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Essays on Product Portfolios in Pharmaceutical Markets

Tese de Doutoramento em Economia

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Nota Biográfica

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Resumo

No mercado farmacêutico, a prevalência de empresas multi-produto e a co-existência de diversos sub-mercados permitem-nos estudar vários aspectos acerca da gestão de portfolios de produtos. Em termos de política, as decisões sobre portfolios são importantes porque elas implicam a disponibilidade de produtos, que é normalmente uma das preocupações das autoridades de Saúde. Assim sendo, nós concentramos a nossa análise em dois tipos de decisão: a decisão de lançar um produto no mercado e a decisão de retirar um produto do portfolio.

Este trabalho tem dois objectivos principais: primeiro, testar se a evidência de outras indústrias se aplica ao mercado farmacêutico; e segundo, testar os efeitos da regulação sobre as decisões de portfolio das empresas.

Começamos por estudar como as empresas decidem quando e onde lançar novos produtos (Essay 1: Product Entry in Pharmaceutical Markets). Depois, estudamos as decisões de retirada de produtos. Fazemos isso estudando as decisões de retirada de medicamentos de marca, em Portugal (Essay 2: Survival of Branded Drugs), e comparando as decisões de retirada de produtos em Portugal, Suécia e Nova Zelândia (Essay 3: Survival of Pharmaceutical Products: a Cross-Countries Analysis).

As nossas principais conclusões são: a concorrência intra-empresa e inter-empresa são importantes para explicar a entrada de produtos, tal como esperado, mas os seus efeitos sobre a retirada de produtos não são claros; o sistema de preços de referência não tem um efeito claro sobre a probabilidade de saída de produtos mas tem um efeito positivo sobre a probabilidade de entrada de produtos.

Abstract

Within the pharmaceutical market, the prevalence of multi-product firms and the co-existence of various sub-markets enable us to study several aspects about management of product portfolios. Portfolio decisions are important for policy purposes because they implicate the availability of products, which is usually one of the concerns of Health authorities. Therefore, we concentrate our analysis on two types of portfolio decisions: the decision to launch new products and the decision to withdraw existing products.

This work has two main purposes: first, to test if evidence for other markets applies to pharmaceutical markets; and second, to test the effects of regulation on portfolio decisions, by firms.

We start by studying how firms decide when and where to launch new products (Essay 1: Product Entry in Pharmaceutical Markets). Then, we study the decisions on withdrawing the existing products. We do it by studying the exit decisions of branded drugs, in Portugal (Essay 2: Survival of Branded Drugs), and by comparing the exit decisions of pharmaceutical products on Portugal, Sweden and New Zealand (Essay 3: Survival of Pharmaceutical Products: a Cross-Countries Analysis).

Our main conclusions are: intra-firm and inter-firm competitions are important to explain the entry of pharmaceutical products, as expected, but the effects on product's exit are more misleading; the reference price system has no clear effect on exit probability, but it affects positively product entry.

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Preamble

With the following essays, we intend to better understand the decisions on product portfolios in pharmaceutical markets. The initial driving force for this work was to study competition and market structure on pharmaceutical markets. The singularity and complexity of pharmaceutical markets drove us to focus our research on firm's choices about their own portfolios.

We observe that almost all pharmaceutical firms are, at some point of their life cycle, multi-product firms. Unlike other industries where multi-product firms are predominant, on pharmaceutical industry firms may have a portfolio where substitute, complementary or independent products co-exist. In fact, pharmaceutical markets can be divided into sub-markets, according with the therapeutic use of the products and/or their chemical composition. These sub-markets can be more or less close to each other and the number of sub-markets increases as scientific research and technology deliver new medicines.

Within pharmaceutical markets, the dispersion of portfolio has another implication than the diversity on the degree of substitution or complementary between products: it implicates that products from the same firm face different market structures. In fact, a firm may simultaneously be monopolist in one sub-market (protected or not by a patent) and face competition in other sub-market (from branded or generic products or both). Also, firms may encounter specific regulation for each sub-market.

The prevalence of pharmaceutical multi-product firms and the co-existence of various sub-markets enable us to study several aspects about management of product portfolios. Portfolio decisions are important for policy purposes because they implicate the availability of products, which is usually one of the concerns of Health authorities. Therefore, we concentrate our analysis on two types of portfolio decisions: the decision to launch new products and the decision to withdraw existing products.

This work has two main purposes: first, to test if evidence for other markets applies to pharmaceutical markets; and second, to test the effects of regulation on portfolio decisions.

We start by studying how firms decide when and where to launch new products (Essay 1: Product Entry in Pharmaceutical Markets). Then, we study the decisions on

withdrawing the existing products. We do it by studying the exit decisions of branded drugs, in Portugal (Essay 2: Survival of Branded Drugs), and by comparing the exit decisions of pharmaceutical products on Portugal, Sweden and New Zealand (Essay 3: Survival of Pharmaceutical Products: a Cross-Countries Analysis). Two main econometric frameworks were used: for Essay 1, a selection model applied to firm-month panel data; and for Essays 2 and 3, a survival model applied to product-month panel data.

We leave the specificities and particular results of each of the Essays for the main text, but we want to highlight some major outcomes. Even though their differences, the three essays have some common points.

All essays discuss and compare the impact of intra-firm competition (competition between products within the firm's portfolio) and inter-firm competition (competition between products from different firms), both on entry and exit decisions. While intra-firm and inter-firm competitions are important to explain the entry of pharmaceutical products, as expected, the results for product's exit are more misleading. Intra-firm competition is important to explain the survival of branded drugs in Portugal (Essay 2), but not to explain the survival of drugs in the three countries under analysis (Essay 3). However, results on Essays 2 and 3 cannot be directly compared because Essay 2 is for branded drugs and Essay 3 is for all drugs. We believe that the differences on intra-firm competition effects derive from that: branded drugs suffer more the effect of intra-firm competition than generic drugs (included on Essay 3). In fact, after to patent expiration, the firm may gain on substituting the branded drug by a generic similar, especially if the reimbursement system is more favourable for generic drugs.

One result that is common to Essay 2 and Essay 3 is the difference between survival odds of prescription and non-prescription drugs. The results are consistent: under the same circumstances, non-prescription drugs have a higher probability of surviving when compared with prescription drugs. Usually, non-prescription drugs have not to be conformed to heavy regulation and reimbursement rules as prescription drugs. So, this is a signal that market regulation pressure firms to increase product turnover.

Another common topic is the impact of the reference price system on portfolio decisions. There is a vast literature on reference price systems, but none of the previous work was about portfolio decisions. We find that the reference price system has no clear effect on exit probability; but it affects positively product entry. The reference price system creates opportunities for cheaper medicines to entry, although without “expulsing” the existing medicines. We suppose that the effects on existing products should be observed on prices and market shares, two variables that are not available for this work.

We innovate on several aspects with this work. First, we perform a simultaneous analysis of the decision on when and where to launch new products. There is literature on the firm’s decisions on international diffusion of pharmaceutical drugs, but not how pharmaceutical firms decide about their portfolio’s dispersion within a single-country. Second, we applied a single-country analysis for product survival to a pharmaceutical market (the Portuguese market). Similar studies exist for other industries, but none for the pharmaceutical market. Furthermore, we do not limit our analysis to the dynamics of exit, but we also consider the possibility of transforming a product, during its lifetime, from branded to generic drug. Third, we extend the analysis of product survival to a cross-countries study, while all similar studies about product survival were single-country analysis.

Essay 1: Product Entry in Pharmaceutical Markets

1. Introduction

The aim of this paper is to explain the choice between launching products close to existing ones (concentration) and launching products in completely new markets (diversification). In this process, firms have to make two sequential decisions: first, whether or not to launch new products; and second, if they enter in new markets or concentrate in markets in which they already sell products. We use the Brander and Eaton (1984) model as a theoretical framework to address this issue. This model develops a sequential game of product entry decisions by multi-product firms: in the first stage, firms decide how many products they are going to launch (“the launch decision”); in the second stage, firms decide in which markets they launch the products (“the line decision”), and, finally, in the third stage, firms make “the output decisions”. The authors show that, under different conditions, it is possible to have two equilibriums: one of market segmentation (firms concentrate in a part of the product spectrum) and other of market interlacing (different firms produce close substitutes). They also show that monopoly power and potential entry are important determinants for launching decisions by firms.

This model is particularly appropriate for pharmaceutical markets for the following reasons: 1) pharmaceutical firms are usually multi-product firms; 2) the pharmaceutical market can be divided in several almost independent sub-markets (in the Portuguese case, we divide the pharmaceutical market in 224 sub-markets, corresponding to pharmacological subgroups within the same therapeutic subgroup); 3) monopoly power and potential entry can be related with the existence of patents.

This topic was not object of analysis within the pharmaceutical market. However, portfolio management is a key element to understand the availability of medicines in certain markets.

We apply a selection model that enable us to simultaneously study both decisions (“the launch decision” and “the line decision”) using explanatory variables that characterize the market, the firms and the regulatory framework.

We find that the market size has a positive effect on product launches. Also, we find empirical evidence that, as firms repeat the strategic game of launch and line decisions, the market structure tends to become interlaced. We show that firm heterogeneity, ignored by Brander and Eaton, is important to explain the final market structure. Regulation concerning entry and competition is important to explicate the “launch decision”, but not to explicate the “line decision”.

The rest of the paper is organized as follows. Section 2 reviews the relevant literature on both product entry and product entry in pharmaceutical markets. In section 3, we summarize and discuss the Brander and Eaton model. Section 4 describes the data. Section 5 has parametric estimations and the discussion of results. In the last section, we draw our main conclusions.

2. Background

2.1 Literature on product entry

Literature about product selection for multi-product firms can be divided into two categories: demand side models and cost side models, with the latter usually focused on the importance of “economies of scope”. While cost-side models propose that firms become multi-product in order to exploit economies of scope, demand-side theories defend that, even in the absence of those economies, there can be room for multi-product firms because of demand interactions between products. If so, firms would benefit from producing a range of products.

This paper is based on a “demand side model” developed by Brander and Eaton (1984). Products differentiate from each other through substitution effects: intra-group cross elasticity is higher than inter-group cross elasticity. Two possible outcomes are derived: market segmentation (each firm controls certain parts of the product spectrum) and market interlacing (in which close substitutes are produced by different firms). The model is discussed, in depth, in the next section.

Other researchers keep on the analysis of multi-product launch decisions, beyond the traditional framework of economies of scope. Raubitschek (1987) examines the decision of multi-product firm on launching new brands within the same market,

where there is no entry. The model has the limitation of ignoring the cross effects between brands of the same firm. Therefore, it assumes that firms do not exploit portfolio externalities. The problem of pharmaceutical firms is even more complicated, because the market is divided in sub-markets: they have to decide to launch products in new sub-markets or to launch products in sub-markets where they already have products.

Shaked and Sutton (1990) propose a model to test the relationship between market size and concentration. The equilibrium is the result of the balance between: the expansion effect (demand for the new product net of any loss of sales incurred on own existing products; therefore, incumbents have less incentive to launch new products than entrants) and the competition effect (the gap between prices under a competitive outcome and those under a monopolistic one; therefore, incumbents have higher incentives to launch new products). The degree of substitutability between products affects both effects. When assuming sequential entry, preemption of the market is not always the equilibrium. The expansion effect assumed by Shaked and Sutton (1990) is close to the demand growth considerations of Brander and Eaton (1984), when these authors discussed that under too low or too high demand the outcome of their model would not prevail.

An alternative way of designing the groups of products is to associate each group to a firm. For markets with strong firm-brand effects and where all products are not very distant to each other, this choice may be adequate. For the second reason, this approach is not satisfactory for the pharmaceutical market, where products vary from perfect substitutability to total independence¹. However, the insights from Anderson and De Palma (1992) and Allanson and Montagna (2005) can be useful to understand the decision on the first stage of the Brander and Eaton (1984) model. For the three papers, the two outcomes are the total number of firms (or nests) and the number of products of each firm. The first two papers show that market equilibrium implies too much firms and each firm provides too few products. The latter shows that two results are possible: one with many firms offering few products (usually, on “young” industries); and the other with few firms offering many products (usually, on “mature” industries).

¹ Despite that the approach of Anderson and De Palma (1992) and Allanson and Montagna (2005) is not ours; we do not ignore firm-brand effects on our empirical analysis since we include it as a fixed effect for each firm.

Berry (1992) focuses on two aspects relevant for profitability on a new market: the strategic interaction between firms and firm heterogeneity. This latter issue was ignored by previous literature (that usually consider that firms are homogeneous), because of the complexity brought by heterogeneity. The application to airlines industry shows that firm heterogeneity is important to explain entry patterns. In the Brander and Eaton (1984) model, the only source of firm heterogeneity is the existing portfolio that can be different. As Berry (1992), we intend to control for other differences between firms.

Finally, Burton (1994) made an empirical application of Brander and Eaton (1984). However, his work focuses on the use of a characteristics approach in which products are valued for their inherent characteristics, and he only analyses the “line decision” stage. Unlike this, our work will include both the decisions on the number of products and the lines of products.

2.2 Literature on entry in pharmaceutical markets

Literature on entry in pharmaceutical markets is mainly about generic drugs entry decision or on the international diffusion of innovation. For both issues, studies usually try to explain how market characteristics and regulation influence launches of generics or innovations.

Studies on generic drugs entry (e.g., Caves et al., 1991; Grabowski and Vernon, 1992; Scott Morton, 1999, 2000; Bergman et al., 2003) typically focus on the effects of generic drugs entry or on the effects of entry deterrence by incumbents (producers of branded drugs). Price effects and market structure effects of generic drugs entry are broadly covered by the literature. The results have different policy implications for regulators in order to stimulate competition.

Another topic covered by literature is international diffusion of innovation (e.g., Acemoglu and Linn, 2004; Danzon, Wang and Wang, 2005; Grabowski and Wang, 2006). Several studies focus on subjects such as: time to launch in new markets after the first launch or which markets are more attractive to innovative firms. Results show that market size and market regulation are important to explain the introduction of an innovative product.

Close to our analysis of the “line decision”, Yu (1984) analyze the rate of entry on therapeutic drug markets, in United States between 1964 and 1974. However, her work is at the sub-market level, instead of firm level. She concludes that market growth is an incentive for entry, while product differentiation, market concentration and drug innovation are barriers to entry into therapeutic sub-markets.

Few works use firm characteristics to explain product entry. Exceptions are Kyle (2006, 2007) analyzing how firms spread innovation through different countries. She finds a mix of effects to explain product entry strategies: market and regulation effects, firm effects and product effects. Firm effects, namely local and international experience and the number of products, are substantial to explain launch patterns.

Our paper focuses on strategies of firms for one single country, divided in sub-markets, and we do not distinguish if the product is a branded or a generic product, even though we control for the percentage of generics on firms portfolio. We study how market, firm and regulation characteristics affect the choice between concentration and diversification of portfolios, given that the firm decides to launch a new product. The role of market regulation, important component of the pharmaceutical markets, is also included.

3. The model of Brander and Eaton (1984)

We intend to empirically apply the Brander and Eaton (1984) model to the Portuguese pharmaceutical market. The market does not fulfill all the assumptions of the model. The authors discuss the sensibility of results to a change on assumptions but it is not proved nor even tested. The basics of the Brander and Eaton model are as following.

The market has four possible products, grouped on two pairs. Each pair includes two close substitutes and the products of each pair are more distant substitutes of the products of the other pair. In the pharmaceutical market each therapeutic sub-group is a “pair” of close substitutes. The differences on proximity of products imply that new products have more impact on demand for close substitutes than for distant ones.

The demand function is drawn from an additive utility function with two parts: a quadratic function in the vector of quantities of the relevant products (X) and a numeraire good, m (representing all the other products demanded by consumers). The distance between products is defined by cross-price elasticity.

$$u = aX - X'BX + m$$

We will not assume any restriction on the number of possible products or groups of products, and we will not restrict the number of firms. Brander and Eaton also note that the two discussed outcomes (segmentation and interlacing) were only “two of many possibilities”, that could arise for the four-product framework or for any other number of products. However, we maintain the substitutability assumption - the only important distinction is if products are in the same sub-market or not.

Firms decide sequentially: (i) how many products to produce; (ii) how many sub-groups to be in; and (iii) which quantity to produce. The implication is that firms decide price or quantity taking their own portfolios and the competitor's portfolios as given. The game is solved backwards. Brander and Eaton argue that it would be acceptable to assume that the two first stages are not separated, but separation helps to understand all issues under consideration. Whatsoever, the main idea is that firms make the two firsts decisions given that there are profitable prices and quantities in the last stage.

The profit function is the same for every firm (homogeneity in cost). It includes two types of costs, for each product: a constant marginal cost (c) and a fixed sunk cost (K). For firm i , with n_i products:

$$\pi_i = \sum_{j=1}^{n_i} (p_j q_j - c q_j) - n_i K$$

This formulation has three main limitations: first, it implies that all firms are equally efficient; second, it ignores cost differences between products, even if they belong to different sub-markets; and third, it ignores any scope economies for products in the same sub-market. The rationale for using such a narrow cost formulation is that the analysis is focused on the demand side. Therefore, a new product has three effects on the profit of the firm: the negative effect of the sunk cost; the direct profit of the new

product and the impact of the new product on the profit of existing products. This last effect is higher if the new product is close to existing products and smaller if otherwise.

We can discuss the implication of firm heterogeneity in costs. Heterogeneity in costs could be two folders: scope economies and differences in efficiency. Economies of scope would be an incentive for segmentation, as defended by Brander and Eaton, since firms would have an incentive to produce all the products of a group. Differences in efficiency would be an incentive to diversification. In fact, the most efficient firm would become monopolist or quasi-monopolist for the sub-markets where she is present. Therefore, as demonstrated by Brander and Eaton, the monopolist has incentives to diversify.

The outcome of the first decision, the number of products, is based on the assumption that demand is on an intermediate range: not so low that there is any sub-market with no products in and not so high that all firms will be in all the sub-markets.

The basilar Brander and Eaton model is applied to an oligopoly market structure. They show that concentration (and consequently, market segmentation) is expected to happen, under oligopoly, if the number of firms is fixed. In fact, if there is no potential entry, firms divide the market and each one provides products for different sub-markets. This equilibrium is robust for any sequence of decisions. Because they expect a non-cooperative game at the last stage, they know that the negative impact of a close competitor is higher than a more distant one, therefore they have an incentive to “divide” the market.

The outcome of the Brander and Eaton static game is questioned if the game is to be repeated. The authors expect that market segmentation would be replaced by market interlacing, if the game is repeated with an on-growing market. At the limit, if demand is big enough, all the firms sell all the products.

The Brander and Eaton model is extended to other two scenarios: oligopoly, with potential entry, and monopoly. This set of market structures is adequate to study pharmaceutical markets where the sub-markets have different structures². We may have monopolies or oligopolies with no potential entry (if all the substances in the same sub-

² The usual is to have more than one firm in each therapeutic sub-group. In 1990, nearly 25% of the sub-markets were monopolies. In 2006, the monopolies were less than 15% of all sub-markets.

market are under patent protection and it is not realistic to assume that other substances enter on that sub-market) and monopolies or oligopolies with potential entry (after patent expiration).

If entry is possible, under oligopoly, firms have an incentive to diversify (generating an interlaced market). Market interlacing is a more competitive structure and, thereafter, it is expected that it lead to lower prices, which will difficult entry. Marketing interlacing is effective as entry deterrence than market segmentation if there is a high enough difference between degrees of substitutability. If a firm is a monopolist, she has an incentive to diversify. The goal is to increase profits without damaging current demand.

