneer drug—a proxy for the age of the molecule and therefore of the maturity of the drug's market—points out that it attracts generic entry.

TABLE 6
Marginal effects in count data regressions and diagnostic tests

	Poisson		NB2		NB1		Generalized NB		ZIP		ZINB	
	<i>dY/dX</i>	<i>z</i>	<i>dY/dX</i>	<i>z</i>	<i>dY/dX</i>	<i>z</i>	<i>dY/dX</i>	<i>z</i>	<i>dY/dX</i>	<i>z</i>	<i>dY/dX</i>	<i>z</i>
Generic drug entrants												
Revenue drug	0,2686935***	7,58	0,2414827***	5,23	0,2410283***	5,29	0,253932***	5,37	0,0956557**	2,36	0,1091837**	2,22
Log of the ratio total revenues all single API drugs/specific drug	-0,113694***	-2,90	-0,078291	-1,61	-0,1098209**	-2,20	-0,1194399**	-2,16	-0,0961941**	-2,14	-0,0710171	-1,36
Log of the ratio total ver. of the ATC 3 class/total single API drugs	-0,4976481***	-5,67	-0,5547964***	-4,84	-0,5119915***	-4,73	-0,5139489***	-4,19	-0,3452434***	-3,54	-0,4433733***	-3,84
Share pioneer drug's seller's in drug Mkt	-0,9547895***	-10,45	-1,399753***	-10,20	-1,021175***	-8,81	-1,106961***	-6,51	0,4292445***	3,24	0,2172213*	1,24
Firms in class	0,0086796***	4,79	0,009248***	3,74	0,0077471***	3,29	0,0091379***	3,44	0,0056652***	2,70	0,0069579***	2,75
HHI class (single-API)	-0,0001808***	-7,45	-0,0001434***	-4,68	-0,0001708***	-5,67	-0,0001711***	-4,75	-0,0001188***	-4,21	-0,0001255***	-3,83
drugs in class	0,0132002***	2,88	0,011185*	1,66	0,0084785	1,40	0,0169227**	2,27	0,0043895	0,87	0,0012977	0,19
Drugs in class X form (single-API)	-0,0221893***	-3,28	-0,0150618*	-1,52	-0,0107963	-1,22	-0,0208555**	-1,88	-0,0031849	-0,43	0,0023195	0,23
Non-generic brands in same drug	0,0313574***	10,24	0,0385368***	6,78	0,0333255***	8,12	0,0286894***	6,17	0,0208239***	5,58	0,0294583**	5,68
Share phyto. class	0,3203397	0,27	1,300434	0,98	1,88364	1,60	0,8711673	0,48	-3,148763**	-2,13	-1,592521	-1,08
Extended release brands in same drug	-0,0340952*	-1,89	-0,0779116**	-2,54	-0,0219007	-0,91	-0,0179572	-0,72	-0,0261896	-1,56	-0,0520909**	-2,11
Own-generics in same drug	0,2777355***	3,27	0,2032483	1,47	0,3508542***	3,16	0,2343427**	2,01	0,1895702**	2,27	0,296744**	2,56
Brands of pioneer drug's firm in same drug	-0,0818866***	-3,12	0,0897238	1,61	-0,1024544***	-2,95	-0,0956266***	-2,71	-0,0626598**	-2,31	-0,0601817	-1,44
Share own-generics drug	1,344553***	5,05	1,228538**	2,77	1,41561***	4,26	1,405098***	3,19	0,2732264	0,98	0,4255435	1,12
Share own-generics class (single-API)	0,0215445***	11,41	0,0229559***	8,37	0,0203999***	8,55	0,0248361***	7,25	0,0041921*	1,70	0,0060822**	2,03

(cont.)

