Entry Time Effects and Follow-on Drugs Competition

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DT n° 49

Juin 2012

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Abstract

Pharmaceutical firms have been criticized for concentrating their efforts of R&D on the so called "me-too" or "follow-on" drugs. There have been many comments against and favourable to the dissemination of these incremental innovations but few papers have broached the subject from an empirical point of view, possibly because identification of "me-too" is not so obvious. This paper focuses on the impact of entry order on "follow-on" drugs competition in the French market between years 2001 and 2007. More precisely, this study examines the effects on market share of first entrants in the follow-on drug market and how this possible competitive advantage changes over time. Our results are coherent with theoretical microeconomic issues concerning the importance of being first. We find evidence that first movers in the follow on drug market have the ability to capture and maintain greater market share for a long period of time. The hierarchical market position of follow on drugs does not seem to be affected by generic drugs emergence. From a dynamic perspective, our analysis shows that market share is positively correlated with the ability of follow on drugs to set prices higher than the average follow-on drug price in a specific therapeutic class (ATC) which means that market power remains considerably important for first movers. Finally we found that the optimum level of innovation to maximize market share is the highest one.

Keywords: Incremental innovation; Follow-on drugs; Entry timing; Market share.

JEL Classification: I18, I12, L65, L51.

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Résumé

L'effet du délai d'entrée sur la concurrence des médicaments *follow-on*

Les critiques auxquelles fait face l'industrie pharmaceutique sont axées notamment sur sa capacité à innover. La concentration des efforts de recherche et développement sur la production et dissémination des médicaments du type *me-too* ou *follow-on* est une préoccupation majeure des institutions responsables de la régulation du marché pharmaceutique. Le débat autour de cette problématique s'est considérablement répandu ces dernières années mais très peu d'études empiriques sur le sujet ont vu le jour, probablement en raison de la difficulté à établir un consensus sur la « vraie » définition de ces produits.

Cet article propose une analyse empirique de l'impact du délai d'entrée sur la concurrence des médicaments *follow-on* en France entre 2001 et 2007. Plus précisément, nous cherchons à mettre en évidence la relation entre ordre d'entrée dans une classe thérapeutique et parts de marché et comment l'avantage compétitif des premiers entrants évolue dans le temps. Les premiers résultats sont cohérents avec les prédictions de la théorie économique selon laquelle les premiers *follow-on* détiennent d'importantes parts de marché sur longue période. La position hiérarchique sur le marché des *follow-on* semble ne pas être affectée par l'émergence des médicaments génériques et les leaders de l'innovation incrémentale ont un pouvoir de marché relativement fort. Nous constatons également que le niveau optimal d'innovation pour maximiser les parts de marché est le plus élevé.

Mots-clefs : Innovation thérapeutique incrémentale, médicaments *follow-on*, délai d'entrée, parts de marché.

Codes JEL : I18, I12, L65, L51.

1. Introduction

There have been many concerns about the emergence of incremental innovation in the pharmaceutical industry. According to DiMasi and Paquette (2004) the debate on pharmaceutical products that duplicates the effects of previous drugs started on early 1960's when the US senate promoted discussions related to market power and pricing strategies of drug companies. This debate on incremental pharmaceutical innovation introduced new terms to define drugs with relatively less therapeutic advances but there is still no consensus about the exact definition of me-too and follow on drugs. The context is that pharmaceutical markets are characterized by a patent system that creates legitimate barriers to entry but firms can nevertheless opt to develop new products with a similar chemical structure aimed to treat the same conditions. Hence, by obtaining a slightly level of differentiation, drug companies are able to patent new chemical entities derived from research on incremental innovation.

Many authors have mentioned the benefits of new follow-on drugs while detractors argue that efforts concentrating R&D on these products represent a misallocation of resources. In fact, there are two distinct types of authors as regarding to the definition of "me-too" and "follow- on" drugs : those who believe that these drugs are merely copy of first-in-class drugs and those who postulate that "me-too" and "follow-on" drugs are considerably different from first entrants in a therapeutic class. According to Sloan *et al.* (2007) "me-too" drugs consist of new chemical entities which have similar features compared to already existing patented drugs. Hollis (2004) presents "me-too" drugs as products that largely duplicate the mechanism of action of drugs already existing in the market. DiMasi and Paquette (2004) define a me-too or follow-on drug as being any new entrant in an existing therapeutic class defined by similarity chemical structure and aimed to treat the same conditions of existing medicines. By contrast, Wertheimer and Santella (2001) argue that me-too drugs are not exact copies of pre-existing drugs and that in order to obtain a new patent the drug must contain a medical improvement and hence a "me-too" represent a medical advancement. Chada and Blomqvist (2005) define me-too as being a new drug similar to the first-in-class drug but sufficiently different for being patented. Many authors have defined me-too drugs in a pejorative way while others have focused on more technical and medical characteristics of molecules to class them in the perimeter of me-too drugs. These different points of view haven't brought a consensus about the use of the words "me-too" or "follow-on" drug and their definition has become wider. In this article, we decided to employ the term "follow-on drug" because, according to certain authors (DiMasi and Paquette, 2004) it has a more neutral-value component compared to "me-too drug" that may have a negative connotation.