We explain the two decisions (launch and line), adding some variables in order to test the effects that are not in the basic model, but are suggested by the authors as probable to change outcomes. Three main sets of variables are used: firm characteristics, market characteristics and regulation variables.

Since firms are equal in the basilar model, the expected result is symmetric (equal number of products with the same degree of substitutability, but not necessarily the same products). However, evidence shows that our market has very diverse firms. In order to capture these differences we introduce heterogeneity between firms. Three variables control for differences between firms: the percentage of generics within the portfolio; the time since the last launch; and, the age of the firm.

In order to integrate the “monopoly effects”, we use two variables: the number of sub-markets where the firm is a monopolist and the degree of concentration of own products in the sub-markets. Following Brander and Eaton, we expect that firms with more monopolies or with heavily concentrate portfolios to follow a diversification strategy.

4. Data

We use data on pharmaceuticals marketed in Portugal until October 2006, from INFARMED³. Using data from that cross-sectional dataset, we construct a firm-month

³ INFARMED is the Portuguese public agency for pharmaceuticals.

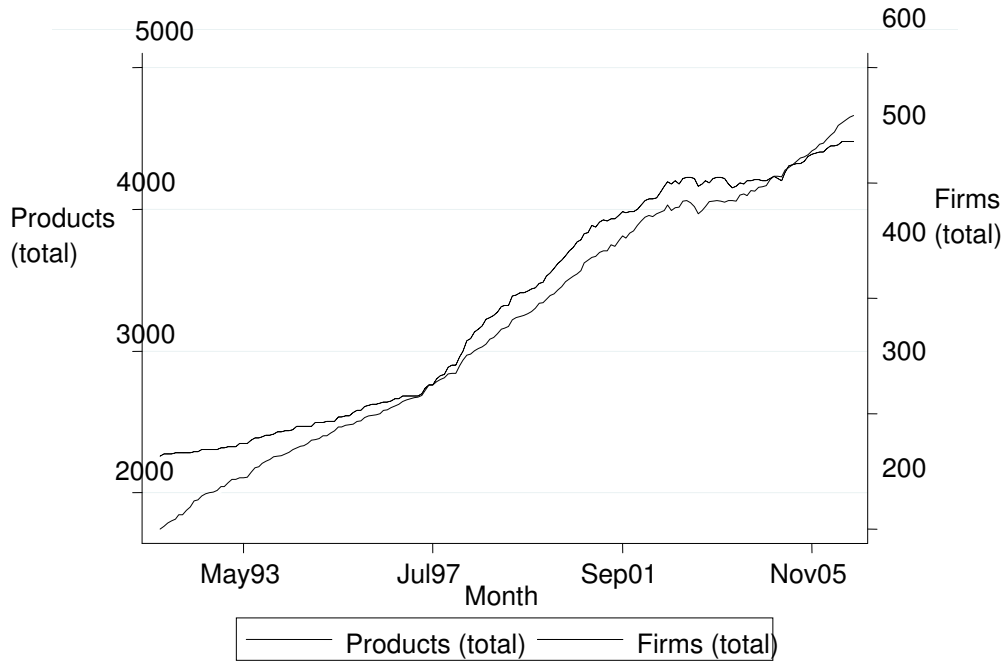
panel covering the period between January 1990 and October 2006 (202 months). We choose this timeframe for two reasons: first, this represents almost 17 years, which seems sufficient to capture the main characteristics of the Portuguese pharmaceutical market; and second, for computational reasons. The dataset includes 669 firms. Table 1 shows the descriptive statistics.

Table 1: Descriptive statistics (firm-month observations)

Variable	Obs	Mean	Std. Dev.	Min	Max
Month	82012	474.71	56.31	360	561
Entry of Firm (month)	82012	269.31	174.47	-128	560
Exit of Firm (month)	14061	520.39	23.13	472	561
Products (total)	82012	3565.03	907.58	1745	4982
Products, by Firm	82012	82.13	13.76	1	191
Firms	82012	431.80	97.21	263	553
New Products (total)	82012	24.72	14.09	0	62
New Products, by Firm	82012	0.06	0.30	0	16
Withdrawn Products (total)	82012	8.63	13.36	0	69
Withdrawn Products, by Firm	82012	0.02	0.20	0	15
% of Generics, by Firm	82012	6.88	22.16	0	100
Concentration Index, by Firm	82012	0.53	0.38	0	1
Monopolies, by Firm	82012	0.10	0.35	0	11
New Sub-Markets, by Firm	82012	0.03	0.20	0	7
Sub-Market Exits, by Firm	82012	0.01	0.13	0	8
Sub-Markets, by Firm	82012	5.89	8.27	1	80
Age of the Firm	82012	205.39	162.19	0	689
If after January 1995	82012	0.79	0.41	0	1
If after October 1999	82012	0.52	0.50	0	1
If after December 2002	82012	0.30	0.46	0	1
New Products=1	82012	0.04	0.21	0	1
Entry in New Sub-Markets=1	82012	0.03	0.17	0	1
Entry in New Sub-Markets=1, if New Products=1	3662	0.67	0.47	0	1
Time since last launch	82012	45.60	45.95	1	202

Variables, as the number of firms and products and product entries and product exits, reflect market evolution and market dynamics. We expect that a growing number of firms and products to be a signal of demand growth. From 1990 to 2006, the total number of products in the market grew almost linearly, as did the number of firms (Figure 1). There is a high correlation between the two variables (the Correlation Coefficient is of 0.99). Market dynamics are described by two variables: new products and withdrawn products. The number of products launched in the market, each month, had also grown. However, the pattern was more irregular. Product withdraws are only significant since 1998.

Figure 1: Market evolution



Because pharmaceutical markets are heavily regulated, we also control for the impact of regulation changes on launch and line decisions, during the period under analysis.

The first change is the introduction of the European centralized process, in January 1995. Before 1995, firms had to apply separately for each national market, within Europe. Since 1995, firms may choose between apply for each country or do a centralized application valid for all European Union member states, plus Iceland, Liechtenstein and Norway. This is expected to facilitate entry, because firms may get the necessary introduction authorizations for several countries with only one application process, lowering entry costs. It equals lowering K , in the Brander and Eaton model. Our variable “If after January 1995” is expected to have a positive effect on launch of new products.

The second change in regulation, introduced in October 1999, is the obligation of carrying economic evaluation studies when asking for public co-payment. This is expected to deter entry for two reasons: it increases entry costs and it is expected that proposed prices are lower, decreasing market attractiveness.

And the third is introduction of the reference price system⁴, in December 2002, that is expected to increase price competition for close products and, therefore, to lead to concentration strategies. The effect on product launch may be positive due to the incentive for launching generic drugs that are protected with this new rule.

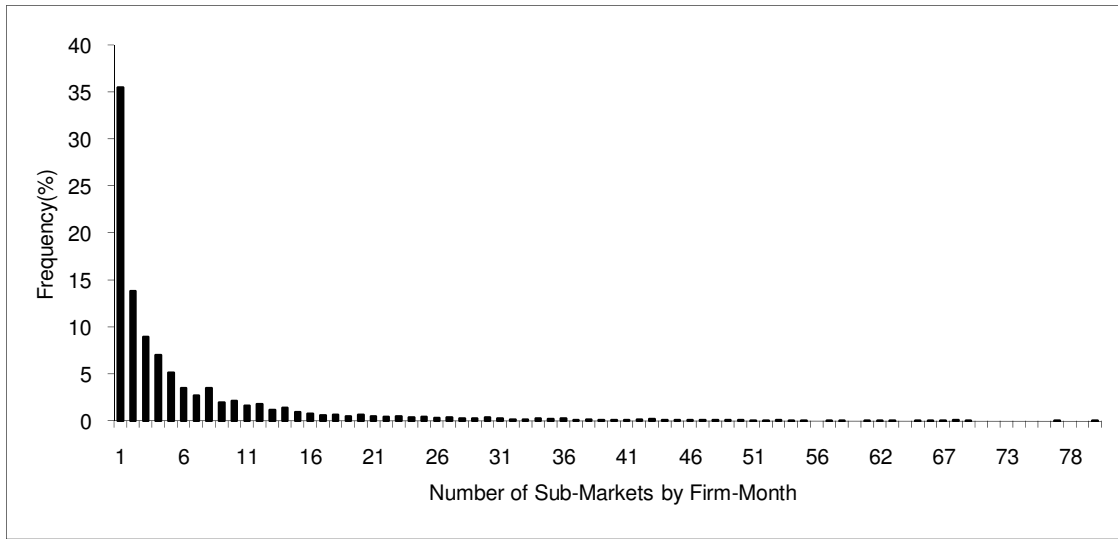
We control for firm characteristics in order to account for firm heterogeneity. The first firm entered the market in 1949. The last one entered the market in September 2006. Therefore, age of firms vary from 0 to 57 years.

Firms have from one single product to 191 products, in the same month. The global market can be divided in several sub-markets. Within the original dataset, products were grouped according to their Anatomical Therapeutic Chemical (ATC) code. The ATC system is the drug classification system developed by the World Health Organization. In the ATC classification system, the drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties⁵. The first 4 digits of the code give the ATC-4 code, which corresponds to the pharmacological subgroup that aggregate close substitutes, even if not with the same active substance. Each ATC-4 code corresponds to a sub-market, in our model. We identify 224 ATC-4 sub-markets. The number of sub-markets (ATC-4), in which the firm is present, goes from 1 to 80 (Figure 2). One sub-market, for firm-month observation, is the most frequent situation (35.48%). The firm-month observations with more than 45 sub-markets represent only 0.64% of the database. Almost 60% of the firms were in more than one sub-market simultaneously, at some point of the period under analysis, while the remaining (276 firms) never were at more than one sub-market, and, within these, 247 firms never had more than one product. In fact, almost all the pharmaceutical firms were single-product when starting but the natural evolution is to become multi-product and with a diversified portfolio.

Figure 2: Sub-markets, by firm-month

⁴ The Portuguese reference price system was defined as follow: for products chemically identical, the public co-payment is, at top, the co-payment for the most expensive generic substitute. For products with no generic substitutes, the public co-payment is a fixed percentage of the price.

⁵ For a full description of the ATC classification system, see <http://www.whooc.no/atcddd/>.



By firm, the maximum number of new products, in one single month, is 14. A firm entered on 7 new sub-markets utmost, in one single month. When the firm launch new products, she usually does it only in new ATC-4s (57%) or only in old ATC-4s (33%) (the remaining 10% of the cases are of simultaneous launch in new and old ATC-4s). Every time there is entry in a new ATC-4 sub-market, we treat it as a diversification option even if simultaneously there is also an entry in existing sub-markets.

Table 2: New Sub-markets and new products, by firm-month

	New Sub-markets							Total
	0	1	2	3	4	5	7	
0	78350	0	0	0	0	0	0	78350
1	1056	1951	0	0	0	0	0	3007
2	117	234	127	0	0	0	0	478
3	25	57	34	8	0	0	0	124
4	6	8	7	8	2	0	0	31
5	3	3	1	3	0	0	0	10
6	1	1	0	0	0	1	0	3
7	0	2	1	0	0	0	0	3
8	1	0	0	0	0	0	0	1
9	0	0	1	0	1	0	0	2
10	0	0	0	1	0	0	0	1
14	0	0	0	0	0	0	1	1
16	0	0	0	1	0	0	0	1
Total	79559	2256	171	21	3	1	1	82012

Product withdraws and sub-market exits, by firm, are also accounted. Product withdraws that happened because of the end of the firm represent only 12.5% of the total of observations with product withdraws. Sub-markets exits that happened because of the end of the firm represent 17% of the total of observations with sub-market exits. Therefore, the end of products or sub-market exits does not entail the end of the firm. It is usually the result of a portfolio profit maximization decision.

Pharmaceutical firms sell branded drugs or generic drugs or both. There is a dominance of firm-month observations (86.2%) with portfolios of branded drugs, exclusively. Though, firm-month observations with portfolios with just generic drugs are few (3.6%).

Another variable that measures firm heterogeneity is a concentration index (CI). We compute the CI as follow:

$$CI_{Firm\ i, Month\ t} = \sum_{k=1}^n \left(\frac{\text{Products on sub - market}_k}{\text{Total Products}} \right)^2$$

This index measures the degree of sub-market concentration within the firm's portfolio. A CI of zero means a completely dispersed portfolio and a CI of one means a completely concentrated portfolio. The mean value of the CI, in our sample, is 0.58, but with a large standard deviation. As expected there is a negative relation between the number of products and the index: larger firms have lower concentration indexes, e.g., diversified portfolios.

The “Number of monopolies, by firm” varies from zero to eleven. However, the average value is low. The relation between the number of sub-markets where the firm is a monopolist and the number of own products is not as clear as for the CI.

Independent variables, as market and firms variables, are lagged. In fact, entry decision is previous to entry, namely because of the duration of the authorization process. From the INFARMED's reports, responsible for national authorizations, and the European Medicines Agency (EMA)'s reports, responsible for central authorizations, the average time for the analysis of applications is usually higher than 12 months. Therefore, we use a lag of 18 months. Because of this, we loose observations, using only observations posterior to June 1991.

5. Estimation and Discussion

First, firms decide if they launch new products or not. After, they decide if that launch is to be on a new sub-market, diversifying its portfolio, or not. We assume: $y_1^* = x_1\beta_1 + u_1$ and $y_2^* = x_2\beta_2 + u_2$. y_1 is 1 if the firm takes a profitable launching opportunity, that will increase profit by $y_1^* > 0$, and zero otherwise. The same happens for y_2 (it is 1 if the firm takes a profitable opportunity for entering a new sub-market, that will increase profit by $y_2^* > 0$, and zero otherwise).

Entering in new sub-markets only happens if the firm launches new products. We know that y_2 is zero if y_1 is zero, but not the contrary. Despite we observe the values of y_2 for any value of y_1 , we cannot ignore the selection problem. When y_1 is zero, we do not know if the reasons for not entering in new markets are the reasons for not launch new products or even if there were any new products y_2 would remain zero. Therefore, we assume that $E(u_2|x_2, y_1) \neq 0$. In order, to obtain valid estimators of the coefficients, we use the two-step procedure developed by Heckman (1979): first, the selection regression (in our case for the variable y_1) is estimated by a probit; then, the results are used to correct the estimations of the regression for the variable y_2 .

5.1 The launch decision

We start by estimating the launch decision. The binary variable “New products=1” is y_1 . All the regressions included two types of “fixed effects”: time effects, through binary variables for each month, and firm effects, through binary variables for each firm. Marginal effects for probit regressions are on table 3.

Table 3: Marginal Effects

	Probit I	Probit II
Products (total)		0.000*** (0.001)

Firms	0.001*** (0.000)	
New Products (total)	-0.001** (0.018)	0.001*** (0.003)
Withdrawn Products (total)	-0.001*** (0.000)	-0.000*** (0.002)
Products, by Firm	-0.001*** (0.006)	-0.001*** (0.006)
New Products, by Firm	0.003** (0.016)	0.003** (0.016)
Withdrawn Products, by Firm	-0.004 (0.117)	-0.004 (0.117)
Time since last launch	0.000*** (0.000)	0.000*** (0.000)
% of Generics, by Firm	0.001*** (0.000)	0.001*** (0.000)
Sub-Markets, by Firm	0.002*** (0.000)	0.002*** (0.000)
Concentration Index, by Firm	-0.044*** (0.000)	-0.044*** (0.000)
Monopolies, by Firm	-0.003 (0.204)	-0.003 (0.204)
Age of the Firm	-0.001*** (0.000)	-0.001*** (0.000)
(Age of the Firm) ²	0.000*** (0.009)	0.000*** (0.009)
If after January 1995	-0.008 (0.675)	0.023** (0.001)
If after October 1999	0.023*** (0.007)	0.002 (0.850)
If after December 2002	0.035*** (0.007)	0.066*** (0.004)

Notes: Dependent variable is one if the firm launched a new product, and zero otherwise. The marginal effects of the binary variables for month effects and firm effects are omitted. P-values are in parentheses. Observations are 77205.

*Significantly different from zero at the 10% level. ** Significantly different from zero at the 5% level. *** Significantly different from zero at the 1% level.

The results are mainly according to our hypotheses. Market dimension effects are somehow difficult to isolate, because of high correlation between explanatory variables. That is the reason for the two regressions, one with the number of firms (I) and the other with the number of products (II). Nevertheless, we see that both variables have a positive effect on product launch, although very small. That is consistent with the notion that firms launch more products within bigger markets. Market dynamics are misleading to describe launch decisions. The variable “New Products (total)” has opposite effects from regression I to regression II. Product exits have a negative effect

on the launch decision, but it is approximately zero for the second regression. However, this is a signal that for declining markets there is less incentive for launch new products.

The effect of regulation is not exactly as expected. Note that time effects are controlled. Doing so, we expected to control for changes that occurred over time, other than changes on regulation. “If after January 1995” is significant only for the second regression, where the coefficient is consistent with the assumption that the introduction of the European centralized process has a positive effect on product launch. The request of economic evaluation for public co-payment (“If after October 1999”) has a positive effect on entry. It was expected that this additional entry cost would have a negative effect on entry, which does not occur. One possible explanation is the existence of a reputation effect associated with the economic evaluation. If the benefit of this reputation effect exceeds the cost for evaluation, then firms have an incentive to launch products that are capable to succeed on evaluation. The introduction of reference price system has a positive effect on entry. In fact, it was an opportunity for generics. Also, firms may launch products chemically different from the existing ones in order to escape from the reference price system.

Firm characteristics are important to explain the probability of product launches. Therefore, firm heterogeneity, despite ignored by Brander and Eaton (1984), must be included in the model. Firms with higher percentage of generics have higher probability of launch new products. Young firms are more willing to launch new products. Additionally, firms with more products are less probable of launching new products. Both effects seem to spread the idea of firm-life cycle: in the beginning of their life firms have fewer products and are willing to launch more; as time goes by and the portfolio enlarges, the odd of launches diminishes. Portfolio dynamics are accounted for the number of withdrawn products and new products, on the moment of decision, and the time since last entry. Only the two last variables are significant but only “New products, by firm” have a positive effect on product launch. Therefore, launch decisions do not seem to be a consequence of previous withdraws.

Three variables account for dispersion or concentration of firm’s portfolio. The first is the number of sub-markets, by firm, which has a positive effect on product entry (one additional sub-market increases the probability of launch new products by 0.2%). The second is the concentration index that has a negative effect on product launch. That

is to say that firms with more disperse portfolios have a higher odd of launching products. The third, that has not a significant effect on product launch, is the number of sub-markets where the firm is a monopoly. Therefore, we may conclude that portfolio dispersion has a positive effect on the probability of product launch. In fact, experience on different sub-markets probably increases the ability to exploit other launching opportunities.

5.2 The line decision

The binary variable “Entry in New Sub-Markets=1, if New Products=1” is y_2 . As before, all the regressions included time effects and firm effects. The marginal effects of the Heckman selection regressions are on table 4.