TABLE 7
Estimate of ordered multinomial models

(The corresponding z-statistics is reported below each coefficient)

Variable	Ord. probit	Ord. logit
Revenue drug	0,111689*** 4,24	0,2460708*** 4,51
Log of the ratio total revenues all single API drugs/specific drug	-0,0502489* -1,8	-0,0871018 -1,5
Log of the ratio total revenues of the ATC 3 class/total single API drugs	-0,2981047*** -4,83	-0,5879211*** -4,66
Share pioneer drug's seller's in drug Mkt	-0,7317407*** -9,16	-1,243268*** -8,41
# Firms in class	0,0048406*** 3,25	0,0083408*** 2,92
HHI class (single-API)	-0,0000708*** -4,17	-0,0001522*** -4,4
# Drugs in class	0,0037927 0,92	0,0057502 0,74
# Drugs in class X form (single-API)	-0,0007033 -0,12	-0,0004259 -0,04
# Non-generic brands in same drug	0,0397903*** 11,07	0,0699114*** 10,64
Share phyto. class	1,056434 1,54	2,552637* 1,97
# Extended release brands in same drug	-0,0316522 -1,62	-0,0407389 -1,17
# Own-generics in same drug	0,2534096*** 2,82	0,4593692*** 2,91
# Brands of pioneer drug's firm in same drug	-0,0156781 -0,49	-0,0227111 -0,37
Share own-generics in same drug	0,8658164*** 3,03	1,482304*** 3,08
Share own-generics class (single-API)	0,0108573*** 6,79	0,0205919*** 6,87
Age of pioneer drug	2,261448 2,876530	4,703722 5,853069
cut1	3,378179	6,836828
cut2	3,672663	7,443343
cut3	4,080883	8,321563
cut4	0,111689***	0,2460708***
cut5	4,24	4,51

Source: Authors' compilation.
Note: Dummies for years omitted.

TABLE 8
Marginal effects of ordered probit models for each count bracket

	c1	c2	c3	c4	c5	c6
Revenue drug	-0,01702378 -4,28	0,0110211 4,24	0,0040641 4,17	0,00105055 3,89	0,0006273 3,74	0,00026067 3,35
Log of the ratio total ver. all single API drugs/ specific drug	0,007659 1,8	-0,0049584 -1,8	-0,0018285 -1,79	-0,00047264 -1,77	-0,0002822 -1,75	-0,00011728 -1,71
Log of the ratio total rev. of the ATC 3 class/ total single API drugs	0,04543749 4,87	-0,029416 -4,81	-0,0108474 -4,71	-0,00280398 -4,3	-0,0016743 -4,09	-0,0007297 -3,59
Share pioneer drug's seller's in drug Mkt	0,11153282 9,28	-0,0722058 -8,95	-0,0266265 -8,22	-0,00688278 -6,46	-0,0041099 -5,77	-0,00170782 -4,52