Few papers have broached the subject of follow-on drugs, especially with an empirical angle of analysis.

One of the main purposes of this paper is in fact to fulfil the existing gap concerning the empirical literature relative to follow on drugs competition. More than only trying to understand sales trends in the French pharmaceutical market we aim more precisely at dissecting market share for each follow on drug in relation to the entry order of the molecule in the class.

The rationale for better understanding the impact of entry order on follow-on drug competition is based on two opposite forces co existing in the drug segment, one which tends to prevent new products from gaining market shares and the other one which tends to promote the dissemination of new products. First of all, pharmaceuticals are

experience goods and physicians are more likely to prescribe products based on their medical practice (Kwong, 2006). Moreover patients can be attached to their medicines and notably elderly may be more reticent to switch to new products (Spinewine *and al.* 2005). This attachment to the first-chosen drug is also related to the fact that patients are characterized by being risk averse which explains why people can be less motivated to switch away to new products or even generic formulations of the same molecule (Crawford & Shum, 2005). Hence there may be cases in which older products may be prescribed even if there is a range of new products available. However it is interesting to note that the French case may be an exception considering studies which pointed out the fact that in France physicians are more likely to prescribe new innovative products unlike most of the European countries. This would explain the higher level of pharmaceutical expenditure in France compared to other countries (Cnamts, 2007). This trend on the nature of the demand could explain why some new pharmaceuticals may find barriers to capture market shares. On the other hand, there is an institutional force coming from pharmaceutical firms intending to launch in the market new innovative products with more added value because innovation is one of the main drivers in the economy and more innovative products could increase profits of firms and may bring more therapeutic advances to patients. The rationale for the link between innovation and profits can be analysed in the light of some Schumpeterian theories that correlates R&D with innovation and market power. In fact, the first Schumpeterian hypothesis is that market power is often considered as an important stimulus for research and development activities (Roberts, 2001). Interest on innovation comes equally from government institutions that often provide incentives for firms to innovate. Patients and physicians attitudes toward medicines are able in fact to determine some trends in the pharmaceutical market because their preferences may directly affect drug consumption, but there is no doubt that new drug introductions contributed largely to enhance quality of life and social benefits for the society (Grabowski, 2002).

The principle that the nature of demand could affect pharmaceutical sales is amongst many other relevant theories that integrate the fact that pharmaceutical markets may face important entry barriers. According to Agarwal and Gort (2001) the main obstacles for entry in high technological sectors such as the big pharma industry are: product differentiation advantages, expenditure on advertising, possibility to control scare resources, high sunk costs and economies of scale. Grabowski (1978) also points out the fact that pharmaceutical products would be experience goods which could generate a shift on the demand for older products and hence, new products could face more difficulties in capturing market shares. This economic environment, associated with some empirical evidence on low level of innovation in the drug market, has made emerge a growing number of interrogations concerning the ability of new incremental innovations to successfully enter the market. That is why we presume that market share and ability to exert market power can change considerably between different follow-on drugs in the same market, notably if we take into account the date in which the molecule appeared in the ATC class. Market share may also vary considerably across different drugs and entry order is supposed to have an important impact on consumption of follow-on drugs notably in reason of arguments mentioned above.

This paper aims at analysing the relationship that may exist between market shares and entry order of follow-on drugs in a panel analysis based on French data. This research also intends to contribute to the literature concerning incremental innovation on pharmaceutical markets and to what extend the diffusion of incremental innovation may affect the competitive pharmaceutical environment. Hence, the definition of follow-on drug was a very important point in the construction of our analysis line

and selection of groups. To clarify the concept of similar drugs, we provide below a table that shows some different definitions of the drugs analysed here, and we point out the fact that many authors suggested a wide range of different meanings for these pharmaceutical products. This leads to different appreciations of the real value of incremental innovation for the society.