Table 4: Marginal Effects

	Heckman I	Heckman II
Products (total)		-0.000 (0.364)
Firms	-0.002 (0.537)	
New Products (total)	-0.012** (0.046)	-0.003 (0.532)
Withdrawn Products (total)	0.004 (0.389)	0.002 (0.652)
Products, by Firm	0.014*** (0.000)	0.014*** (0.000)
New Sub-Markets, by Firm	-0.070*** (0.003)	-0.070*** (0.003)
Sub-Market Exits, by Firm	-0.049 (0.532)	-0.049 (0.532)
Time since last launch	0.001 (0.273)	0.001 (0.273)
% of Generics, by Firm	-0.002 (0.441)	-0.001 (0.441)
Sub-Markets, by Firm	-0.033*** (0.000)	-0.033*** (0.000)
Concentration Index, by Firm	-0.067 (0.695)	-0.067 (0.695)
Monopolies, by Firm	0.027 (0.353)	0.027 (0.353)
Age of the Firm	0.000 (0.845)	0.000 (0.845)

(Age of the Firm) ²	0.000**	0.000**
	(0.043)	(0.043)
If after January 1995	0.382	-0.183
	(0.622)	(0.746)
If after October 1999	0.070	0.373
	(0.903)	(0.573)
If after December 2002	-0.203	-0.100
	(0.332)	(0.691)

Notes: Dependent variable is one if the firm enter in a new sub-market, given that she had launched new products, and zero otherwise. The marginal effects of the binary variables for month effects and firm effects are omitted. P-values are in parentheses. Observations are 77205, and the value of y_2 is non-missing for 3443 observations.

*Significantly different from zero at the 10% level. ** Significantly different from zero at the 5% level. *** Significantly different from zero at the 1% level.

Market variables, such as the total number of products, the number of firms and products withdraws, have no impact on the “line decision”. On regression I, the effect of the number of new products is significant and negative. The impact of new products, whatever the sub-market they belong to, is contrary to what was expected. In fact, if we assume that product entries are a signal of market growth, we expected it to increase diversification and not the contrary.

There is a positive effect of the number of products of the firm on sub-market entry. One additional product increases the probability to enter into new markets by 1.4%, e.g., large firms disperse more than smaller ones. Therefore, if large firms occupy the entire market, the expected market structure is of market interlacing.

Previous sub-market entry makes new sub-market entries less probable. Also, there is a negative effect of the number of sub-markets, where the firm already is, on diversification. Firms that are in less sub-markets, and firms that were not diversifying when deciding new launches, have higher probability of entering into new markets. That is consonant with the hypothesis of market dynamic: the repetition of the game makes that all firms will diversify, and market converge to an interlacing market. Sub-market exits have no effect on sub-market entries. If sub-market entries were a consequence of sub-market exits, we could not say that the entry on new sub-markets would lead to a more diversified portfolio. In this case, we do not see a relation between previous exits and current entries.

The number of monopolies has no effect on diversification or concentration. So, the Brander and Eaton conclusions do not apply because it seems that monopolists do

not increase profits through diversification. Also, other characteristics of firms have no influence on the “line decision”. In fact, firm heterogeneity seems to matter only for the “launch decision”.

Despite regulation changes are important to explain the launch decision, the concentration / diversification decision suffers no effect from regulation. The most surprising is the absence of influence from the introduction of the reference price system (“If after December 2002”). It was expected that firms would change their portfolios in order to protect the existing products from aggressive competitors or to exploit new opportunities (for example, in the case of generics drugs).

6. Conclusions

Brander and Eaton (1984) find that markets with differentiate products and multi-product firms have two possible outcomes: market segmentation (each firm controls certain parts of the product spectrum) and market interlacing (in which close substitutes are produced by different firms). In this paper, we test this model in the context of the Portuguese pharmaceutical market.

Usually, the pharmaceutical firms were single-product when starting but the natural evolution is to become multi-product and with a diversified portfolio. Product launches that are, simultaneously, entries in new sub-markets are common.

We show that the “demand size effect” happens. As predicted by Brander and Eaton, firms launch more products as market grows. Also, there is evidence that, as firms repeat the strategic game of launch and line decisions, they diversify more and market structure becomes interlaced. Regulation only matters for the “launch decision”. Regulation affects the decision of launching new products, but not the decision of at which distance from the existing products of the firm. Therefore, we may conclude that the regulation measures analyzed did not change the substitution pattern within the sub-markets and, consequently, did not change the incentives for concentration or diversification.

Launch decisions do not seem a consequence of previous withdraws, as sub-market entries are not a consequence of sub-market exits. However, our work does not

include the reverse analysis: if launches and entries have effect on future withdraws and exits, respectively. There is evidence that firm characteristics, ignored by Brander and Eaton, are important to explain the “launch decision”. However, the same is not proved for the “line decision”.

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Essay 2: Survival of Branded Drugs

1. Introduction

The mainstream literature on the economics of entry and exit is focused on the decision by a firm with a portfolio of a single product. Usually, this analysis is reduced to a problem of location in relation to other firms, assuming that such firms also sell just one product (Bresnahan and Reiss (1990, 1991), Berry (1992)).

However, multi-product firms face a much more complex set of decisions as they have to simultaneously choose the location of all the products of their portfolios and the composition of such portfolios.

When firms may be present in several distinct sub-markets, sometimes even with more than one product in each of those sub-markets, product entry and exit becomes the result of a more complex portfolio's profit maximization. Therefore, each product is likely to face two kinds of competition: the first, from substitutes produced by other firms (inter-firm competition); the second, from other products of the same firm (intra-firm competition). Understanding which of these two forces is more relevant and under what circumstances is a question that has not been properly addressed.

In reality, the literature on portfolio location for multi-product firms is still very scarce. Previous empirical studies have analyzed the driving forces of portfolio management. For example, Ruebeck (2005), Requena-Silvente (2005), and Greeinstein et al. (1998), found evidence of a relationship between greater sub-market intra-firm competition and a higher probability of product exit. Greeinstein et al. (1998) analyzed simultaneously entry and exit patterns, by sub-markets, showing that once a product is introduced, other products of that firm are more likely to exit. Two explanations are proposed: first, products exit because new and similar products are available; second, products enter because existing products are close to obsolescence.

Another relevant feature on what drives products out of market is the disaggregation of product and firm effects. Identical products have different survival spells just because the firms that produce them have specific strengths that make survival more likely (Stavins, 1995; Asplund et al., 1999; Figueiredo et al., 2006). At the firm level, the scale effect is somewhat puzzling. Larger firms usually have

competitive advantages, due to scope and scale economies. However, with scarce resources, because of their minor weight in the total revenue of the firm, it is more probable that a large firm drops a product that, in a small firm, would be kept. In this domain, empirical results are dissonant. While Stavins (1995) found no evidence of scale effects on product survival, in the personal computer market, Asplund et al (1999) showed that, in the Swedish beer market, products from firms with high market shares have a higher probability of exit, and Figueiredo et al (2006) found little evidence that a firm's size increases product survival, on the laser print industry. It is not clear if the dissonance of results is consequence of different methodological techniques or cost structure differences across industries.

Pharmaceutical firms often sell a portfolio of products, which can be either for similar or different therapeutic categories, branded or generics, innovative or mere copies. Branded drugs are often divided into two kinds: those who are, or were, innovative drugs; and those that were launched with a brand name, but are merely copies of innovative drugs. In Portugal, for example, the proliferation of copies was one of the main reasons for authorities to allow, in 2001, the transformation of branded drugs into generic drugs¹. However, this regulatory change only became effective with new legislation in October 2003. Therefore, two kinds of generics can be identified: those who were introduced in the market as such, and those that were introduced in the market as brands, and later transformed. Those specificities make the Portuguese pharmaceutical market an interesting field of research on brand and multi-product competition and market structure.

The pharmaceutical market is divided into several sub-markets, each one of them with its own characteristics. A single firm, present in several sub-markets, may face different market structures, and may have a specific relative position in those sub-markets. Therefore, in order to study branded drugs survival, it is necessary to incorporate all those questions into a conceptual framework.

Furthermore, in pharmaceutical markets, firms are always facing new technological opportunities, with a continuous expansion of the product space. Therefore, it is expectable to observe frequent product turnover. Hence, the role of innovation is of striking importance and we will analyze the existence of a survival

¹ Preamble to the Decree-Law no 249/2003, 11 October 2003.

advantage of innovative products. Figueiredo et al (2006) showed that innovative products last longer on the market.

The aim of this work is to analyze why firms decide to drop a branded drug, and how the possibility of transformation into a generic drug changes the product life cycle. We model branded drug survival assuming that brands may disappear by exiting the market or by being transformed into generics. In this perspective, product exit in pharmaceutical markets has not been a subject of analysis yet, despite the existence of several studies about entry, namely the impact of generics entry over price and market share of branded drugs (Caves et al., 1991; Frank et al., 1997; Kyle, 2006, 2007). In this paper, we study the impact of regulatory changes over branded drug's survival. Three regulatory changes are included: first, in September 2000, the introduction of a major public reimbursement for generics², relative to branded drugs; second, in December 2002, the introduction of the reference-price system of reimbursement for some products³; and third, in October 2003, the possibility of transforming branded drugs into generics. All three measures intended to improve the substitution of branded drugs for generics, in order to achieve a reduction of public expenses.

The main contribution of this paper is two-folded. First, we do not limit our analysis to the dynamics of exit, but we also consider the possibility of transforming a product, during its lifetime, from brand to generic drug; second, we analyze a market with a heavy regulatory framework and see how the changes in regulation, described above, change branded drug survival.

We find evidence of scale and scope effects in the evaluation of “death” rates. Additionally, there is evidence that number of products from competing firms have lower impact on exit and transformation of branded drugs. We also find that regulation plays an important role on the decision to drop out or to transform a branded drug. On markets not so regulated on prices and selling rules, as non-prescription drugs market, branded drugs have higher survival rates. After October 2003, with the complete regulatory framework implemented, branded drugs have a lower probability of surviving than before.

² The reimbursement rates are 10 percentage points higher if the product is a generic.

³ The reference-price is established if the product has, at least, one generic substitute. The reference-price is the price of the most expensive generic.

The rest of the paper is organized as follows. Section 2 formulates the hypothesis to be tested. In section 3, we describe the data, and present the results of non-parametric estimation. Section 4 has parametric estimations and the discussion of results. In the last section, we draw our main conclusions.

2. Hypotheses for the determinants of branded drugs survival

We assume a multiproduct firm with j products and with a profit function $\pi(\cdot)$, in a context of scarce resources. The j^{th} product exits if one of two alternatives happens. First, if the firm has lower profits with that product in its portfolio, than without it:

$$\pi(1, 2, \dots, j) < \pi(1, 2, \dots, j-1).$$

Second, when the introduction of new products requires the exit of product j , if a portfolio with product j and no new product is less profitable than a portfolio with new products and without product j :

$$\pi(1, 2, \dots, j) < \pi(1, 2, \dots, j-1, j+1, \dots)$$

Therefore, the product will exit the market if it becomes unprofitable or if shifting scarce resources from its production to the production of new products increases the firm's profitability. We are interested in the analysis of the causes of the decrease of absolute or relative profitability of a product, and consequently its exit from the market.

According to the product life cycle theory (Levitt, 1965; Cox, 1967), products pass through four distinct phases: Introduction, Growth, Maturity, and Decline. These phases are defined by the behaviour of revenues, which are expected to grow during the first two phases, to stabilize in the third, and to decline in the last one, when products usually exit the market. However, the lengths of each phase and of the whole life cycle do not have to be the same for all products. As Cox (1967) remarked, the length of the product life cycle depends on the "other products in the firm and the products of competing firms".

Regardless of the recognition of the importance of competing products on the shape of the life cycle of a product, the theory does not provide a fully integrated framework for this relationship. In fact, there is a lack of theoretical papers about

product survival⁴. In order to overthrow it, our strategy is to integrate several distinct theories, controlling for several variables that could have some impact on product survival, in order to test empirically our central hypothesis.

One of the perspectives is that a firm's number and type of products could extend or reduce the product survival. The total number of products of the firm has a positive impact on product profitability (and survival) if the products share costs within the firm, and, therefore, the larger the number of products the smaller the part of the cost to each product. These are scale effects, which are a competitive advantage when facing products from firms with a less extended portfolio (Stigler, 1968).

Despite the positive effect expected from the total number of products, the number of existing and new close products in the firm may have a negative impact on product survival. First, new products could replace old ones, for the same firm, as proposed by Schmalensee (1978). As products get close of the Decline phase, it is expected that firms introduce innovative products, accelerating the "death" of the older product (Levitt, 1965; Cox, 1967). Second, the existing products represent competitive pressure over each other. Both effects are intra-firm competition, usually called cannibalization.

Not only is the number of products important to explain product survival, but also the type of products within the portfolio of the firm. Products are more profitable if they are able to exploit scope economies (Panzar et al., 1981). The existence of products with some similar characteristic within the firm benefits each product if they share any input with a sub-additive cost function. Common examples of such inputs are marketing or sales force.

In addition to the impact that a firm's portfolio may have on the survival of a product, Cox (1967) suggests that inter-firm competition by products of other firms is

⁴ "Although researchers have invested substantial effort in analyzing *firm* survival and turnover (...), there are far fewer studies of the determinants of *product* survival, despite the obvious role of products in firm profitability. Theoretical papers are especially scarce on this topic, and rarely consider both market forces and portfolio decisions simultaneously." (Figueiredo et al., 2006)

also relevant. According with him, the larger the number of competitors the smaller is the profitability of the product, due to price decrease, the decrease of quantity sold, or both. Therefore, a negative effect on product survival is expected. In pharmaceutical markets, there is evidence that brand market shares and brands profitability decrease with generic introduction (Aronsson et al., 2001; Bergman et al., 2003; Brekke et al., 2007).

Despite competition, pioneer products may have a survival advantage. Pioneer products were monopolists until a competitor entered into the market. During the length of monopoly, the consumers experienced the product. After the introduction of a substitute, they would be reluctant to switch because of uncertainty of trial (Schmalensee, 1982). The higher is the cost of switching or brand loyalty, the higher is the pioneer advantage. Both Caves et al. (1991) and Frank et al. (1997) show evidence of brand loyalty in pharmaceutical markets.

Following the literature, previously mentioned, we control for all those effects on branded drugs survival. However, our central hypothesis concerns the impact of the introduction of an alternative destination on brand survival.

Cox (1967) analyzes the product life cycle of ethical drugs. He draws the different curve for each drug and classifies it within six types of product life cycles. He finds that the predominant curve has the form of fourth-degree polynomials, with two local maximums instead of one as usually presented by the product life cycle framework. His explanation for the second maximum is “the use of a promotional “hypo””. However, the exploitation of any new competitive advantage, as a price competitive advantage, can create this effect. The transformation of a branded drug into a generic drug enables a firm to set the price of reference, if under a reference price system, or to benefit from a larger public reimbursement. Both situations increase the incentives to turn a brand drug into a generic. This is the argument for our main hypothesis:

Hypothesis: With higher incentives to turn a branded drug into a generic, the typical duration of a branded product is expected to decrease. Therefore, the possibility of transforming a brand into a generic drug changes the patterns of exit, becoming it less

probable. We expect that less products exit the market, because they have an alternative destination.

Product exit determinants were already tested, for other markets by Stavins (1995), Greeinstein et al. (1998), Asplund et al. (1999), Ruebeck (2005), Requena-Silvente (2005), and Figueiredo et al. (2006), but not on the pharmaceutical market. As showed on section 1, their results are diverse. Within the pharmaceutical market, we have multi-product firms that are simultaneously present in several sub-markets. Each firm is able to sell several drugs, and several preparations for each drug. Each preparation faces the competition of similar chemical drugs in close sub-markets, but it also faces competition from other drugs that have similar therapeutic usage, even been chemically different. Firms have to choose, in each sub-market, at each period, which preparations remain and which are dropped out. The market is regulated, and regulation changes along the period. This is the context, in which we intend to test our hypothesis, and it is distinct from previous studies. It is the fact that we have multi-product competition and market regulation that makes this market so important to be tested.

3. Data and non-parametric estimation

We use a random sample of branded drugs, extracted from the database of INFARMED⁵, which contains all pharmaceuticals licensed in Portugal until October 2006. The observation unit is a drug preparation. For each observation, we have some characteristics that are constant over time, and we are able to construct some variables to describe changes in market and firms over time. Our database has 44190 preparations from which he obtained a random sample of 2315 preparations (representing 10% of the products that were introduced in the market as brands). We had to select this sample for computational reasons, but we check the robustness of our findings by running the same analysis for different random samples. The results did not differ significantly. We follow those preparations from January 1996 to October 2006 (130 months). Table 1 shows some descriptive statistics.

⁵ INFARMED is the Portuguese public agency for pharmaceuticals.

From the 2315 brands, 486 left the market (corresponding to 21%) and 83 (3.6%) became generics, during the period under study. The other 1746 preparations have right-censored durations. Notice that 816 preparations were already in the market before 1st January 1996. Those are left-censored observations.

We may observe that the average age at exit of the market is 132.6 months. For branded drugs that had been transformed into generic, they were transformed at the average age of 67.7 months. Our sample has products launched since 1953 until 2006. Only 6.1% of the preparations are non-prescription drugs. All the transformed branded drugs are prescription drugs. The majority of the products were introduced in the market by the national process (8.9% were introduced by the European central process and 32.4% by mutual recognizing). None of the drugs that received license approval through a centralized process was transformed into a generic, which is not surprising given that the oldest drug introduced by this process is only 132 months old.

Table 1: Summary statistics

Variable	All Sample			Transformed			Exits		
	Obs	Mean	Std. Dev.	Obs	Mean	Std. Dev.	Obs	Mean	Std. Dev.
Central Process=1	2315	0.089	0.284	83	0.000	0.000	486	0.063	0.244
National Process=1	2315	0.587	0.492	83	0.855	0.353	486	0.736	0.440
Mutual Recognition=1	2315	0.323	0.467	83	0.144	0.353	486	0.199	0.400
Non-prescription Drug=1	2315	0.061	0.240	83	0.000	0.000	486	0.051	0.221
Year of Entry	2315	1995.396	885.628	83	1998.711	4.652	486	1991.895	9.594
Age at Transformation	83	67.662	55.242	83	67.662	55.242	0		
Age at Exit	486	132.578	111.084	0			486	132.578	111.084
Therapeutic Class 1 =1	2315	0.129	0.335	83	0.216	0.414	486	0.174	0.380
Therapeutic Class 2 =1	2315	0.164	0.370	83	0.156	0.365	486	0.096	0.295
Therapeutic Class 3 =1	2315	0.167	0.373	83	0.313	0.466	486	0.170	0.376
Therapeutic Class 4 =1	2315	0.032	0.177	83	0.012	0.109	486	0.016	0.127
Therapeutic Class 5 =1	2315	0.034	0.181	83	0.012	0.109	486	0.045	0.208
Therapeutic Class 6 =1	2315	0.059	0.236	83	0.180	0.387	486	0.059	0.237
Therapeutic Class 7 =1	2315	0.022	0.148	83	0.024	0.154	486	0.012	0.110

Therapeutic Class 8 =1	2315	0,073	0,2602	83	0,012	0,109	486	0,076	0,265
Therapeutic Class 9 =1	2315	0,087	0,282	83	0,072	0,260	486	0,179	0,383
Therapeutic Class 10 =1	2315	0.019	0.139	83	0.000	0.000	486	0.026	0.161
Therapeutic Class 11 =1	2315	0.028	0.167	83	0.000	0.000	486	0.008	0.090
Therapeutic Class 12 =1	2315	0.077	0.267	83	0.000	0.000	486	0.049	0.216
Therapeutic Class 13 =1	2315	0.037	0.190	83	0.000	0.000	486	0.028	0.167
Therapeutic Class 14 =1	2315	0.005	0.074	83	0.000	0.000	486	0.002	0.045
Therapeutic Class 15 =1	2315	0.016	0.125	83	0.000	0.000	486	0.014	0.119
Therapeutic Class 16 =1	2315	0.037	0.190	83	0.000	0.000	486	0.030	0.173
Therapeutic Class 17 =1	2315	0.007	0.087	83	0.000	0.000	486	0.008	0.090

The products were categorized into one of 17 Therapeutic Classes, according to the classification used by INFARMED⁶. For products classified simultaneously in several Therapeutic Classes, the class chosen was the first on the list of therapeutic classes for that product, which is usually the most relevant one. We may observe that there were not transformations in classes 10 to 17⁷. Each Therapeutic Class is divided in several sub-classes that we use to define therapeutic substitutes, in estimation procedures.