# Firms in class	-0,00073781 -3,25	0,0004777 3,24	0,0001761 3,2	0,00004553 3,05	2,719E-05 2,97	0,0000113 2,77
HHI Class (single-API)	0,0000108 4,22	-6,99E-06 -4,18	-2,58E-06 -4,12	-6,66E-07 -3,85	-3,98E-07 -3,69	-1,65E-07 -3,32
# Drugs in class	-0,00057809 -0,92	0,0003743 0,92	0,000138 0,92	0,00003567 0,91	0,0000213 0,91	8,85E-06 0,91
# Drugs in class X form (single-API)	0,0001072 0,12	-0,0000694 -0,12	-2,559E-05 -0,12	-6,62E-06 -0,12	-3,95E-06 -0,12	-1,64E-06 -0,12
# Non-generic brands in same drug	-0,00606489 -9,76	0,0039264 9,55	0,0014479 8,31	0,00037427 6,48	0,0002235 5,78	0,00009287 4,59
Share phyto. class	-0,16102301 -1,54	0,1042455 1,54	0,0384415 1,54	0,00993685 1,52	0,0059336 1,51	0,00246563 1,48
# Extended release brands in same drug	0,00482447 1,62	-0,0031233 -1,62	-0,0011518 -1,61	-0,00029772 -1,59	-0,0001778 -1,58	-0,00007387 -1,55
# Own-generics in same drug	-0,03862501 -2,8	0,0250056 2,79	0,0092211 2,75	0,00238358 2,67	0,0014233 2,61	0,00059144 2,45
# Brands of Pioneer drug's firm in same drug	0,00238967 0,49	-0,00154706 -0,49	-0,00057049 -0,49	-0,00014747 -0,49	-0,00008806 -0,49	-0,00003659 -0,49
Share own-generics in same drug	-0,13196881 -3,02	0,08543594 3,01	0,03150527 2,97	0,0081439 2,85	0,00486296 2,79	0,00202075 2,6
Share own-generics in class (single-API)	-0,00165488 -6,92	0,00107136 6,76	0,00039507 6,45	0,00010212 5,5	0,00006098 5,07	0,00002534 4,18
Age of pioneer drug	0,0075718 0,64	-0,00493286 -0,63	-0,00179471 -0,64	-0,00045964 -0,65	-0,00027255 -0,65	-0,00011204 -0,66
Year 2001	0,00170228 0,14	-0,0011036 -0,14	-0,00040575 -0,14	-0,00010467 -0,14	-0,0000624 -0,14	-0,00002587 -0,14
Year 2002	0,03059214 3,08	-0,02030278 -3	-0,00708824 -3,12	-0,00176587 -3,09	-0,00102601 -3,08	-0,00040923 -2,95
Year 2003	0,01528036 1,39	-0,0100166 -1,37	-0,00359543 -1,41	-0,0009124 -1,42	-0,00053732 -1,43	-0,00021861 -1,44
Year 2004	0,01836707 1,71	-0,01206952 -1,69	-0,00430891 -1,73	-0,00108947 -1,75	-0,00063987 -1,76	-0,00025928 -1,76
Year 2005	0,04534741 5,23	-0,03044598 -5,01	-0,01034468 -5,2	-0,00253282 -4,82	-0,00145383 -4,61	-0,0005701 -3,98
Year 2006	0,06177623 8,29	-0,04197633 -7,81	-0,01384758 -7,73	-0,0033314 -6,33	-0,00189037 -5,73	-0,00073055 -4,54
Year 2007	-0,01702378 -4,28	0,0110211 4,24	0,0040641 4,17	0,00105055 3,89	0,0006273 3,74	0,00026067 3,35