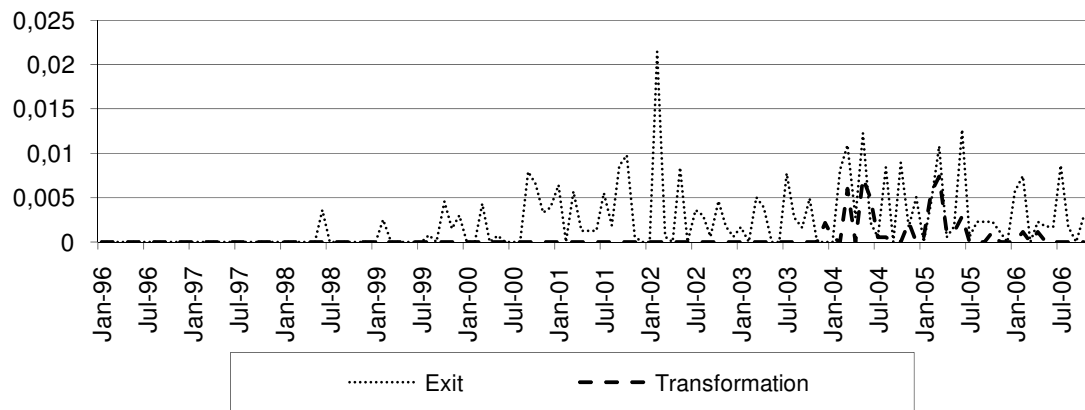
On Figure 1, we observe the behavior of the average rate of exit and the average rate of transformation into generic⁸. During 1996 and 1997, there were no exits. Indeed, exit rate increased mainly after 2000. The possibility of transformation seems to do not diminish the average rate of exit. During 2004 and the beginnings of 2005 the average rate of transformation had its larger values, but it decreased to values near zero, after middle 2005.

⁶ INFARMED classifies drugs in 20 Therapeutic Classes (using the “Código da Classificação Farmacoterapêutica” - Code of Pharmacotherapeutic Classification). Classes 18 to 20 were excluded from database because they were very small and residual classes. Observations with no information about Therapeutic Class were excluded too. This classification is similar to the one used by The European Medicines Agency.

⁷ For the entire population, we observe that there were 7 branded drugs of class 10 transformed into generics. However, they were not captured by our sample. In classes 11, 12, 14 and 17 there was no transformation at all.

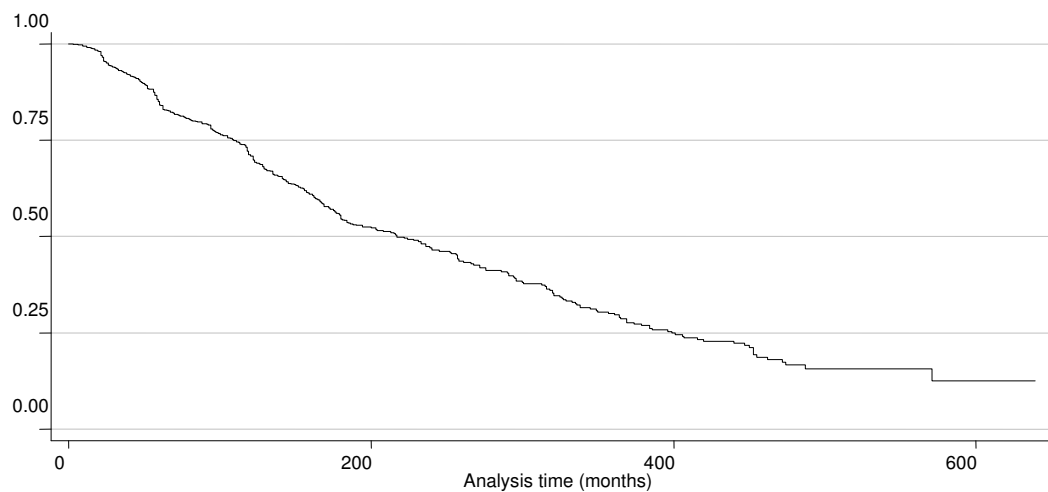
⁸ Average rate of exit is the proportion of exits on total products in the market, for each month; and average rate of transformation is the proportion of transformations on total products in the market, for each month.

Figure1: Average Rates



We begin our brand survival analysis by estimating the non-parametric survivor and hazard functions, for the complete sample. We treat exits and transformations into generics as “deaths”. Analysis time unit is the month.

Figure 2: Survival function



From Figure 2, the hazard rate is relatively constant. Half of the brands survive at least 216 months (near 18 years), and 12.5% of the brands survive more than 639 months (more than 53 years).

4. Estimation and discussion

Now we use regression analysis to test the hypothesis of section 3.

First, we use the data from January 1996 to September 2003, in order to estimate a model with only one destination for branded drugs: market exit. We choose the proportional hazard model, using the semi-parametric approach (commonly referred as the “Cox’s model”).

$$\lambda(t, X, \beta) = \lambda_0(t) e^{X\beta}$$

Using this model, we could estimate the effect of the explanatory variables, X , on the hazard rate, $\lambda(t, X, \beta)$, without having to make any assumptions about the shape of the baseline hazard function, $\lambda_0(t)$. Under this specification, the Hazard Ratio is:

$$HR(t, X_i, X_j, \beta) = \frac{\lambda_0(t) e^{X_i \beta}}{\lambda_0(t) e^{X_j \beta}} = e^{(X_i - X_j) \beta}$$

This is very appellative, in the sense that if we have two observations (i and j) that are identical but on the value of variable x , then:

$$HR(t, X_i, X_j, \beta) = \frac{\lambda_0(t) e^{X_i \beta}}{\lambda_0(t) e^{X_j \beta}} = e^{\beta_x (x_i - x_j)}$$

The interpretation is that the hazard rate of i is $e^{\beta_x (x_i - x_j)}$ of the hazard rate of j . Therefore, we have a measure of the impact of variable x on the hazard rate. This may be applied to all explanatory variables.

We have some observations that are left-censored. They were already in the market on the 1 January 1996, time of the beginning of the analysis. Therefore, for those observations we don’t observe the complete survival spell, but this is accounted for in the estimation procedure.

Cox’s model is appropriate for estimation of continuous time models. That is not the case of our data. Although survival times are measured in days, we group data by

month, in order to be computationally feasible to work with the panel. However, as our spell lengths are usually several years and there is a relatively low prevalence of ties, it is expected that Cox's model provide acceptable estimation's results. In order to account for the discreteness of data, we also use a discrete time proportional hazard model (the complementary log-log model). The dependent variable is a binary variable that is equal to one if the product exits the market in that month, and zero otherwise. Besides the independent variables used in Cox's model, we also include binary variables⁹ for spell lengths. Using the exponential form of the results, we get hazard rates that could be interpreted in the same way as the results of Cox's model.

In a second step, we use data from October 2003 to October 2006, having two competing destinations for branded drugs: exit or transformation into generic. The hazard rate is now the sum of the destination-specific hazard rates:

$$\lambda(t) = \lambda_{exit}(t) + \lambda_{transformation}(t).$$

We estimate this model using a multinomial logit framework. The use of the multinomial is adequate for discrete time models, as in our case, with competing events (Jenkins, 1995, 2004; Portugal et al., 2008)

The interpretation of coefficients of multinomial logit is not as straightforward as that of the Cox's model. In fact, having a model with two alternative destinations, 1 for exit and 2 for transformation, and a 0 alternative (to continue in the market as a brand), we have:

$$\frac{p(y = m|X)}{p(y = 0|X)} = \exp(X\beta_m), m = 1,2$$

where β_m is the vector of coefficients associated with the m^{th} alternative and

$\frac{p(y = m|X)}{p(y = 0|X)}$ is the odds ratio, or the relative probability of prefer m instead of 0. The

interpretation of β_m is given by:

$$\frac{\partial \log \left[\frac{p(y = m|X)}{p(y = 0|X)} \right]}{\partial X} = \beta_m, m = 1,2.$$

This result extends to a more generic one:

⁹ Then, we don't have to make any assumptions about baseline hazard. (Jenkins, 2004)

$$\frac{\partial \log \left[\frac{p(y = m|X)}{p(y = k|X)} \right]}{\partial X} = \beta_m - \beta_k; m, k = 1, 2; m \neq k .$$

The coefficient β_m (or $\beta_m - \beta_k$, in the generic case) measures the impact of a variable on the log odds ratio. Using this, we are able to see if the variable has a positive or negative effect on relative probabilities.

The database was organized has an unbalanced panel. We cluster observations by product, because we expect that observations are independent across products but not within the lifetime of each product.

4.1. Before October 2003

We start by estimating the regression for the period between January 1996 and September 2003. During that period, transformation into generic is not possible, and all the “deaths” are exits from the market.

The independent variables contain characteristics of products, firms and of the market, measured on a monthly basis. The market is characterized by the total number of products and by binary variables that mark the type of regulation in each period. The number of products, the percentage of generic drugs within firm’s portfolio, and a binary variable, equal to one if the firm launched new products for the same therapeutic class of the product in that month, characterize firms. Product characteristics are a binary variable that says whether it is a non-pioneer drug, another if it is a non-prescription drug, the type of marketing authorization (national, central or mutual recognition procedure) and year of entry; the age of the product; and binary variables for each therapeutic class¹⁰. For each product-month observation, we also use variables to characterize the internal and external competition that the product faces: we divided the market for each product in two levels: first, we have a sub-market that aggregates products that are chemically identical¹¹; and, second, there is a sub-market that aggregates products in the same therapeutic sub-class¹², even if they are not chemically

¹⁰ There are 17 therapeutic classes. On this first set of regressions, we exclude two binary variables, representing two therapeutic classes (10 and 14), from estimations, due to the lack of variability.

¹¹ Those products have the same active substance, the same pharmaceutical form, and the same dosage.

¹² Those products are in the same therapeutic sub-class (they have the same classification, according to the Code of Pharmacotherapeutic Classification).

identical. For each sub-market level, we have variables for the number of competitors and the number of own products.

In Table 2, we present the results of estimation using the Cox's model and the complementary log-log (cloglog) model. The results are similar¹³.

The number of products of the firm in the sub-market of therapeutic substitutes is significant for all the regressions, increasing the hazard rate. Those results are consistent with several empirical studies reviewed (Ruebeck, 2005; Requena-Silvente, 2005; Greeinstein et al., 1998). By the contrary, the number of products of the firm in the sub-market of chemical substitutes is significant for all the regressions, and it has a positive impact on survival probability. Usually, the range of own products at the same sub-market of chemical substitutes is not of self-competitors but different packages of exactly the same product. Therefore, it is expected that firms take advantage from scope economies of those portfolios.

Now, let us look to the effect of firm characteristics on exit. A higher proportion of generics in the portfolio of the firm increased brand's probability of exit, but it lose significance when we account for regulation binary variables. According to the results, it seems that firms do some sort of specialization, opting for portfolios of generics or portfolios of brands. Products from larger firms (measured by the number of products) have a smaller hazard rate. Therefore, scale effects seem important for branded drugs survival; especially if these scale effects are not only achieved on production but also on marketing and distribution phases.

The number of close competitors decreases the probability of exit. The number of competitors, at sub-market of chemical substitutes, is significant but it has an effect opposite to what was expected. A drug with one more competitor has an hazard rate 0.962 times the hazard rate without that extra competitor. One possible explanation is that markets with higher number of competing products are more profitable markets and, therefore, even with competition, products tend to last longer in those markets. The number of therapeutic competitors and the number of total products in the market are not statistical significant.

¹³ In Appendix, we show the same estimations with an additional variable: *Product is under Decree 1278/2001*. This variable is a binary variable that assumes the value one for products that are included in a list of products that have to accomplish new packaging rules, between December 2001 and November 2002. It was expected that the inclusion on the list would increase the probability of exit. However, the results are only conclusive on the second formulation, but contrary to what was expected.

The improvement of generic competition due to regulatory changes had a negative effect over branded drug survival. Binary variables measure the effect of regulatory changes. The first indicates the period between the increase of public reimbursement for generic and the introduction of reference price system. During that period, between September 2000 and November 2002, the expected hazard rate was more than four times the hazard rate during the period before September 2000, and more than two times the hazard rate during the period after December 2002, everything else being constant. The introduction of reference pricing (in December 2002, accounted by the second binary variable) seems to not increase the probability of brand's exit. The evidence that, during this period, no product under reference pricing exited the market reinforces this. This a surprising result, because we were expecting that stronger competition due to reference price system would make branded drugs survival harder.

One interesting result is that non-prescription drugs, that are much less regulated and whose demand is decided by patients (not doctors), have a hazard rate approximately of 60% the hazard rate of prescription drugs. This suggests that branded drugs within a less regulated market have a higher probability of surviving.

It was expected that pioneer products have a survival advantage, according with the brand loyalty argument. However, evidence does not show that. The variable "Non-pioneer Drug=1" is not significant to explain the hazard rate.

Table 2: Estimations for the period January 1996 – September 2003

	(i)		(ii)	
	Cox	Cloglog	Cox	Cloglog
Year of Entry			0.723 (1.44)	0.719 (1.47)
Non-pioneer Drug=1	1.198 (1.09)	1.214 (1.09)	1.191 (1.04)	1.208 (1.13)
No. Products (all market)	1.000*** (11.65)	1.000*** (11.96)	1.000** (2.42)	1.000** (2.51)
No. Products (own firm)	0.997*** (6.34)	0.997*** (6.49)	0.996*** (6.30)	0.996*** (6.46)
Proportion of generics (own firm)	2.301* (1.69)	2.318* (1.10)	2.209 (1.61)	2.227 (1.62)
No. Products (other firms, chemical substitutes)	0.963*** (4.24)	0.962*** (4.30)	0.962*** (4.25)	0.961*** (4.31)

No. Products (own firm, chemical substitutes)	0.985** (1.98)	0.859** (1.92)	0.983** (2.11)	0.983** (2.07)
No. Products (own firm, therapeutic substitutes)	1.011*** (5.19)	1.013*** (5.53)	1.011*** (4.91)	1.012*** (5.27)
No. Products (other firms, therapeutic substitutes)	1.000 (0.07)	1.000 (0.02)	1.000 (0.20)	1.000 (0.13)
If firm launched products=1 (in the same therapeutic class)	1.261 (1.23)	1.308 (1.43)	1.283 (1.31)	1.332 (1.52)
Between Sept. 2000 and Nov. 2002 = 1			4.402*** (3.88)	4.304*** (3.82)
Between Dec. 2002 and Sept. 2003 = 1			2.021 (1.30)	1.933 (1.23)
Non-prescription drug = 1	0.593* (1.78)	0.583* (1.83)	0.595* (1.76)	0.585* (1.81)
Central Process = 1	0.587 (1.10)	0.581 (1.12)	0.564 (1.19)	0.559 (1.20)
National Process =1	4.162*** (5.48)	4.460*** (5.70)	3.697*** (5.04)	3.959*** (5.26)
Therapeutic Class 1 =1	8.457** (2.10)	8.582** (2.11)	8.253** (2.08)	8.351** (2.09)
Therapeutic Class 2 =1	6.518* (1.84)	6.540* (1.84)	6.291* (1.80)	6.333* (1.81)
Therapeutic Class 3 =1	14.203*** (2.62)	14.511*** (2.64)	13.806*** (2.59)	14.153*** (2.61)
Therapeutic Class 4 =1	5.005 (1.48)	5.072 (1.50)	4.754 (1.44)	4.836 (1.45)
Therapeutic Class 5 =1	9.082** (2.10)	9.163** (2.11)	9.148** (2.11)	9.271** (2.12)
Therapeutic Class 6 =1	14.401** (2.59)	14.780*** (2.61)	13.836** (2.55)	14.310*** (2.58)
Therapeutic Class 7 =1	3.242 (0.96)	3.274 (0.97)	3.189 (0.95)	3.222 (0.95)
Therapeutic Class 8 =1	12.644** (2.43)	12.917** (2.45)	11.856** (2.37)	12.148** (2.40)
Therapeutic Class 9 =1	14.027*** (2.59)	14.407*** (2.62)	13.227** (2.54)	13.591*** (2.56)
Therapeutic Class 11 =1	5.365 (1.43)	5.800 (1.50)	5.126 (1.39)	5.560 (1.47)
Therapeutic Class 12 =1	7.367* (1.80)	7.420* (1.81)	7.113* (1.77)	7.175* (1.78)
Therapeutic Class 13 =1	3.230 (1.08)	3.235 (1.08)	3.131 (1.05)	3.142 (1.05)
Therapeutic Class 15 =1	13.007** (2.39)	13.215** (2.40)	12.636** (2.36)	12.832** (2.37)
Therapeutic Class 16 =1	13.476** (2.48)	13.453** (2.48)	12.503** (2.41)	12.494** (2.41)
Log-Likelihood	-1203.475	-1277.571	-1174.069	-1247.913

Notes: Dependent variable is one if the product exits the market, and zero otherwise. The complementary log-log regressions also include a set of age binary variables that are not presented on the table. The results are expressed in hazard ratios. Robust z statistics are in parentheses. Observations are 122066.

*Significantly different from zero at the 10% level. ** Significantly different from zero at the 5% level. *** Significantly different from zero at the 1% level.

From the results for the period before October 2003, we conclude that we have no evidence that inter-firm competition was a driving force of branded drugs' exit. However, we found evidence that intra-firm competition, in the same therapeutic class, was relevant to explain exit. This may mean that firms are aware of the necessity to innovate, in order to keep profitability. If so, the product turnover is ensured, and consumers have access to innovative drugs. The consequence is that expenses with drugs would probably grow up, as more innovative drugs are likely to be higher-priced.

4.2. Since October 2003

Since October 2003, “deaths” are of two kinds: exits or transformations into generics. The base category is the maintenance in the market, as a brand. We estimate a multinomial logit, in order to include these two competing alternatives. Table 3 shows the results¹⁴.

Internal competition is important to explain “death”, either through exit or transformation. Launches of new products increase the probability of “death” for firm's own brands. If a firm launches a new drug, the relative probability of transformation increases, both related with the probability of stay in the market (the log odds ratio increases 0.845) or with the probability of exit (the log odds ratio increases 1.126). The number of own products in the same therapeutic sub-class has a positive and significant effect on the relative probability of exit, as before, but a negative and significant effect on the relative probability of transformation. The number of own products that are chemical substitutes is only significant to explain transformation with a positive signal, in the last two regressions.

The dimension of the firm, measured by the number of products, decreases the relative probability of exit (the log odds ratio decreases 0,002), but has no effect over

¹⁴ As previously, in Appendix, we show the same estimations with an additional variable: *Product is under Decree 1471/2004*. That is a binary variable that assume the value one for products that are included in a list of products that have to accomplish new packages' rules, after 2004. It was expected that the inclusion on the lists would increase the probability of exit. Unexpected, *Product is under Decree 1471/2004* has a negative effect on exit, despite not significant, and a positive effect on transformation.

transformation. Therefore, scale effects seem to be important, but only to explain exit. The proportion of generics has a positive effect on the relative probability of transformation and on the relative probability of exit. When comparing both probabilities (of exit and transformation), the proportion of generics increases the probability of transformation relatively to exit (the log odds ratio increases 2,001). Therefore, it seems that firms can exploit some kind of scope economies from the specialization of its portfolios, focusing on brand or generic products.

The number of chemical competitors is significant both for exit and for transformation, but with a different signal. This variable has a negative effect on the relative probability of exit, but a positive effect on the relative probability of transformation. The number of therapeutic competitors is not significant for exit neither for transformation. The number of total products in the market has no impact over the probability of exit or transformation. As before, the only competition that matters is competition from chemical substitutes.

Pioneer brands have a survival advantage. The relative probability of pioneer brands to exit the market or to be transformed is lower, as expected. Also, it is more probable that non-pioneer drugs are transformed than dropped out, compared with pioneer drugs (the log odds ratio increases 0.09).

Table 3: Estimations for the period October 2003 – October 2006

	Exit		Transformation	
	(1)	(2)	(1)	(2)
Age	0.010*** (4.79)	0.002** (2.37)	-0.075* (-1.85)	-0.071* (-1.80)
Age ²	-0.000*** (-3.96)		0.000 (0.76)	
Year of Entry	-0.002*** (-3.07)	-0.002*** (-2.99)	-0.703 (-1.51)	-0.689 (1.50)
Reference Price = 1	-2.689*** (-2.74)	-2.575*** (-2.62)	1.820*** (5.39)	1.816*** (5.37)
No. Products (all market)	0.000** (-2.35)	0.000** (-1.98)	0.000 (0.46)	0.000 (0.43)
No. Products (own firm)	-0.002*** (-4.23)	-0.002*** (-4.03)	0.000 (0.12)	0.000 (0.05)
Proportion of generics (own firm)	0.935*** (2.70)	0.895*** (2.58)	2.936*** (6.91)	2.931*** (6.89)
No. Products (other firms, chemical substitutes)	-0.005* (-1.85)	-0.004 (-1.51)	0.011*** (3.07)	0.011*** (3.07)

	(-1.87)	(-1.57)	(3.53)	(3.52)
No. Products (own firm, chemical substitutes)	-0.002	-0.003	0.052***	0.053***
	(-0.74)	(-1.03)	(2.67)	(2.69)
No. Products (own firm, therapeutic substitutes)	0.005*	0.005*	-0.024***	-0.024***
	(1.91)	(1.91)	(-2.60)	(-2.61)
No. Products (other firms, therapeutic substitutes)	0.001**	0.000**	0.001	0.001
	(2.35)	(2.13)	(1.43)	(1.44)
Non-pioneer Drug=1	0.637***	0.576***	0.727*	0.733*
	(4.10)	(3.72)	(1.68)	(1.69)
If firm launched products=1 (in the same therapeutic class)	-0.281	-0.305	0.845***	0.847***
	(-1.32)	(-1.44)	(3.12)	(3.11)
Non-prescription drug = 1	-0.425	-0.506	-45.976	-45.941
	(-1.28)	(-1.52)	(.)	(.)
Central Process = 1	0.034	0.011	-43.624	-43.645
	(0.11)	(0.04)	(.)	(.)
National Process =1	-0.053	0.103	0.980**	0.971**
	(-0.27)	(0.55)	(2.30)	(2.29)
Therapeutic Class 1 =1	-0.288	-0.240	1397.945	1370.063
	(-0.56)	(-0.45)	(1.51)	(1.50)
Therapeutic Class 2 =1	-1.539***	-1.560***	1398.005	1370.149
	(-2.79)	(-2.70)	(1.51)	(1.50)
Therapeutic Class 3 =1	-1.074**	-0.995*	1397.246	1369.454
	(-1.96)	(-1.74)	(1.51)	(1.49)
Therapeutic Class 4 =1	-2.072**	-1.979**	1397.286	1369.454
	(-2.40)	(-2.24)	(1.51)	(1.49)
Therapeutic Class 5 =1	-0.186	-0.177	1398.557	1370.691
	(-0.34)	(-0.31)	(1.51)	(1.50)
Therapeutic Class 6 =1	-0.775	0.751	1397.445	1369.563
	(-1.36)	(-1.27)	(1.51)	(1.50)
Therapeutic Class 7 =1	-0.805	-0.778	1398.590	1370.715
	(-1.16)	(-1.10)	(1.51)	(1.50)
Therapeutic Class 8 =1	-0.546	-0.448	1397.651	1369.751
	(-0.98)	(-0.78)	(1.51)	(1.50)
Therapeutic Class 9 =1	0.291	0.358	1398.390	1370.513
	(0.57)	(0.67)	(1.51)	(1.50)
Therapeutic Class 10 =1	0.437	0.442	1,354.225	1326.359
	(0.78)	(0.75)	(.)	(.)
Therapeutic Class 11 =1	-1.999*	-1.979*	1353.565	1325.694
	(-1.78)	(-1.74)	(.)	(.)
Therapeutic Class 12 =1	-0.135	-0.012	1345.258	1317.266
	(-0.24)	(-0.02)	(.)	(.)
Therapeutic Class 13 =1	-0.734	-0.676	1354.618	1326.760
	(-1.22)	(-1.08)	(.)	(.)
Therapeutic Class 14 =1	-1.560	-1.328	1356.447	1328.566
	(-1.54)	(-1.28)	(.)	(.)
Therapeutic Class 15 =1	-46.171	-46.016	1355.882	1328.006
	(.)	(.)	(.)	(.)

Therapeutic Class 16 =1	-1.601** (2.11)	-1.536** (-2.00)	1353.876 (.)	1325.980 (.)
Pseudo R ²	0.9737	0.9735		

Notes: Dependent variable is two if the branded drug is transformed into generic, is one if the product exits the market, and zero otherwise. Robust z statistics are in parentheses. Observations are 66017.

*Significantly different from zero at the 10% level. ** Significantly different from zero at the 5% level. *** Significantly different from zero at the 1% level.

Inter-firm competition has little impact on branded drug's "deaths". One possible explanation is that the number of competitors is not the relevant variable to explain survival, and others variables, as prices or market shares if available, should capture better the effect of inter-firm competition. As before, the intra-firm competition effect, the firm's portfolio and its size are important to explain exit. However, the effect over transformation is more misleading: we observe a intra-firm competition effect with chemical substitutes, but the opposite with therapeutic substitutes, and scale effects seem not significant.

4.3. From 1996 to 2006: testing the effect of transformation on exit

Now, we can test our central hypothesis: the possibility of transforming a brand into generic changes exit patterns. In order to do that, we get back to our first estimations with one single destination: exit from market, but now we estimate it for the all period. We treat the transformed products as no censored observations, meaning that we ignore the transformation as an end for the product. We included a binary variable that indicates the period since October 2003, in estimations.

Table 4: Estimations for the period January 1996 – October 2006

	Cox	Cloglog
<i>Since Oct. 2003=1</i>	3.731** (2.37)	7.388*** (3.91)
Year of Entry	0.699** (2.06)	0.666** (2.59)
Non-pioneer Drug=1	1.327** (2.34)	1.367*** (2.86)
No. Products (all market)	1.000* (1.91)	1.000** (2.38)
No. Products (own firm)	0.998*** (5.15)	0.998*** (8.24)
Proportion of generics (own firm)	2.234***	2.586***

	(3.24)	(3.58)
No. Products (other firms, chemical substitutes)	0.990***	0.988***
	(3.53)	(4.59)
No. Products (own firm, chemical substitutes)	0.998	0.998
	(0.45)	(0.68)
No. Products (own firm, therapeutic substitutes)	1.005***	1.007***
	(3.52)	(4.72)
No. Products (other firms, therapeutic substitutes)	1.000*	1.000**
	(1.90)	(2.08)
If firm launched products=1 (in the same therapeutic class)	0.993	1.011
	(0.05)	(0.08)
Between Sept. 2000 and Nov. 2002 = 1	4.628***	9.054***
	(4.61)	(7.16)
Between Dec. 2002 and Sept. 2003 = 1	2.929**	5.604***
	(2.33)	(4.11)
Non-prescription drug = 1	0.706	0.648**
	(1.51)	(1.98)
Central Process = 1	0.897	0.863
	(0.27)	(0.65)
National Process =1	1.639**	1.712***
	(2.27)	(3.56)
Therapeutic Class 1 =1	0.973	1.011
	(0.05)	(0.02)
Therapeutic Class 2 =1	0.555	0.515
	(1.09)	(1.26)
Therapeutic Class 3 =1	0.903	0.936
	(0.19)	(0.13)
Therapeutic Class 4 =1	0.439	0.376
	(1.24)	(1.59)
Therapeutic Class 5 =1	1.204	1.296
	(0.34)	(0.47)
Therapeutic Class 6 =1	1.003	1.078
	(0.01)	(0.14)
Therapeutic Class 7 =1	0.603	0.566
	(0.73)	(0.88)
Therapeutic Class 8 =1	1.052	1.091
	(0.09)	(0.16)
Therapeutic Class 9 =1	1.755	1.820
	(1.10)	(1.16)
Therapeutic Class 10 =1	1.446	1.577
	(0.61)	(0.79)
Therapeutic Class 11 =1	0.506	0.422
	(0.83)	(1.21)
Therapeutic Class 12 =1	0.942	1.095
	(0.10)	(0.16)
Therapeutic Class 13 =1	0.570	0.506
	(0.97)	(1.19)

Therapeutic Class 14 =1	0,310 (1.12)	0,194 (1.47)
Therapeutic Class 15 =1	0.818 (0.30)	0.809 (0.34)
Therapeutic Class 16 =1	0.754 (0.45)	0.770 (0.46)
Log-Likelihood	-2391.761	-2723.188

Notes: Dependent variable is one if the product exits the market, and zero otherwise. The complementary log-log regressions also include a set of age binary variables that are not presented on the table. The results are expressed in hazard ratios. Robust z statistics are in parentheses. Observations are 187832.

*Significantly different from zero at the 10% level. ** Significantly different from zero at the 5% level. *** Significantly different from zero at the 1% level.

The variable “Since October 2003 = 1” is significant and has a positive effect on exit. However, the probability of exit does not increase after October 2003, when compared with every other period. Comparing with the immediately previous period (between December 2002 and September 2003), the hazard of exit since October 2003 is more or less 1.3 times the previous hazard of exit. However, comparing with the period between September 2000 and November 2002, the hazard of exit since October 2003 is smaller (near 0.8 times the first). Therefore, we conclude that the introduction of a major public reimbursement for generics had a large impact on branded drugs exit. That impact was reduced, after the introduction of the reference price system, and it was recovered with the possibility of transformation of branded drugs on generics.

Even with the possibility of transformation, the relative probability of exit is not reduced which seems to contradict our hypothesis that drugs, that would exit other way, now will be transformed. However, it is possible that, after October 2003, the transformation of competing products (internal or external to the firm) increased the probability of branded drug’s exit, just because there are more generics in the market and a complete regulatory framework that stimulates brand-generic competition. Notice that the regulatory measures were cumulative, and since October 2003 all three are effective simultaneously.

5. Conclusions

This paper analyzes branded drugs survival, assuming that brands may disappear either by exiting the market or by being transformed into generics, extending the initial life cycle.

We show that different regulatory measures, such as prices, co-payments, and selling rules, have an impact on the substitution of older products for more innovative ones, and more expensive drugs for cheaper ones, when they are taken. Of the factors that influence the “death” of branded drugs, we verify that, more than competing products, it is the type and number of products of the same firm that have an important effect on “death” rates. We also observe that the variables that explain exit are different from those that explain transformation. Branded drugs were transformed into generics on a different age compared with the decision to completely exit the market.

Despite the possibility of transformation, the average rate of exit did not diminish after 2003, by the contrary. We observe that with the complete regulatory framework (taken as that achieved on October 2003) branded drugs have less probability of surviving. This suggests that only regulatory measures fully integrated are able to incentive competition and product turnover. The difference on survival patterns of non-prescription drugs, compared with prescription drugs, help to bear that conclusion.

The main caveat of this work is the lack of data on prices and market shares. With that kind of data we would be able to include a hedonic price approach, similar to what was done by Stavins (1995), Ruebeck (2005), or Figueiredo et al. (2006). The hedonic price approach, more than a mere comparison of prices, would enable us to measure if the product is under or over-priced. It would allow us to draw more accurate conclusions about competition and product turnover, namely if survival was explained also by quality or cost differentiation. That should be the approach for future work.

Appendix

**Table 2-A: Estimations for the period January 1996 – September 2003
(With the Decree 1278/2001 effect)**

	(i)		(ii)	
	Cox	Cloglog	Cox	Cloglog

Year of Entry			0.726 (1.42)	0.721 (1.45)
Non-pioneer Drug=1	1.198 (1.09)	1.214 (1.17)	1.184 (1.01)	1.198 (1.08)
No. Products (all market)	1.000*** (11.65)	1.000*** (11.85)	1.000*** (2.86)	1.000*** (2.94)
No. Products (own firm)	0.997*** (6.34)	0.997*** (6.49)	0.997*** (6.34)	0.997*** (6.48)
Proportion of generics (own firm)	2.297* (1.68)	2.316* (1.70)	2.154 (1.57)	2.168 (1.57)
No. Products (other firms, chemical substitutes)	0.963*** (4.23)	0.962*** (4.29)	0.963*** (4.24)	0.962*** (4.30)
No. Products (own firm, chemical substitutes)	0.985** (1.97)	0.985** (1.92)	0.984** (2.08)	0.984** (2.05)
No. Products (own firm, therapeutic substitutes)	1.011*** (5.19)	1.013*** (5.54)	1.012*** (5.03)	1.012*** (5.33)
No. Products (other firms, therapeutic substitutes)	1.000 (0.09)	1.000 (0.03)	1.000 (0.46)	1.000 (0.39)
If firm launched products=1 (in the same therapeutic class)	1.263 (1.23)	1.309 (1.43)	1.307 (1.41)	1.350 (1.59)
<i>Product is under Decree 1278/2001</i>	<i>0.942 (0.29)</i>	<i>0.971 (0.14)</i>	<i>0.532*** (2.07)</i>	<i>0.544*** (2.63)</i>
Between Sept. 2000 and Nov. 2002 = 1			3.473*** (3.30)	3.423*** (3.26)
Between Dec. 2002 and Sept. 2003 = 1			1.137 (0.23)	1.107 (0.18)
Nonprescription drug = 1	0.592* (1.78)	0.583* (1.83)	0.592* (1.77)	0.582* (1.83)
Central Process = 1	0.587 (1.10)	0.581 (1.12)	0.553 (1.23)	0.549 (1.23)
National Process =1	4.183*** (5.49)	4.470*** (5.70)	3.813*** (5.13)	4.058*** (5.33)
Therapeutic Class 1 =1	8.553** (2.11)	8.632** (2.12)	9.580** (2.22)	9.703** (2.23)
Therapeutic Class 2 =1	6.548* (1.84)	6.555* (1.84)	6.601* (1.80)	6.648* (1.86)
Therapeutic Class 3 =1	14.401*** (2.11)	14.612*** (2.64)	16.558*** (2.76)	16.942*** (2.78)
Therapeutic Class 4 =1	5.005 (1.48)	5.072 (1.50)	4.700 (1.43)	4.777 (1.44)
Therapeutic Class 5 =1	9.082** (2.10)	9.164** (2.11)	9.133** (2.10)	9.274** (2.12)
Therapeutic Class 6 =1	14.410** (2.59)	14.805*** (2.61)	13.900** (2.55)	14.407*** (2.59)
Therapeutic Class 7 =1	3.246 (0.96)	3.275 (0.97)	3.237 (0.96)	3.268 (0.97)
Therapeutic Class 8 =1	12.653**	12.921**	11.777**	12.609**

	(2.43)	(2.45)	(2.37)	(2.39)
Therapeutic Class 9 =1	14.219***	14.506***	15.627***	16.033***
	(2.61)	(2.63)	(2.70)	(2.72)
Therapeutic Class 11 =1	5.374	5.804	5.139	5.569
	(1.43)	(1.50)	(1.39)	(1.47)
Therapeutic Class 12 =1	7.353*	7.416*	7.003*	7.105*
	(1.80)	(1.81)	(1.76)	(1.77)
Therapeutic Class 13 =1	3.232	3.236	3.130	3.143
	(1.08)	(1.08)	(1.05)	(1.05)
Therapeutic Class 15 =1	13.027**	13.225**	12.750**	12.955**
	(2.39)	(2.40)	(2.37)	(2.38)
Therapeutic Class 16 =1	13.472**	13.452**	12.423**	12.443**
	(2.48)	(2.48)	(2.40)	(2.40)
Log-Likelihood	-1203.434	-1277.561	-1170.221	-1244.289

Notes: Dependent variable is one if the product exits the market, and zero otherwise. The complementary log-log regressions also include a set of age binary variables that are not presented on the table. The results are expressed in hazard ratios. Robust z statistics are in parentheses. Observations are 122066.

*Significantly different from zero at the 10% level. ** Significantly different from zero at the 5% level. *** Significantly different from zero at the 1% level.