Source: Authors' compilation.

Ordered multinomial models display similar results, but some magnitudes of the marginal effects vary considerably, especially along the categories. A difference worth mentioning is that the share of the own-generic has a positive significant sign.

5.4 DIAGNOSTIC TESTS AND COMMENTS

Wald tests comparing Poisson to NB1, NB2 and generalized NB models reject equidispersion. Vuong tests reject both Poisson and NB2 models in favor of Zero-inflated Poisson and Zero-inflated NB2 models, respectively. Both Akaike and Bayesian Information Criteria also suggest that the zero-inflated models are the best models (see Tables 6 and 9).

On the other hand, proportion of counts predicted by NB2 seem to be closer to the observed proportions than ZIP (see Figure 3 and Tables 9-A to 9-E). ZINB predicts fits particularly better the proportions of ones and twos than regular NB2. The worst fit is the regular Poisson's.

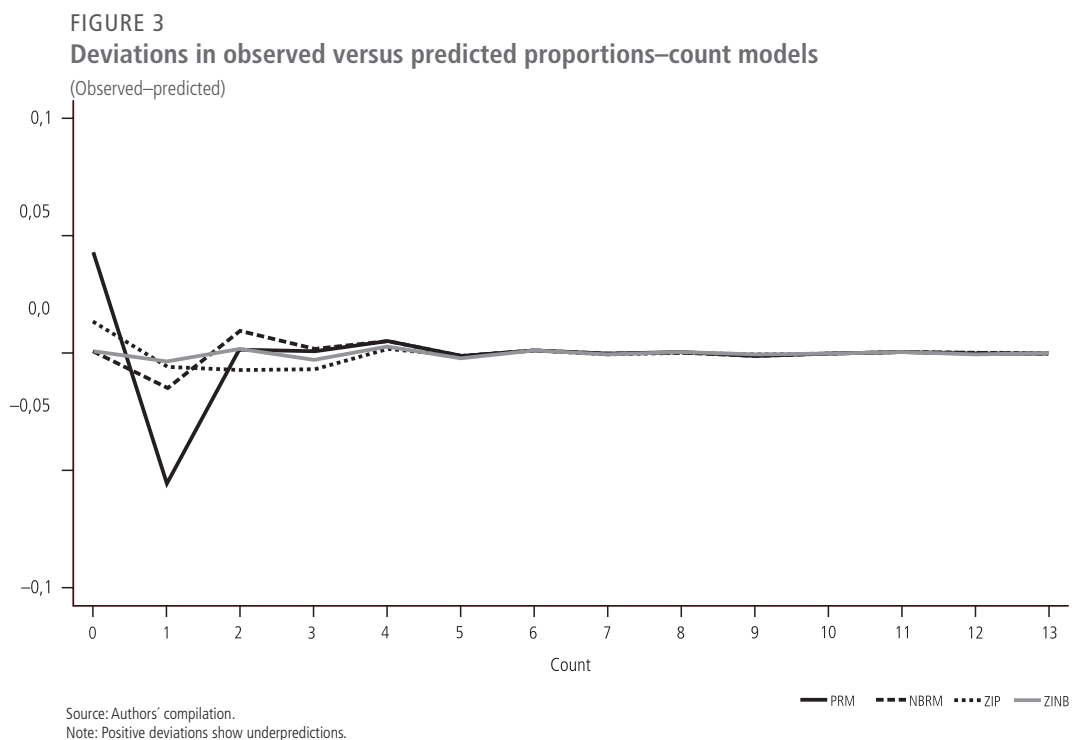


TABLE 9
Comparing information criteria among the four major count models

PRM	BIC = -56987.351	AIC = 1.096	Prefer	Over	Evidence
	BIC = -57721.664	dif = 734.313	NB2	PRM	Very strong
vs NB2	AIC = 0.995	dif = 0.103	NB2	PRM	
	LRX2 = 743.212	prob = 0.000	NB2	PRM	p = 0.000
	BIC = -57833.217	dif = 845.866	ZIP	PRM	Very strong
vs ZIP	AIC = 0.975	dif = 0.121	ZIP	PRM	
	Vuong = 10.794	prob = 0.000	ZIP	PRM	p = 0.000
	BIC = -58101.225	dif = 1113.874	ZINB	PRM	Very strong
vs ZINB	AIC = 0.938	dif = 0.159	ZINB	PRM	
NB2	BIC = -57721.664	AIC = 0.995	Prefer	Over	Evidence
	BIC = -57833.217	dif = 111.553	ZIP	NB2	Very strong
vs ZIP	AIC = 0.975	dif = 0.020	ZIP	NB2	
	BIC = -58101.225	dif = 379.561	ZINB	NB2	Very strong
vs ZINB	AIC = 0.938	dif = 0.057	ZINB	NB2	
	Vuong = 10.190	prob = 0.000	ZINB	NB2	p = 0.000
ZIP	BIC = -57833.217	AIC = 0.975	Prefer	Over	Evidence
	BIC = -58101.225	dif = 268.008	ZINB	ZIP	Very strong
vs ZINB	AIC = 0.938	dif = 0.038	ZINB	ZIP	
	LRX2 = 276.907	prob = 0.000	ZINB	ZIP	p = 0.000

Source: Authors' compilation.

PRM = Poisson.

NB2 = Negative binomial.

ZIP = Zero-inflated poisson.

ZINB = Zero-inflated negative binomial.

TABLE 9A
Comparison of mean observed and predicted count

Model	Maximum difference	At value	Mean diff
NB2	-0,015	1	0,003
ZIP	0,014	0	0,003
ZINB	0,003	1	0,001

Source: Authors' compilation.

TABLE 9B
PRM: predicted and actual probabilities

	Actual	Predicted	Diff	Pearson
0	0,857	0,813	0,044	17,404
1	0,076	0,132	0,056	175,434
2	0,035	0,032	0,002	1,393
3	0,013	0,011	0,001	0,001
4	0,010	0,005	0,005	39,768
5	0,003	0,003	0,000	0,000
6	0,003	0,001	0,002	16,036
7	0,001	0,001	0,000	1,521
8	0,001	0,000	0,001	9,195
9	0,000	0,000	0,000	1,616
10	0,000	0,000	0,000	1,216
11	0,000	0,000	0,000	0,001
12	0,000	0,000	0,000	21,103
13	0,000	0,000	0,000	3,057
Sum	1,000	1,000	0,113	289,266

Source: Authors' compilation.