Table 3-A: Estimations for the period October 2003 – October 2006
(With the Decree 1471/2004 effect)

	Exit		Transformation	
	(1)	(2)	(1)	(2)
Age	0.010*** (4.78)	0.002** (2.29)	-0.082** (-2.02)	-0.078** (-1.97)
Age ²	-0.000*** (-3.97)		0.000 (0.81)	
Year of Entry	-0.002*** (-3.14)	-0.002*** (-3.06)	-0.788* (-1.69)	-0.773* (1.68)
Reference Price = 1	-2.689*** (-2.73)	-2.572*** (-2.61)	1.836*** (5.38)	1.829*** (5.37)
No. Products (all market)	0.000 (-0.84)	0.000 (-0.62)	0.000 (-0.34)	0.000 (-0.37)
No. Products (own firm)	-0.002*** (-4.24)	-0.002*** (-4.03)	0.000 (0.14)	0.000 (0.07)
Proportion of generics (own firm)	0.918*** (2.65)	0.876** (2.52)	2.927*** (6.98)	2.923*** (6.96)
No. Products (other firms, chemical substitutes)	-0.005* (-1.85)	-0.004 (-1.56)	0.011*** (3.55)	0.011*** (3.52)
No. Products (own firm, chemical substitutes)	-0.002 (-0.72)	-0.003 (-1.00)	0.051** (2.55)	0.052*** (2.57)
No. Products (own firm, therapeutic substitutes)	0.005* (1.91)	0.005* (1.91)	-0.024** (-2.54)	-0.024** (-2.56)
No. Products (other firms, therapeutic substitutes)	0.001**	0.000**	0.001	0.001

	(2.36)	(2.14)	(1.37)	(1.38)
Non-pioneer Drug=1	0.639***	0.579***	0.743*	0.752*
	(4.11)	(3.72)	(1.70)	(1.72)
If firm launched products=1 (in the same therapeutic class)	-0.274	-0.298	0.821***	0.824**
	(-1.28)	(-1.41)	(3.02)	(3.02)
<i>Product is under Decree 1471/2004</i>	-0.232	-0.219	1.198***	1.193***
	(-1.07)	(-1.01)	(2.76)	(2.75)
Nonprescription drug = 1	-0.440	-0.522	-45.899	-45.864
	(-1.32)	(-1.56)	(.)	(.)
Central Process = 1	0.046	0.022	-43.640	-43.664
	(0.15)	(0.07)	(.)	(.)
National Process =1	-0.053	0.102	0.988**	0.981**
	(-0.27)	(0.55)	(2.30)	(2.29)
Therapeutic Class 1 =1	-0.282	-0.235	1572.713*	1542.927*
	(-0.55)	(-0.44)	(1.70)	(1.68)
Therapeutic Class 2 =1	-1.469***	-1.495***	1572.653*	1542.893*
	(-2.68)	(-2.60)	(1.70)	(1.68)
Therapeutic Class 3 =1	-0.961*	-0.889	1571.713*	1541.947*
	(-1.73)	(-1.54)	(1.70)	(1.68)
Therapeutic Class 4 =1	-1.972**	-1.888**	1571.733*	1542.010*
	(-2.27)	(-2.12)	(1.70)	(1.68)
Therapeutic Class 5 =1	-0.099	-0.097	1573.095*	1543.323*
	(-0.18)	(-0.17)	(1.70)	(1.68)
Therapeutic Class 6 =1	-0.685	0.664	1571.853*	1542.068*
	(-1.19)	(-1.12)	(1.70)	(1.68)
Therapeutic Class 7 =1	-0.717	-0.689	1572.938*	1543.160*
	(-1.02)	(-0.97)	(1.70)	(1.68)
Therapeutic Class 8 =1	-0.435	-0.344	1571.996*	1542.238*
	(-0.77)	(-0.59)	(1.70)	(1.68)
Therapeutic Class 9 =1	0.404	0.465	1572.800*	1543.024*
	(0.78)	(0.86)	(1.70)	(1.68)
Therapeutic Class 10 =1	0.433	0.439	1529.191	1499.422
	(0.76)	(0.74)	(.)	(.)
Therapeutic Class 11 =1	-2.007*	-1.984*	1528.461	1498.692
	(-1.78)	(-1.74)	(.)	(.)
Therapeutic Class 12 =1	-0.031	0.088	1519.800	1490.903
	(-0.06)	(-0.15)	(.)	(1.63)
Therapeutic Class 13 =1	-0.611	-0.557	1529.011	1499.253
	(-1.01)	(-0.89)	(.)	(.)
Therapeutic Class 14 =1	-1.558	-1.325	1530.325	1500.539
	(-1.53)	(-1.27)	(.)	(.)
Therapeutic Class 15 =1	-46.136	-45.982	1530.612	1500.828
	(.)	(.)	(.)	(.)
Therapeutic Class 16 =1	-1.491**	-1.431*	1528.302	1498.501
	(1.96)	(-1.86)	(.)	(.)
Pseudo R ²	0.9737	0.9736		

Notes: Dependent variable is two if the branded drug is transformed into generic, is one if the product exits the market, and zero otherwise. Robust z statistics are in parentheses. Observations are 66017.

*Significantly different from zero at the 10% level. ** Significantly different from zero at the 5% level. *** Significantly different from zero at the 1% level.

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Essay 3: Survival of Pharmaceutical Products: a Cross-countries Analysis

1. Introduction

The purpose of this work is to understand the determinants of survival of pharmaceutical products and how their effect varies across countries. Departing from differences and similarities between three countries, Portugal, New Zealand and Sweden, we intend to analyze the impact of different regulatory environments on product survival.

Portugal, New Zealand and Sweden's pharmaceutical markets are relative small pharmaceutical markets. Furthermore, their evolution has been very similar in the most recent years. In 2005, the total expenditures on pharmaceuticals in these three countries were far under OECD average. From 1997 to 2005, their real annual growth rates for pharmaceutical expenditures were between 3.9% and 4.1%. Public share of pharmaceutical expenditures, on the other hand, was above OECD average (OECD, 2008). That explains the concern of national governments with the magnitude and the trend of pharmaceutical expenditures and the subsequent implementation of measures to control it.

The three countries under study implemented, at some point between January 1990 and October 2006 (the time length of our analysis), a reference price system for reimbursement of pharmaceuticals. The reference price systems are different between countries and they are complemented with other measures in order to increase competition or simply to reduce expenditures with pharmaceuticals. Therefore, we intend to test if reference price systems encourage competition, in our case decreasing the rate of survival of pharmaceutical products, or if differences in rates result from other complementing measures.

There are several studies that perform international comparisons on pharmaceutical markets, but none of them focused on the determinants of the survival of pharmaceutical products. In fact, the entry of pharmaceutical products has been the purpose of most studies. However, product survival is particularly important to

understand competition, price evolution, profitability of drugs and the pressure that firms face to withdraw the less profitable ones. On the other hand, studies for other markets that not pharmaceutical markets were carried for a single country (Stavins, 1995; Greeinstein et al., 1998; Asplund et al., 1999; Ruebeck, 2005; Requena-Silvente, 2005; Figueiredo et al., 2006). In this paper, we innovate by presenting a cross-countries analysis of product survival.

A survival model is developed, taking into consideration the characteristics of the national markets, such as regulation, dimension, degree of competition, and also firm and product characteristics. The survival model is applied both on separated estimations for each country, and on estimations using data of the three countries.

We conclude that there is no evidence of intra-firm competition effects on pharmaceutical product survival, but inter-firm competition is relevant to explain it. We believe that the absence of evidence of intra-firm competition is the consequence of the prevalence of scale or scope economies over the dispute for scarce resources within firm's portfolios. The introduction of a reference price system does not imply, *de per se*, an increase of the likelihood of pharmaceutical product exit. The results are as ambiguous as other results on the impact of reference price system on competition variables. Finally, there are country specificities that have an impact both on product survival and on the effect of other variables on product survival.

The rest of the paper is organized as follows. In Section 2, we present the pharmaceutical market environment within the three national markets under comparison and the theoretic background. Section 3 describes the data and shows non-parametric estimations. Section 4 has semi-parametric estimations and the discussion of results. In the last section, we draw our main conclusions.

2. Background

2.1 The pharmaceutical markets in Portugal, New Zealand and Sweden

2.1.1 Portugal

The Portuguese national health system ensures that all citizens have access to health care, for free or paying only small co-payments. For pharmaceutical products, the

public subsidization is low, forcing consumers to bear a significant share of the cost through out-of-pocket payments. On average, prescription drugs have a relative high weight compared with other countries, but the consumption of generics, despite being growing, is still relatively low. The pharmaceutical production is insipient with almost all products being imported. The number and dispersion of pharmacies is better than in many European countries, ensuring an easy access to pharmaceutical products (APIFARMA, 2002, 2008). Hospitals have a service for dispensing prescriptions to outpatients, but only for a limited set of pharmaceuticals, which carry no coinsurance (Barros et al., 2007).

Several regulatory changes were introduced on the pharmaceutical market, in Portugal, since 1990. These changes aimed to rationalize the consumption of medicines because evidence showed that the consumption and, consequently, both public and private expenditure with medicines were relatively high when compared with other countries. Many of those measures intended to stimulate the use of generic drugs, which are usually cheaper. In September 2000, the Government increased the reimbursement rate of generic drugs by 10 percentage points (the cost of a generic drug is always supported by the State on more 10 percentage points than the branded drugs, reducing the cost with generic drugs born by patients).

Another important measure was the introduction of the reference price system for some products in December 2002. The reference-price, which is the price of the most expensive generic preparation of that active substance, is only established if the product has, at least, one generic substitute. The scope of this price reference system is relatively narrow because it only compares the prices between chemical substitutes, ignoring therapeutic alternatives.

The prices of pharmaceuticals are controlled through international comparison. Prescription is not subject to any budget restriction. INFARMED (the Portuguese public agency for medicines) centralizes both market authorization and subsidization processes.

2.1.2. New Zealand

Health care services, including pharmaceutical products, are supported mainly by taxes. In fact, patient co-payments for pharmaceutical were only introduced in 1985.

In international comparisons, New Zealand appears as one of the countries where prices of pharmaceuticals are lower (Danzon et al, 2005; OECD, 2008). However, that was not always the case: in the late 80s and early 90s, the evidence that New Zealand had high-priced off patent drugs led to important reforms (Braae et al., 1999).

In 1993, reference price system was implemented¹ and PHARMAC (Pharmaceutical Management Agency Limited) was established. The reference price is the lowest price in each therapeutic subgroup, regardless of patent status or market share. The New Zealander system embraces more products within each comparative group than the Portuguese system, and consequently it should induce more competition. The reference price system acts as a *de facto* price control system, since high-priced drugs are not reimbursed. Additionally, PHARMAC only admits reimbursement for new products if they have a lower price than the reference, within the respective therapeutic subgroup (Danzon et al., 2004). Doing so, PHARMAC maintains the price of pharmaceuticals low, holding down the public cost with pharmaceuticals (Miller, 2006).

In 1997, PHARMAC became in charge of defining a positive list of drugs that are eligible for reimbursement and of establishing subsidy levels. PHARMAC acts as a public monopoly purchaser. Having considerable bargaining power, PHARMAC controls pharmaceutical expenditure through agreements and contracts with pharmaceutical suppliers (French et al., 2001), namely by having introduced public tenders for sole subsidized supply, which guarantees a temporary monopoly for the winner of the tender. Incumbent firms are pressured to decrease prices, but entry of lower priced products is not possible during the temporary monopoly.

The market authorization process (under responsibility of the Ministry of Health) is separated from the subsidization process (under responsibility of PHARMAC). There are examples of prescription and over-the-counter drugs that are commercialized without any subsidy (Braae et al., 1999). Contrary to Portugal and Sweden, New Zealand permits direct-to-consumer advertising of prescription drugs. The rationale is that paying for higher-priced drugs should be a patient's choice, and they must be informed in order to opt (Miller, 2006).

¹ Before 1993, reference price was applied for some isolated cases, but not as a structured system of reimbursement.

2.1.3 Sweden

Pharmaceutical expenditure per capita in Sweden is lower than the average of OECD countries. Moïse et al. (2007) suggest that relatively low pharmaceutical expenditures in Sweden are due to its low retail prices, rather than to low levels of consumption. In fact, the retail prices for pharmaceuticals are relatively low, in contrast to average prices received by manufacturers, which are high. That is due to low retail and wholesale's margins and the inexistence of VAT for prescribed medicines (Moïse et al., 2007).

The Swedish pharmacy market structure is a monopoly. The public monopolist, Apoteket, ensures the coverage of market but pharmacy density is low, limiting consumer convenience.

There is no explicit regulation on pharmaceutical prices in Sweden. However, *de facto* regulation exists through the reimbursement system. In 1993, a reference price system for reimbursement was developed, which implied the creation of a positive list for reimbursement, the List of Substitutable Products (Andersson et al., 2007). The reference price is the lowest-price generic substitute. The chemical substitution is the reference (as in Portugal). However, therapeutic substitutes are accounted at the previous decision of including the products on the List of Substitutable Products. The rate of public subsidization differs with the level of consumption of the patient. There is a ceiling for patient co-payments, above which the drugs are fully subsidized. The process for subsidization (responsibility of The Dental and Pharmaceutical Benefits Agency) is separated from the processes of market authorization and the decision on which drugs are exchangeable (responsibility of the Medical Products Agency) (Glenngård et al., 2005).

The generic substitution policy, mandatory since October 2002, has enabled Sweden to achieve fairly high penetration of generic drugs into the market in terms of volume, with a considerably low share of the total value of the market. However, the use of the lowest-priced listed drug, as the reference for substitution, risks undermining the competitiveness of the generic drug industry, which is an important sector in Sweden (Moïse et al., 2007).

2.2 Previous work

Pharmaceutical product survival should be treated within literature on portfolio location by multi-product firms. Pharmaceutical firms are usually multi-product firms and the decisions to launch a new product or to withdraw an existing one can be independent of the decision of entry or exit, respectively, of the firm itself. Additionally, pharmaceutical multi-product firms face different types of market structure on each of the distinct sub-markets where they are present, sometimes even with more than one product in each of those sub-markets. Therefore, all these aspects should be incorporated when studying pharmaceutical product survival.

The literature on product survival within multi-product firms is not vast. Some previous empirical studies (Ruebeck, 2005; Requena-Silvente, 2005; Greeinstein et al., 1998) show the existence of a positive relationship between sub-market intra-firm competition (also known as “cannibalization”) and the probability of product exit. Also, there is evidence that inter-firm competition is also important to explain exit. Other studies focus on the desegregation of firm effects and product effects. Firm specificities (which could signify scale or scope economies) may imply different survival spells for identical products (Stavins, 1995; Asplund et al., 1999; Figueiredo et al., 2006). However, what characteristics matter is not clear from all these works that have dissonant results.

For the pharmaceutical market, one work is available concerning product exit. Virabhac et al (2008) conclude, for the American market, that the impact of competition on branded drug exit is small, and the only competition that matters is that from generic substitutes. Their study ignores firm characteristics, using only product and market effects.

One caveat of those works is that they are single-country analysis. Therefore, differences in results could be explained by differences between the countries under study, among other reasons.

Within the pharmaceutical market’s literature, the international comparative studies are common for studying: launch delay of innovative drugs, price levels, and regulatory systems. Some recent examples of cross-countries analysis are Danzon et al. (2004, 2005, 2008), Kyle (2006, 2007), and Lanjouw (2005). However, as for other industries, international comparison was not used to study product exit.

The reference price system is a reimbursement system where a reference price is established for a group of medicines. The public reimbursement for all products within the reference group is calculated using the reference price as basis. Reference price systems around the world vary in the definition of the group of reference and the price of reference, the rate of reimbursement, the range of patients covered by the system, the cumulative existence (or not) of other regulatory rules. The rationale for the introduction of a reference price system is two-folders: first, to increase price-sensitivity of patients or doctors and achieve a more cost-efficient consumption of pharmaceuticals; second, to pass for patients the over-cost of more expensive drugs, alleviating the public budget. As a consequence of the increase of demand price-sensitivity, it is also expected that competition between products will increase, after the introduction of a reference price system.

The panoply of descriptive studies describing and comparing reimbursement systems, usually focus on the reference price system. Mossialos et al (2005), comparing the regulatory systems of France, Germany, the Netherlands and the United Kingdom, argue that does not exist such a unique policy or policy combination right for all countries, and different countries have to find the adequate policy approach to their own environment. Empirical papers on the impact of the reference price system are fewer and show inconclusive results. Cost savings, which are the main objective of the system, do not occur always, depending on other regulatory measures. Danzon et al. (2004) found that, in Germany, the Netherlands and New Zealand, the reference price system did not stimulate competition, lowering prices as expected. They confirm that other measures to control prices (and costs) were adopted because the reference price could not reach that objective.

We broadly study the determinants of pharmaceutical product survival within Portugal, Sweden and New Zealand. We do a cross-country analysis of pharmaceutical product survival. We consider covariates that literature on product survival analysis applied to other industries had demonstrated to be relevant, controlling for country effects. Also, we build on the previous analysis by considering the reference price system and other country-specific regulatory changes.

Additionally, we test two specific hypotheses. First, the idea that differences between countries have impact not only on the survival rates itself but also on the effect

of other variables on survival rates (*Hypothesis 1*). Therefore, such characteristics should be accounted when performing single-country analysis. Second, the isolate effect of reference price on product survival may be ambiguous, as it does not guarantee *de per se* a more competitive environment (*Hypothesis 2*).

3. Data and non-parametric estimation

Our dataset includes 3543 products, marketed in Portugal (1612 products), Sweden (986 products) or New Zealand (945 products), between January 1990 and October 2006, representing a random sample of 25% of the complete dataset of products of the three countries². Each product-observation corresponds to all the preparations (different dosages and pharmaceutical forms) of a medicine, marketed by one firm at one of the three countries. The moment of entry is that of the entry of the first preparation of the medicine on the market and the moment of exit is the time of exit of the last preparation on the market. Table 1 shows some descriptive statistics of the characteristics of the products that remain constant over the period.

On average, the year of firm's entry is lower in New Zealand. The same happens for product entry³ and exit, followed by Portugal. The proportion of medicines that exit the market, during the period under analysis, is larger in New Zealand (24.13%), followed by Portugal (22.46%) and Sweden (12.58%). New Zealand is also the country with the highest rate of non-prescription medicines. That is mainly explained by the influence of the Maori traditional medicine (Miller, 2006).

In table 1, it was also shown the 14 binary variables that indicate the Anatomical Therapeutic Chemical (ATC) group of the drug. In the ATC classification system the drugs are divided according to the organ or system on which they act (group division) and their chemical, pharmacological and therapeutic properties (subgroup division)⁴.

² The proportion of products of each country, within the original dataset, remains equal to the sample. Data is from: *INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde* (Portugal), *Läkemedelsverket – Medical Products Agency* (Sweden) and *MEDSAFE – New Zealand Medicines and Medical Devices Safety Authority* (New Zealand).

³ In New Zealand, the average month of entry is 330.21, corresponding to July 1987, and the average month of exit is 477.77, corresponding to October 1999.

⁴ The World Health Organization formally adopts the ATC system, which is used worldwide. Drugs are classified at five different levels: the 1st level corresponds to the main anatomical group; the 2nd level is

There are some differences concerning dispersion through ATC groups, between countries, statistically confirmed through a Kruskal-Wallis test (table 2). The test shows that the null hypothesis of equality of populations, concerning the distribution through ATC groups, is refused by evidence.

Table 1: Descriptive Statistics (product observations)

	Total		Portugal		Sweden		New Zealand	
	Obs.	Mean	Obs.	Mean	Obs.	Mean	Obs.	Mean
Year of firm's entry	3543	1974.75	1612	1976.72	986	1978.26	945	1967.71
Month of Entry	3543	394.95	1612	407.22	986	436.93	945	330.21
Month of Exit	714	508.46	362	515.45	124	544.95	228	477.77
If non-prescription drug =1	3543	0.12	1612	0.11	986	0.06	945	0.22
If in ATC group A = 1	3543	0.12	1612	0.12	986	0.11	945	0.11
If in ATC group B = 1	3543	0.07	1612	0.07	986	0.06	945	0.07
If in ATC group C = 1	3543	0.14	1612	0.15	986	0.14	945	0.12
If in ATC group D = 1	3543	0.07	1612	0.07	986	0.04	945	0.10
If in ATC group G = 1	3543	0.06	1612	0.06	986	0.07	945	0.06
If in ATC group H = 1	3543	0.01	1612	0.02	986	0.01	945	0.02
If in ATC group J = 1	3543	0.12	1612	0.13	986	0.10	945	0.12
If in ATC group L = 1	3543	0.05	1612	0.04	986	0.06	945	0.05
If in ATC group M = 1	3543	0.07	1612	0.08	986	0.07	945	0.05
If in ATC group N = 1	3543	0.16	1612	0.14	986	0.18	945	0.15
If in ATC group P = 1	3543	0.01	1612	0.00	986	0.00	945	0.01
If in ATC group R = 1	3543	0.07	1612	0.06	986	0.06	945	0.08
If in ATC group S = 1	3543	0.03	1612	0.03	986	0.03	945	0.04
If in ATC group V = 1	3543	0.03	1612	0.01	986	0.06	945	0.03

Table 2: Kruskal-Wallis equality-of-populations rank test

	Observations	Rank Sum
Portugal	1612	2720185
Sweden	986	1836348
New Zealand	945	1707497

for the pharmacological/therapeutic subgroup; the 3rd and 4th levels are chemical/pharmacological/therapeutic subgroups and the 5th level is the chemical substance subgroup (in <http://www.whooc.no/atcddd/>).