TABLE 9C
NB2: predicted and actual probabilities

	Actual	Predicted	Diff	Pearson
0	0,857	0,856	0,002	0,032
1	0,076	0,091	0,015	17,321
2	0,035	0,025	0,010	29,367
3	0,013	0,010	0,002	3,407
4	0,010	0,006	0,005	31,022
5	0,003	0,003	0,001	1,036
6	0,003	0,002	0,001	2,458
7	0,001	0,002	0,000	0,828
8	0,001	0,001	0,000	0,000
9	0,000	0,001	0,001	6,068
10	0,000	0,001	0,000	1,547
11	0,000	0,001	0,001	3,708
12	0,000	0,000	0,000	0,000
13	0,000	0,000	0,000	0,838
Sum	1,000	0,998	0,037	97,634

Source: Authors' compilation.

TABLE 9D
ZIP: predicted and actual probabilities

	Actual	Predicted	Diff	Pearson
0	0,857	0,844	0,014	1,666
1	0,076	0,082	0,006	2,816
2	0,035	0,043	0,008	10,195
3	0,013	0,020	0,006	16,059
4	0,010	0,008	0,002	5,164
5	0,003	0,003	0,001	0,755
6	0,003	0,001	0,002	17,357
7	0,001	0,001	0,001	4,665
8	0,001	0,000	0,001	25,931
9	0,000	0,000	0,000	0,677
10	0,000	0,000	0,000	10,042
11	0,000	0,000	0,000	0,124
12	0,000	0,000	0,000	168,845
13	0,000	0,000	0,000	46,424
Sum	1,000	1,000	0,037	284,087

Source: Authors' compilation.

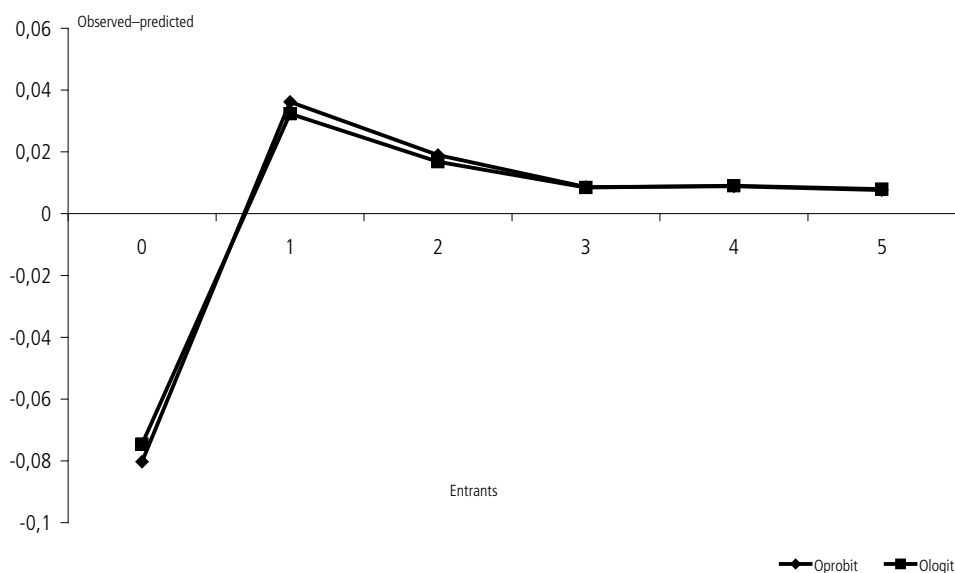
TABLE 9E
ZINB: predicted and actual probabilities

	Actual	Predicted	Diff	Pearson
0	0,857	0,856	0,001	0,011
1	0,076	0,079	0,002	0,858
2	0,035	0,033	0,002	1,001
3	0,013	0,016	0,003	2,649
4	0,010	0,008	0,003	8,393
5	0,003	0,004	0,001	3,092
6	0,003	0,002	0,001	2,391
7	0,001	0,001	0,000	0,180
8	0,001	0,001	0,000	0,949
9	0,000	0,000	0,000	3,595
10	0,000	0,000	0,000	0,051
11	0,000	0,000	0,000	1,571
12	0,000	0,000	0,000	3,437
13	0,000	0,000	0,000	0,081
Sum	1,000	1,000	0,015	28,259

Source: Authors' compilation.

The comparison of predicted proportions given by ordered multinomial probit *versus* ordered multinomial logit (see Tables 9 and 10) does not favor neither one against the other: the success rates⁸ are the same: 85.12%. On the other hand, another crude check (see Figure 4) point out that both ordered models overpredict zero entries in 0.08 p.p., and underpredict entry equal to one in 0.03 p.p. The differences fade out as the numbers of entries increase. Fit is therefore worse than in the count models.

FIGURE 4
Deviations in observed versus predicted proportions—ordered models



Source: Authors' compilation.

It is interesting to note how the variables related to deterrence affect entry. Taking the best model fitted to the data, ZINB, own similar brands and extended-release versions do have some power in deterring entry. But it is worth reminding that our data do not keep track of co-marketing agreements unnotified to the Brazilian antitrust agencies, so the effect of own brands may be severely underestimated. This omitted variable may also explain why the own-generic effect has a sign opposite to the expected one.

8. Success rate measured by the proportion of the "choices" that were predicted correctly (see MADDALA, 1993, p. 77).

TABLE 10
Predicted versus observed counts—ordered probit

	Predicted values						Observed count	
	0	1	2	3	4	5+		
Observed values	0	6.091	89	13	3	1	1	6.198
	1	482	54	17	3	0	0	556
	2	182	51	16	3	2	0	254
	3	61	18	10	1	2	0	92
	4	47	21	5	1	1	0	75
	5+	30	17	8	7	3	0	65
	Predicted count	6.893	250	69	18	9	1	7.240

Source: Authors' compilation.

TABLE 11
Predicted versus observed counts—ordered logit

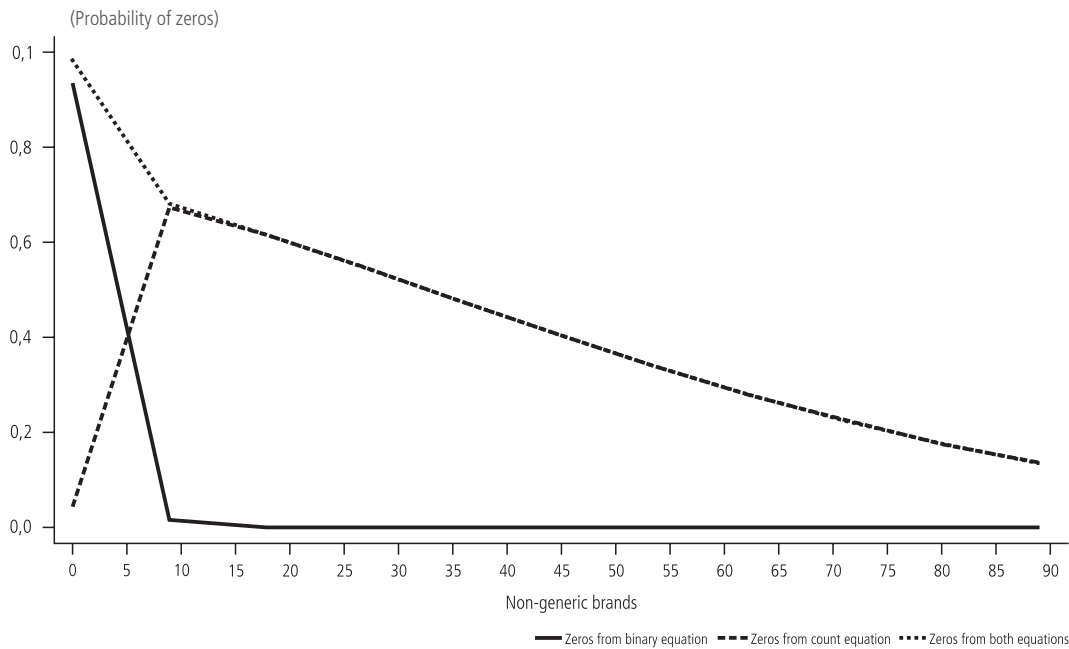
	Predicted values						Observed count	
	0	1	2	3	4	5+		
Observed values	0	6.081	99	15	1	1	1	6.198
	1	479	56	19	2	0	0	556
	2	179	49	21	3	1	1	254
	3	58	20	11	1	2	0	92
	4	46	20	7	1	1	0	75
	5+	29	17	11	4	1	3	65
	Predicted count	6.872	261	84	12	6	5	7.240

Sources: Authors' compilation.