We use two variables in order to capture for other differences among countries: *Population (ln)* and *GDP per capita (ln)*. We also use the data on pharmaceutical sales. All variables were constructed using figures from the *OECD Health Data 2007*. This dataset has annual observations for the three variables (see table 3). From these, we construct monthly series assuming constant growth rates within each year⁵. In the regressions, we use the Neperian logarithm of Population and GDP per capita. On Table 2, we also show the age structure of the population, in 1990 and 2005. We observe that, for Sweden and New Zealand, this structure does not change significantly. In Portugal, we observe that the ageing phenomenon is stronger.

Table 3: Macroeconomic Data

	1990			2005		
	PT	NZ	SE	PT	NZ	SE
Population (Thousands)	9873	3363	8559	10563	4099	9030
0-14 years	20.0%	23.2%	17.90%	15.6%	21.5%	17.4%
15-64 years	66.4%	65.7%	64.30%	67.4%	66.4%	65.3%
65 and over	13.6%	11.1%	17.80%	17%	12.1%	17.3%
Gross domestic product - Million US\$ at X-rate	75391	43799	242129	186277	109778	357503
Gross domestic product - /capita, US\$ x-rate	7636	13024	28289	17635	26782	39591
Pharmaceutical sales – Million US\$ at X-rate	771*	241**	1163	2650	459	3946

Source: OECD HEALTH DATA 2007, July 07

*Data from 1991; **Data from 1993

Using the cross-section data, we expand it to an unbalanced panel. The time unit is the month. We have 202 months covered by the panel, corresponding to 388679 observations. Starting from the initial information on entry and exit of the products, and

⁵ We assume that the monthly growth rate of Population, in 2006, is equal to 2005. For 2006, in Portugal and Sweden, we assume that the monthly growth rate of GDP per capita is equal to the monthly growth rate of GDP. For 2006 in New Zealand, we assume that the monthly growth rate of GDP per capita is equal to 2005. For 1990 in Portugal, we assume that the monthly growth rate of Pharmaceutical sales is equal to 1991. For 1990, 1991 and 1992 in New Zealand, we assume that the monthly growth rate of Pharmaceutical sales is equal to 1993.

country, firm, ATC code and prescription type of each product, we are able to construct several product-month variables for estimation purposes (see table 4).

Table 4: Descriptive Statistics (product-month observations)

	Total		Portugal		Sweden		New Zealand	
	Obs.	Mean	Obs.	Mean	Obs.	Mean	Obs.	Mean
Age (months)	388679	153.10	171619	139.61	89442	141.41	127618	179.42
No. of Products (national market)	388679	2958.58	171619	3572.17	89442	2227.20	127618	2646.02
No. of Firms (national market)	388679	300.78	171619	408.26	89442	286.33	127618	166.38
No. of Products (own firm)	388679	45.01	171619	31.94	89442	33.69	127618	70.50
New Products, last 12 months (own firm)	388679	2.70	171619	2.40	89442	3.26	127618	2.73
No. of Products (own firm, on the ATC-3 subgroup)	388679	4.70	171619	4.51	89442	4.45	127618	5.12
No. of Products (other firms, on the ATC-3 subgroup)	388679	72.57	171619	100.28	89442	47.46	127618	52.90
With Reference Price	388679	0.62	171619	0.31	89442	0.91	127618	0.82
With higher 10% reimbursement for generics, in Portugal	388679	0.21	171619	0.47				
With mandatory substitution for generics, in Sweden	388679	0.10			89442	0.42		
With public tenders for subsidized drugs, in New Zealand	388679	0.21					127618	0.63
Population (ln)	388679	8.87	171619	9.22	89442	9.09	127618	8.24
GDP per capita (ln)	388679	9.71	171619	9.40	89442	10.34	127618	9.68
Pharmaceutical Sales, per capita (USD)	388679	161.96	171619	152.94	89442	301.64	127618	76.20

We observe that the average age of the products is higher in New Zealand when compared with Portugal and Sweden, where they are similar. This is consistent with the low average month of entry of New Zealander products. Another interesting figure is the number of products, by firm: in New Zealand, it is more than the double of the values for Portugal and Sweden. The high number of products, by firm, is a signal of high market concentration. It was expectable that New Zealand, due to its geographic, political and historical distance, would present different characteristics from those in the two European countries. However, we found variables for which Portugal is the outlier. Namely, when compared with the other two countries, Portugal has the highest number of products, firms and competing products, by ATC-3 subgroup.

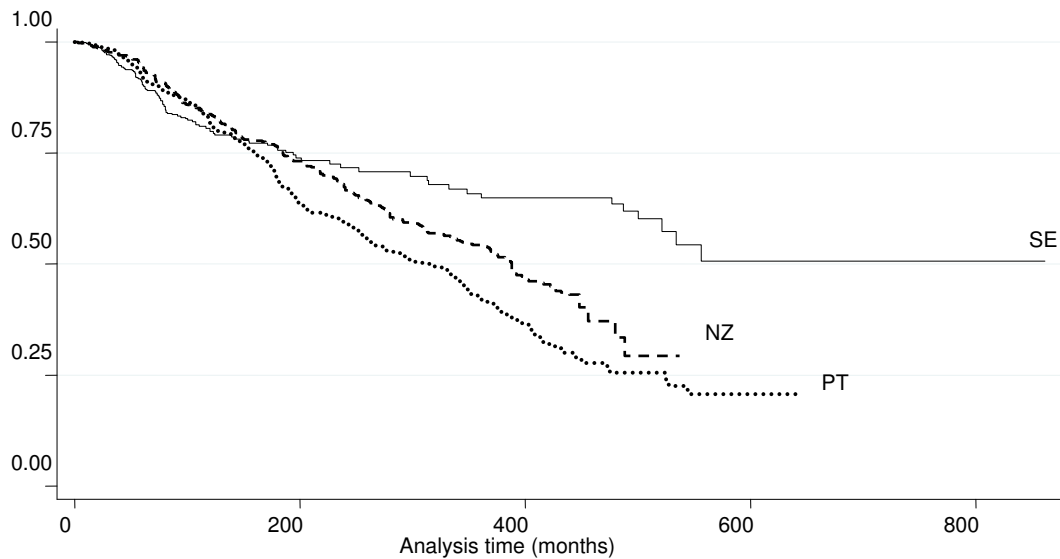
From the log-rank test (table 5), we conclude that there are differences on product survival between countries. The log-rank test shows that the null hypothesis of being equal the survival function between the three countries is refused by evidence.

Table 5: Log-rank test for equality of survival functions

	Events Observed	Events Expected
Portugal	362	309.58
Sweden	124	154.94
New Zealand	228	249.58
Total	714	714.00
$H_0: H_{PT}(t)=H_{SE}(t)=H_{NZ}(t)$ Results of the test: $\chi^2(2) = 17.06$; $\Pr > \chi^2 = 0.0002$		

Figure 1 shows the survival functions for the three countries. We observe that in Portugal pharmaceutical products have shorter survival spells, followed by New Zealand. In Sweden, half of the products survive at least 53 years. However, this pattern is not consistent for all survival spells: nearly 85% of the drugs survive at least 108 months, in Portugal and New Zealand; but only 81% of the drugs survive at least the same time, in Sweden. So, we may conclude that there is a higher rate of withdraws on younger products in Sweden, but those that survive the first months have longer survival spells. We must be aware that this is a very rough analysis, where differences between observations, other than life spell at the moment of analysis, are not accounted for. For a more accurate analysis, we proceed to semi-parametric estimations.

Figure 1: Survival functions



4. Semi-parametric estimations and discussion

We estimate a duration model to test our main hypotheses. Moreover, we will control for characteristics of products, firms and national markets in order to test if the differences on product survival, between countries, remain.

We use the proportional hazard model, with a semi-parametric approach (commonly referred as the “Cox’s model”).

$$\lambda(t, X, \beta) = \lambda_0(t) e^{X\beta}$$

Using this model, we could estimate the effect of the explanatory variables, X , on the hazard rate, $\lambda(t, X, \beta)$, without having to make any assumptions about the shape of the baseline hazard function, $\lambda_0(t)$.

Having two observations (i and j) that are identical but on the value of variable x , the interpretation is that the hazard rate of i is $e^{\beta_x(x_i - x_j)}$ of the hazard rate of j . Therefore, we have a measure of the impact of variable x on the hazard rate, called the Hazard Ratio (HR).

$$HR(t, X_i, X_j, \beta) = \frac{\lambda_0(t) e^{X_i \beta}}{\lambda_0(t) e^{X_j \beta}} = e^{\beta_x(x_i - x_j)}$$

Left-censure (for products already in the market on the 1 January 1990, time of the beginning of the analysis) is accounted for on the estimations. Although Cox’s model is appropriate for estimation of continuous time models and that is not the case of our data, as our spell lengths are usually several years and there is a relatively low prevalence of ties, it is expected that Cox’s model provide acceptable estimation’s results (Jenkins, 1995, 2004).

4.1 Estimations for each country, separately

First, we estimate the duration model for each country. We present two types of regressions: regressions (i) include the variable *No. of Products (national markets)*; regressions (ii) include *No. of Firms (national markets)*. We do not use the two variables simultaneously because the correlation coefficient between them is high (superior to 0.97), for the three countries. All regressions include the set of binary

variables for the ATC group of the product (not shown on Table 6). With this set of variables we intend to control for specificities on survival of drugs that treat different organs or systems.

Table 6: Estimations for each country

	Portugal		Sweden		New Zealand	
	(i)	(ii)	(i)	(ii)	(i)	(ii)
No. of Products (national market)	1.001*** (4.79)		1.003*** (5.94)		1.004*** (4.80)	
No. of Firms (national market)		1.017*** (6.27)		1.030*** (5.62)		1.046* (1.89)
No. of Products (own firm)	0.991*** (3.23)	0.991*** (3.29)	1.010*** (3.41)	1.010*** (3.48)	1.004** (2.23)	1.004*** (2.60)
New Products, last 12 months (own firm)	0.978 (0.89)	0.978 (0.90)	0.941** (2.37)	0.939** (2.44)	0.917*** (2.97)	0.912*** (3.04)
Year of Firm's Entry	1.000 (0.07)	1.000 (0.03)	1.002*** (3.78)	1.002*** (3.84)	0.999 (1.00)	0.999 (0.82)
No. of Products (own firm, on the ATC-3 subgroup)	0.987 (1.16)	0.988 (1.13)	0.966 (1.55)	0.966 (1.54)	0.976 (1.55)	0.976 (1.52)
No. of Products (other firms, on the ATC-3 subgroup)	1.000 (0.55)	1.000 (0.40)	1.007*** (2.98)	1.007*** (3.05)	1.008*** (3.21)	1.009*** (3.45)
Non-prescription drug = 1	0.972 (0.17)	0.977 (0.14)	0.750 (0.52)	0.755 (0.51)	0.576*** (2.71)	0.576*** (2.71)
With Reference Price	0.309*** (6.59)	0.316*** (7.55)			0.554** (2.05)	0.854 (0.56)
With higher 10p.p. reimbursement for generics, in Portugal	6.633*** (7.41)	3.557** (4.93)				
With mandatory substitution for generics, in Sweden			0.589 (0.73)	0.764 (0.38)		
With public tenders for subsidized drugs, in New Zealand					0.194*** (3.92)	0.575 (1.44)
Log-Likelihood	-1904.776	-1892.589	-560.036	-562.765	-1235.533	-1247.106
Observations	170007		88459		126676	

Notes: Dependent variable is one if the product exits the market, and zero otherwise. All the regressions include a set of binary variables for each Therapeutic Group that are not presented on the table. The results are expressed in hazard ratios. Robust z statistics are in parentheses.

*Significantly different from zero at the 10% level. ** Significantly different from zero at the 5% level. *** Significantly different from zero at the 1% level.

First, we look to the variables that characterize the national pharmaceutical markets. For all countries, both the *No. of Products* and the *No. of Firms* have a negative impact on product survival, as expected.

The characteristics of the firm that sell the product are accounted for. The results differ from country to country. In Portugal, the only characteristic of the firm that is significant is the *No. of Products (own firm)*, which has a positive impact on product survival. This is consistent with the existence of economies of scale: products from larger firms have a survival advantage. For the other two countries, the *No. of Products*

(*own firm*) has a positive impact on the hazard ratio (one additional product on the firm's portfolio increase the hazard rate by 1%, in Sweden, and 0.4%, in New Zealand). Therefore, it seems that, in these countries, products do not benefit from being within large portfolios. However, products have a higher survival probability if the firm launched any new product in the previous 12 months. Therefore, it does not appear to exist any "cannibalization" effect, that is to say that new products do not "expulse" old products, from firm's portfolio. The *Year of Firm's Entry* on the market is significant only for Sweden and it has a positive impact on the hazard ratio, meaning that products of more recent firms have less probability of survival.

We use two covariates related with the ATC-3 subgroup of the product (corresponding to the second level of classification, the therapeutic main subgroup, and noted by one letter and two digits): *No. of Products (own firm, on the ATC-3 subgroup)* and *No. of Products (other firms, on the ATC-3 subgroup)*. The main therapeutic subgroup is not the ideal measure of the relevant market for the product, since within it there are different levels of substitution. Although, this was the more disaggregate that we could get with the data available. The first variable is not significant for any of the three countries. The second variable is not significant in Portugal, but it is significant and with a negative impact on product survival, in Sweden and New Zealand. More close competitors have a negative impact on the probability of product survival, as expected. The divergence between Portugal and the other two countries may be a consequence of how the public authorities differently exploit their buyer-power over the pharmaceutical firms. In fact, for the three countries, the State is the major buyer of medicines (directly or indirectly through reimbursement), but only Sweden and New Zealand exercise that buyer-power through centralized purchase processes (in Sweden, through Apoteket; and in New Zealand, through PHARMAC), which are expected to pressure competition between close substitutes.

The binary variable that is equal to one if the product is a non-prescription product is only significant for New Zealand, where non-prescription products have a hazard rate 0.576 times of the hazard rate of prescription products.

We may conclude that the effect of market, firm and product characteristics is different from country to country. Therefore, not only differences between countries

imply different survival rates, *de per se*, but they also imply differences on other variables impact. The results validate hypothesis 1.

Finally, we have to interpret the coefficients of the binary variables that account for the introduction of the reference price system on each country⁶. For Sweden, the variable is not on regression due to the lack of variability on the explained variable before the introduction of the reference price system. In fact, we only have product exit, in Sweden, since 1998 and it makes no sense to account for any regulatory introduction before that. Therefore, the variable is significant for Portugal and for New Zealand, in regression (i), where the introduction of the reference price system increase product survival. Therefore, it does not seem to stimulate competition *de per se*. We may conclude that the isolate effect of the reference price system on product survival is as established on hypothesis 2, even when we control for the impact of other regulatory measures. The other regulatory measures, that are expected to increase competition and, consequently, to increase product exit have different effects: the increase of the public reimbursement of generics, in Portugal, increased the expected hazard of product exit; the mandatory substitution of generics have no impact on product survival, in Sweden; and the introduction of public tenders, in New Zealand decreased the expected odd of product exit. The results for Portugal and New Zealand show that allowing for repeated games for price competition (the Portuguese case) could be more competitive than solving the price competition by a one-stage game.

4.2 Joint estimation

Let us now look to the results of estimations when we add the observations from the three countries. On table 7⁷, regressions (I) to (IV) differ on the way we account for differences between countries and the regulatory changes in each of the countries. Regressions (I) to (III) include fixed effects for the country, through two binary variables: *If in Sweden = 1* and *If in New Zealand = 1* (the default is *If in Portugal = 1*). Regression (III) also includes the *Pharmaceutical Sales, per capita*. Regression (IV)

⁶ The reference price system was introduced on December 2002, in Portugal, on January 2003, in Sweden, and on July 1993, in New Zealand.

⁷ In table 7, regressions include the variable *No. of Firms (national markets)*. In Annex (table 7-A), we show the same regressions substituting the *No. of Firms (national markets)* by the *No. of Products (national markets)*. Results are similar.

includes two variables (*Population (ln)* and *GDP per capita (ln)*) that intend to capture the macroeconomic differences between countries and, simultaneously, to resolve a problem of high correlation between the binary variables for the countries (fixed effects) and the binary variable *With Reference Price*. *Population (ln)* is relatively constant within countries, so it works as a country “fixed effect” variable, but *GDP per capita (ln)* has some variability, even within country.

Table 7: Estimations for the three countries

	(I)	(II)	(III)	(IV)
No. of Firms (national market)	1.016*** (14.93)	1.017*** (7.86)	1.027*** (7.18)	1.016*** (7.56)
No. of Products (own firm)	1.002** (2.00)	1.003** (2.42)	1.003** (2.53)	1.003*** (2.69)
New Products, last 12 months (own firm)	0.960*** (3.13)	0.955*** (3.40)	0.953*** (3.56)	0.952*** (3.62)
Year of Firm's Entry	1.001*** (3.90)	1.001*** (4.14)	1.001*** (4.29)	1.001*** (4.34)
No. of Products (own firm, on the ATC-3 subgroup)	0.975*** (3.26)	0.975*** (3.26)	0.976*** (3.25)	0.976*** (3.25)
No. of Products (other firms, on the ATC-3 subgroup)	1.001 (1.56)	1.001** (2.07)	1.001** (2.17)	1.001** (2.13)
Non-prescription drug = 1	0.753** (2.35)	0.747** (2.42)	0.746** (2.43)	0.745** (2.44)
If in Sweden = 1	5.183*** (10.21)	6.046*** (2.80)	54.879*** (4.36)	
If in New Zealand = 1	85.865*** (12.74)	266.65*** (9.31)	1610.703*** (8.38)	
With Reference Price		0.341*** (8.40)	0.497*** (4.44)	0.458*** (5.40)
With higher 10% reimbursement for generics, in Portugal		2.868*** (4.44)	1.778** (2.25)	3.047*** (4.67)
With mandatory substitution for generics, in Sweden		4.108** (2.51)	5.676*** (3.10)	13.422*** (8.44)
With public tenders for subsidized drugs, in New Zealand		1.636*** (2.94)	1.299 (1.48)	2.569*** (5.51)
Population (ln)				0.008*** (9.29)
GDP per capita (ln)				0.745 (1.02)
Pharmaceutical Sales, per capita (1000USD)			0.991*** (3.78)	
Log-Likelihood	-4509.923	-4452.022	-4444.530	-4458.897

Notes: Dependent variable is one if the product exits the market, and zero otherwise. All the regressions include a set of binary variables for each Therapeutic Group that are not presented on the table. The results are expressed in hazard ratios. Robust z statistics are in parentheses. Observations are 385142.

*Significantly different from zero at the 10% level. ** Significantly different from zero at the 5% level. *** Significantly different from zero at the 1% level.