It is also interesting to note how zero-inflated models predict zeros from the different distributions of the mixture. Figure 5 plots predicted proportions of zeros against the counts of brands in the respective drug markets. We note that the inflate equation predicts almost all zeros, and that drugs with as few as one brand hardly attract any entry, so the entry of branded competitors is an important leading indicator of a generic. In fact, it is easier to introduce a similar brand first. Moreover, as the regulatory board's formula⁹ for entry price takes into account either the average market price or the average firm price, firms had better introduce similar drugs first, because existence of generic drugs bring the average down, due to their mandatory 35% rebate (this explains why a higher lagged number of non-generic brands is positively associated with generic entry).

9. Resolução nº 2 CMED, March 5, 2004.

FIGURE 5
Sources of zeros in the ZINB model



6 CONCLUSIONS

This article is the first effort to estimate generic drug entry in Brazil. Generics are a relatively novel feature of the Brazilian market, as bioequivalence has only been regulated in the country since 1999. We used both count models and ordered multinomial models for this purpose.

As regards count models, we found that a simple Poisson regression provides a poor estimation of generic drug entry because of overdispersion; both the Negative Binomial family and the zero-inflated models improve considerably over Poisson. Most of the explaining variables utilized are significant, in particular:

- the proxy for potential market (the lagged revenues of the particular drug) has significant positive sign, as expected;
- both the two log ratios (total ATC-3 class revenues to total revenues of single-API drugs, and the latter to revenues of the drug) have negative signs, thus

indicating that competition from other drugs is quite important in the decision whether to enter;

- the share of the pioneer drug's seller has an ambiguous sign; in some specifications, has a dissuading (negative) significant effect on entry, but is positive and non-significant for the zero-inflated models;
- a higher number of firms selling in the ATC-3 class apparently attracts prospective entrants;
- a lower drug market concentration as measured by the HHI attracts entry;
- the coefficients of the number of single-API drugs in the therapeutic class have mixed signs: the summation over the entire class has a positive sign (not significant in all specifications), while the summation within the same form in the class has a negative sign (also not significant everywhere);
- the lagged number of non-generic brands is positively correlated with entry; apparently the rules for entry pricing favor entry of branded drugs before generics, so the number of brands seem to work as leading indicators of generic entry;
- the lagged number of own generics surprisingly affects positively entry (although not always significant), but their share has a significant (positive) coefficient only when measured in the restricted drug's market, not in the whole single-API market (excluded from the regressions reported);
- the number of extended release brands (except in the negative binomial specification, where it is non-significant) and the number of brands belonging to the reference drug's seller (barely, and not always significant) mostly seem to affect negatively entry, as expected (market preemption);
- the share of phytotherapeutic revenues is not significant for explaining entry; and
- the significant coefficient for the age of the pioneer drug—a proxy for the age of the molecule and therefore of the maturity of the drug's market—points out that it attracts generic entry.

Ordered multinomial models display similar results, but some magnitudes of the marginal effects vary considerably, especially along the categories. A difference worth mentioning is that the share of the own-generic has a positive significant sign. However, fit is worse than in the count models.

This article is but the beginning of a series of studies on the pharmaceutical industry in Brazil using retail level data. Some extensions are already envisaged, in particular: *i*) a model of entry using firm-level data and sequential decision each year; thereby enabling us to add firm characteristics, as suggested by Kyle (2003) and Scott-Morton (2000), following Berry (1992). In particular, we may use diversification measures, ingredient experience, therapeutic class experience, and form experience; *ii*) incorporating dynamics of drug entry, as modeled by Reiffen and Ward (2005); *iii*) an assessment of diversification of sellers's sales and of market concentration across therapeutic classes and/or relevant markets defined by the Brazilian antitrust system; and *iv*) estimation of entry of NCE—what will require refinement of information on patent status and access to classification of drugs for introductory price regulation purposes—thus providing for a better assessment of welfare associated to innovation.

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