The first evidence is that the coefficients for the variables, others than country or regulatory effects that were used in the previous session do not change significantly

between regressions. The *No. of Firms (national markets)* has a positive effect on product withdrawn, as expected.

The *No. of Products (own firm)* has a positive, although small, impact on the hazard ratio (one additional product on the firm's portfolio increase the expected hazard rate by 0.2% to 0.3%). It is possible that within larger portfolios intra-firm competition is stronger, reducing possible scale effects. Products have a higher survival probability if the firm launched any new product in the previous 12 months. Therefore, and as for single country analysis, it does not appear to exist any "cannibalization" effect. Looking to the effect of these two variables (and also, to the variety of results on single-country estimations), we may say that it is not clear which effect is prevalent: scale effects or intra-firm competition. In fact, additional products, within the portfolio of the firm may induce both effects simultaneously. The *Year of Firm's Entry* on the market is significant and it has a positive impact on the hazard ratio, meaning that products of more recent firms have less probability of survival.

The two regressors related with the ATC-3 subgroup of the product are now significant. The *No. of Products (own firm, on the ATC-3 subgroup)* has a negative effect on the relative probability of exit (one additional product of the own firm, on the same ATC-3 subgroup, decrease the hazard rate by 2.4% to 2.5%). One possible explanation is the existence of scope effects. The *No. of Products (other firms, on the ATC-3 subgroup)* is significant and with a negative impact on product survival. More close competitors have a negative impact on the probability of product survival, as expected.

The binary variable that is equal to one if the product is a non-prescription product is significant. The hazard rate of non-prescription products is near 0.75 times of the hazard rate of prescription products.

Looking to regression (I) the coefficients of the binary variables that capture country fixed effects give a different perspective from the evidence of the non-semi-parametric survival functions. In fact, the non-parametric survival functions do not allow us to infer if differences derive from differences between countries or differences between the products available in each country. When we do not account for market, firm and product's characteristics, Portugal is the country where products have a minor probability of survival, followed by New Zealand (see graphic 1). However, when

accounting for those characteristics, the scenario is completely different: the country with minor probability of survival is New Zealand, followed by Sweden and then Portugal. Therefore, drugs with equal characteristics will have different survival spells according with the country characteristics.

In regression (II), we join the country fixed effects with the binary variables for regulatory changes, namely the introduction of the reference price system. We use the same variable for all countries, to account for reference price system, despite the differences on the design of the system from country to country. Regression (III) also includes the explanatory variable *Pharmaceutical sales, per capita*, which is significant and has a negative impact on the expected probability of exit. This result is as expected, since markets with higher sales are expected to easily ensure the survival of existing products.

Regression (IV) repeats the previous exercise substituting the binary variables for country fixed effects and the *Pharmaceutical sales, per capita*, by *Population (ln)* and *GDP per capita (ln)*. The coefficients are as expected: that both variables would have a positive impact on drugs survival, although that is only significant for *Population (ln)*. This result is consistent with the results from regression (I): as the country is more populated, the relative probability of survival for pharmaceutical products is larger⁸.

Let us now look to the results of the regulatory binary variables on regressions (II) to (IV). The binary variable for the introduction of the reference price system is always significant. The introduction of the reference price system has not the expected effect: it decreases the relative probability of “death” of pharmaceuticals. Therefore, it seems that the reference price system does not improve competition, *de per se*. The other regulatory variables have the expected results, increasing the expected probability of product exit. These results are consistent with Danzon et al (2004), when they say that other measures are necessary to ensure competition pressure that was not achieved by the price reference system.

⁸ See table 2: Macroeconomic Data. The result for *GDP per capita (ln)* may be explained by low income-elasticity of demand for pharmaceuticals.

5. Conclusions

In order to study the determinants of pharmaceutical product survival, we perform a cross-countries analysis. Our survival model is applied both on separated estimations for each country, and on jointly estimations using data for Portugal, Sweden and New Zealand. Regulation, market, firm and product characteristics are taken into account.

We draw some methodological conclusions. First, we should be careful when extrapolating the results from single-country studies to other countries, because the results could vary a lot from country to country. Second, semi-parametric estimations can improve substantially the insights on product survival because it allows us to use multiple explanatory variables. In our case, the semi-parametric estimations add important results to the non-parametric estimation.

On the subject under study, pharmaceutical product survival, our conclusions are not all consistent with previous work. First, we find no evidence of intra-firm competition. In fact, it seems that new products do not lead to the exit of existing products within the same firm. This is contrary to several studies on other industries that show that intra-firm competition is important to explain product survival. Second, we find that inter-firm competition is important to explain pharmaceutical product survival: competition increases the probability of exit, as expected. Finally, we conclude that the introduction of a reference price system do not guarantee, *de per se*, the improvement of competition pressure and the consequent increase of product exit. This result may help explain the ambiguous results on the impact of reference price system on competition variables of previous papers.

Appendix

Table 7-A: Estimations for the three countries

	(I)	(II)	(III)	(IV)
No. of Products (national market)	1.001*** (15.46)	1.001*** (7.22)	1.002*** (6.92)	1.001*** (7.14)
No. of Products (own firm)	1.002**	1.003**	1.003**	1.003***

New Products, last 12 months (own firm)	(2.03) 0.961*** (3.07)	(2.38) 0.956*** (3.39)	(2.44) 0.954*** (3.52)	(2.56) 0.953*** (3.55)
Year of Firm's Entry	1.001*** (4.21)	1.001*** (4.18)	1.001*** (4.29)	1.001*** (4.29)
No. of Products (own firm, on the ATC-3 subgroup)	0.975*** (3.31)	0.975*** (3.28)	0.975*** (3.28)	0.975*** (3.26)
No. of Products (other firms, on the ATC-3 subgroup)	1.001* (1.93)	1.001** (2.12)	1.001** (2.14)	1.001** (2.12)
Non-prescription drug = 1	0.750** (2.38)	0.746** (2.43)	0.746** (2.43)	0.744** (2.45)
If in Sweden = 1	3.989*** (9.28)	4.001** (2.20)	22.638*** (3.71)	
If in New Zealand = 1	3.893*** (8.89)	16.691*** (9.85)	17.088*** (9.54)	
With Reference Price		0.296*** (8.33)	0.365*** (6.41)	0.376*** (6.40)
With higher 10% reimbursement for generics, in Portugal		4.535*** (6.53)	3.160*** (4.66)	4.357*** (6.35)
With mandatory substitution for generics, in Sweden		7.608*** (3.67)	11.577*** (4.36)	26.532*** (9.72)
With public tenders for subsidized drugs, in New Zealand		1.343* (1.77)	0.977 (0.12)	1.729*** (3.39)
Population (ln)				0.079*** (9.88)
GDP per capita (ln)				0.668 (1.39)
Pharmaceutical Sales, per capita (1000USD)			0.992*** (3.27)	
Log-Likelihood	-4550.081	-4461.527	-4456.230	-4464.303

Notes: Dependent variable is one if the product exits the market, and zero otherwise. All the regressions include a set of binary variables for each Therapeutic Group that are not presented on the table. The results are expressed in hazard ratios. Robust z statistics are in parentheses. Observations are 385142.

*Significantly different from zero at the 10% level. ** Significantly different from zero at the 5% level. *** Significantly different from zero at the 1% level.

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Annex

Preparation of Datasets and Estimation Strategies

Both for preparation of datasets and estimation, we use the econometric software Stata SE (versions 8 and 10).

Essay 1 “Survival of Branded Drugs”

1) Original cross-section dataset

The database of INFARMED contains all pharmaceuticals ever marketed in Portugal until October 2006.

The observation unit is drug preparation. The database has 44190 preparations.

For each observation, we know the following characteristics:

- The firm;
- The active substance;
- The pharmaceutical form;
- The dosage;
- The date of market introduction (day-month-year);
- The state of market introduction authorization (AIM) in October 2006, 30th;
- The date of the end of AIM, if it is not valid in October 2006, 30th (day-month-year);
- If it is a prescription or non-prescription drug;
- The type of process for market introduction authorization: centralized; mutual recognition or national;
- If it is a generic drug or not, in October 2006, 30th;
- The date of transformation from branded drug into generic (day-month-year), if that is the case;
- The homogeneous group, if the drug belongs to one (and is under reference price);
- The date of each homogeneous group (day-month-year);
- The Code of Pharmacotherapeutic Classification.

2) Creation of new variables

For qualitative characteristics, we create binary variables for each category. The observation unit is drug preparation. Additional to the variables that characterize drug preparations, we create variables for characteristics that are common to all preparations of a medicine. Also, we create the variables for “Medicine’s entry” (when the first preparation enters the market) and “Medicine’s exit” (when the last preparation exits the market, if all exited the market). Then, we drop duplicates for each medicine. The result is a dataset with 13647 medicines.

Then, we generate the variables that change in time. Due to computational limitations, we cannot work with daily observations (despite we have daily data). We decide to work with monthly data. Therefore, we create the following variables:

Variable	Description
Entry of Firm (month)	The month of entry of the first medicine of that firm.
Exit of Firm (month)	The month of exit of the last medicine of that firm if all medicines exited the market.
Products (total) (*)	Number of total medicines, in the market, at each month
Products, by Firm (*)	Number of total medicines by firm, in the market, at each month
Firms (*)	Number of firms, in the market, at each month
New Products (total) (*)	Number of new medicines that enter the market, at each month
New Products, by Firm (*)	Number of new medicines that enter the market by firm, at each month
Withdrawn Products (total) (*)	Number of medicines that exit the market, at each month
Withdrawn Products, by Firm (*)	Number of medicines that exit the market by firm, at each month
% of Generics, by Firm (*)	Percentage of generics within firm’s portfolio, at each month
Concentration Index, by Firm (*)	Degree of sub-market concentration within the firm’s portfolio, at each month
Monopolies, by Firm (*)	Number of sub-markets where the firm is a monopolist, at each month
New Sub-Markets, by Firm (*)	Number of new sub-markets where the firm enters, at each month
Sub-Market Exits, by Firm (*)	Number of sub-markets from where the firm exits, at each month
Sub-Markets, by Firm (*)	Number of sub-markets where the firm is, at each month
New Products=1 (*)	If the firm launches new products, at each month

Entry in New Sub-Markets=1 (*)	If the firm enters in new sub-markets, at each month
Entry in New Sub-Markets=1, if New Products=1 (*)	If the firm enters in new sub-markets, giving that the firm had launched new products that month
Time since last launch (*)	Number of months since the last launch, by firm.

(*) Those correspond to 202 variables, one for each month. Example: for *Products (total)*, we have *Products (total)_January1990*, *Products (total)_February1990*, ..., *Products (total)_October2006*

3) Sampling and generating the panel dataset

After computing the variables of interest, we drop all duplicates for each firm. We also drop all the firms that exited the market before January 1990. The result is a dataset with 669 firms.

We transform the cross-section dataset (firm observations) into a panel dataset (firm-month observations). The panel is unbalanced. We have 82012 firm-month observations.

After, we create new variables:

Variable	Description
Age of the Firm	Age of the firm, at each month
If after January 1995	If the month is after January 1995
If after October 1999	If the month is after October 1999
If after December 2002	If the month is after December 2002

4) Estimation strategies

New variables are created lagging market and firm's variables by 18 months. Because of this, we lose observations, using only observations posterior to June 1991.

The selection regression is estimated by a probit (the dependent variable is "New products=1"); then, the results are used to correct the estimations (Heckman procedure) of the regression for the variable "Entry in New Sub-Markets=1, if New Products=1". All the regressions included two types of "fixed effects": time effects, through binary variables for each month, and firm effects, through binary variables for each firm.

Essay 2 “Product Entry in Pharmaceutical Markets”

1) Original cross-section dataset

The same that is used on Essay 1.

2) Creation of new variables

For some qualitative characteristics, we create binary variables for each category. That is the case of:

Type of prescription: *Non-prescription drug* = 1

Type of AIM process: *Central Process* = 1; *National Process* = 1

Type of therapeutic class: from *Therapeutic class 1* = 1 to *Therapeutic class 17* = 1 (Note: INFARMED classifies drugs in 20 Therapeutic Classes (using the “Código da Classificação Farmacoterapêutica” - Code of Pharmacotherapeutic Classification). Classes 18 to 20 were excluded from database because they were very small and residual classes. Observations with no information about Therapeutic Class were excluded too. For products classified simultaneously in several Therapeutic Classes, the class chosen was the first that appears in database.)

Degree of innovation: *Non-pioneer drug* = 1 (if the drug was not the first of the chemical substitutes)

Then, we generate the variables that change in time. Due to computational limitations, we cannot work with daily observations (despite we have daily data). We decide to work with monthly data. Therefore, we create the following variables:

Month of entry

Month of exit (missing, if it is not the case)

Month of transformation from branded into generic drug (missing, if it is not the case)

After, for each characteristic of the market, firm or product that changes over time, we create a variable for each month (between January 1996 and October 2006).

For example: in the final dataset, *No. Products (all market)* account for the total number of preparations in the month of interest. Then, we create 130 variables: *No. Products (all market)_January1996*; *No. Products (all market)_February1996*;...; *No. Products*

(*all market*)_October2006. For example, *No. Products (all market)_January1996* count the number of preparations, for which the *Month of Entry* is previous to January of 1996 and the *Month of Exit* is posterior to January 1996 or missing. We replicate it for the other 129 variables.

We use this method to create 130 variables (one for each month) for:

- *No. Products (all market)*
- *No. Products (own firm)*: counts the number of preparations, grouped by firm, for which the *Month of Entry* is previous to the month of interest and the *Month of Exit* is posterior to the month of interest or missing;
- *No. Products (own firm, chemical substitutes)*: counts the number of preparations, grouped by firm, active substance, pharmaceutical form and dosage, for which the *Month of Entry* is previous to the month of interest and the *Month of Exit* is posterior to the month of interest or missing;
- *No. Products (other firms, chemical substitutes)*: counts the number of preparations, grouped by active substance, pharmaceutical form and dosage, for which the *Month of Entry* is previous to the month of interest and the *Month of Exit* is posterior to the month of interest or missing, minus the *No. Products (own firm, chemical substitutes)* for that month;
- *No. Products (own firm, therapeutic substitutes)*: counts the number of preparations, grouped by firm and the complete therapeutic classification²⁸, for which the *Month of Entry* is previous to the month of interest and the *Month of Exit* is posterior to the month of interest or missing;
- *No. Products (other firms, therapeutic substitutes)*: counts the number of preparations, grouped by the complete therapeutic classification, for which the *Month of Entry* is previous to the month of interest and the *Month of Exit* is posterior to the month of interest or missing, minus the *No. Products (own firm, therapeutic substitutes)* for that month;
- *If the firm launched products = 1 (in the same therapeutic class)*
- *Proportion of generics (own firm)*: we create an auxiliary variable (*No. of generics (own firm)*) that counts the number of preparations that are generics in

²⁸ The complete classification by the Code of Pharmacotherapeutic Classification identifies not only the therapeutic class, but also the therapeutic sub-class. Drugs with the same classification are therapeutic substitutes, even if they are not chemical substitutes.

October 2006, 30th, grouped by firm, for which the *Month of Entry* is previous to the month of interest and the *Month of Exit* is posterior to the month of interest or missing, and for which there was no transformation or the month of transformation was previous to the month of interest. Then, we divide this variable for *No. Products (own firm)*, and obtain the proportion.

3) Sampling and generating the panel dataset

After computing the variables of interest, we delete every drug that was introduced as a generic drug and every branded drug that exited the market before January 1996. We extract a random sample with 2315 preparations that were introduced in the market as brands.

We transform the cross-section dataset (product observations) into a panel dataset (product-month observations). The panel is unbalanced. We have 187832 product-month observations.

For each category, the correspondent 130 variables (one for each month) are transformed on one single variable. For example: *No. Products (all market)_January1996*; *No. Products (all market)_February1996*;...; *No. Products (all market)_October2006* disappear and it is generated the variable *No. Products (all market)_m* (the number of products on the market, at month *m*).

After, we create new variables:

- *Age_{im}*: the age of the product *i* at month *m* (months)
- *Reference Price = I_{im}*: if the product *i* is under reference price in month *m*
- *Between Sept. 2000 and Nov. 2002 = I_m*: if the month *m* is between September 2000 and November 2002
- *Between Dec. 2002 and Sept. 2003 = I_m*: if the month *m* is between December 2002 and September 2003
- *Since Oct. 2003 = I_m*: if the month *m* is since October 2003
- *Transition_{im} = I*: if the month *m* is equal to *Month of exit* or *Month of transformation from branded into generic drug*.

4) Estimation strategies

4.1) Cox's model

We use the data from January 1996 to September 2003, in order to estimate a model with only one destination for branded drugs: market exit. From the 2315 brands, 486 left the market and 83 became generics, during the period under study. The other 1746 presentations have right-censored durations. Notice that 816 presentations were already in the market before 1st January 1996. Those are left-censored observations. Both censor types are accounted for in the estimation procedure.

Data was declared to be survival-time data, with multiple-record per subject. The duration variable is Age_{im} . Failure occurs when $Transition_{im}=1$ equals one (within this period the only type of “death” is exit from market).

We use the maximum-likelihood proportional hazard model, for survival-time data (Cox's model).

4.2) Complementary log-log model

In order to account for the discreteness of data, we also use a discrete time proportional hazard model (the). The data is declared to be a cross section of time series (a panel). The dependent variable is $Transition_{im}=1$. Besides the independent variables used in Cox's model, we also include binary variables for spell lengths. This is the piecewise constant specification, assuming that the hazard rate is equal for the same product age interval, but different between intervals. Using the exponential form of the results, we get hazard rates that could be interpreted in the same way as the results of Cox's model.

4.3) Multinomial logit

In a second step, we use data from October 2003 to October 2006, having two competing destinations for branded drugs. The dependent variable is $mtransition$. Since October 2003, “deaths” are of two kinds: exits ($mtransition=1$) or transformations into generics ($mtransition=2$). The base category ($mtransition=0$) is the maintenance in the market, as a brand.

We cluster observations by product, because we expect that observations are independent across products but not within the lifetime of each product. We estimate this model using a multinomial logit framework.

Essay3: “Survival of pharmaceutical products: a cross-countries analysis

1) Original cross-section datasets

Portugal: the same database of INFARMED used on both essays 1 and 2 (cross-section of preparation observations).

Sweden: the Läkemedelsverket’s dataset is similar to the Portuguese dataset (cross-section of medicines observations).

New Zealand: the Medsafe’s dataset is similar to the Portuguese dataset (cross-section of medicines observations).

2) Creation of new variables

For Portugal, we take the same steps as for Essay 1 and create a cross-section dataset with 13647 medicines. The others datasets already have medicine observations.

We only use variables that are common to all datasets and create new variables like in Essay 2.

3) Sampling and generating the panel dataset

Our dataset includes 3543 products, marketed in Portugal (1612 products), Sweden (986 products) or New Zealand (945 products), between January 1990 and October 2006. This set of products is a random sample extracted from the complete dataset of products of the three countries, representing 25% of it. The proportion of products of each country, within the original dataset, remains equal on the sample.

Using the cross-section data, we expand it to an unbalanced panel. The time unit is the month. We have 202 months covered by the panel, corresponding to 388679 observations.

The creation of new variables, within the panel, is similar to Essay 2.

4) Estimation strategies

We use the maximum-likelihood proportional hazard model, for survival-time data (Cox’s model). Estimation procedures are similar to Essay 2.