Table 1
Assessing the definition of "me-too" and "follow-on" drugs

Author	Journal	Year	Main definition of follow-on drug or me-too
Sams-Dodd	Drug discovery today	2007	Follow-on medications are drugs that have the same mode of action (Moa) as an existing drug (first-in-class) and provide minor, although possible important therapeutic advances.
Cohen *et al.*	Journal of Clinical Pharmacy and therapeutics	2006	Follow-on drugs are subsequent classs entrants.
Hollis	WHO repport	2004	Me-too drugs are products which largely duplicate the action of existing drugs and which have similar mechanisms of action of pre-existing drugs. New molecules similar to the pioneering drug.
Di Masi and Paquette	Pharmaeconomics	2004	Me-too drug is a new entrant to a therapeutic class that had already been defined by a separate drug entity that was the first in the class (breakthrough). The authors postulate that me-too drugs have also been defined in a more value-neutral way as "follow-on" drugs.

The proposal of this paper is oriented also to contribute to the current debate on whether there must be a limitation on the approvals or reimbursement rates of new follow-on drugs.

1.1. Competitive Advantage in Pharmaceutical Markets

The rationale behind the study of entry order effects on follow-on drug competition is based on notions of competitive strategies of pharmaceutical firms when there is a patent race for launching in the market new molecules. In the ethical drugs industry, patents systems and regulation confers to the firm a monopoly that could be exploited for a very long period (currently 20 years and can even be extended to 25 years). Patent systems and hence monopoly pricing may be justified by the fact that pharmaceutical industry is mainly defined by very important R&D costs and very low marginal cost.

This monopoly can be achieved using particular market strategies such as Radical Product Innovation (RPI) based on a very important technological progress, Diversified Quality production (DQP) characterized by the use of incremental innovation, and Low Cost Production (LCP) based on merely imitations of previous products (Herrmann, 2008). In the pharmaceutical market all of these three strategies are largely used by firms even if recently there has been a large consensus about the crisis of radical innovation in the pharmaceutical industry (McKinnon *et al.*, 2004). The conceptual framework to better understand pharmaceutical strategies can be drawn focusing on the root of the drug industry sector: the New Chemical Entities (NCE) development. Firms can develop more or less innovative NCE and the level of benefits to society derived from these new molecules can bring important competitive advantages for the owner of the patent. Hence, the strategies of the firms can be directly linked to the characteristics of the molecules commercialized, what would imply also a patent race to put in the market products before concurrent firms in order to obtain advantages of being the first mover entrant. In this paper, we aim at going further in the analysis of entry order and level of innovation which can give us important results concerning the dynamics of incremental innovation development in a regulated market such as France.

2.   Data and methodology

In this paper we consider a follow on drug as being any new entrant in an existing therapeutic class already defined by a first-in-class drug. The first drug in a therapeutic class is also known as "breakthrough drug" and often these medicines enjoy a large period of market exclusivity and provide important amounts of benefits to pharmaceutical firms. The follow on drugs are classified by molecule entity in a specific ATC (Anatomical Therapeutic Chemical) class and the entry order is based on the date of commercialization of the molecule on the respective class. For example, if the molecule Lansoprazole is the first follow-on drug in its class then all the presentations of Lansoprazole (that is to say Lansoprazole 20mg, Lanzoprazole 40mg) will be considered as being the first follow on drug in that class. We do not include generic presentations in our regression analysis because the goal here is to determine trends exclusively on the patented drugs market. However the market share for each presentation is calculated taking into account the generic drugs because we infer that increase or decrease in generic sales affect directly the consumption of patented drugs.

The definition range of the therapeutic class used in this paper to define a follow-on drug is the Anatomical Therapeutic Chemical Class 4th level (ATC4) that is to say the molecular level. The Anatomical Therapeutic Chemical Classification (ATC) system is used for the classification of drugs and is very useful for international comparisons. It is controlled by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC) and was first published in 1976. Since ATC class is defined by an anatomical, therapeutic and chemical component then molecules inside the 4th digit ATC class have similarities in the treatment purpose of a specific conditions and also have a slightly proximity on the chemical structure. Table 2 shows an example of the hierarchical levels in the ATC class.

Table 2
Different levels of ATC classes

Level	Level abbrevation	ATC Code	Level Identification	Example
1st Level	ATC1	A	Anatomical group	Alimentary tract metabolism
2nd Level	ATC2	A10	Therapeutic subgroup	Drugs used in diabetes
3rd Level	ATC3	A10B	Pharmacological subgroup	Blood glucose lowering drugs, excl. insulin
4th Level	ATC4	A10BA	Chemical subgroup	Biguanides
5th	ATC5	A10B A02	Chemical substance	Metformin

For the purpose of our analysis we excluded molecules belonging to specific ATC classes such as those containing the code X because these classes might be too heterogeneous. As a matter of fact, new chemical entities that do not belong clearly to any other ATC class has often been placed in a group containing the code "X" (Other groups, for example ATC code R07 AX means Other Respiratory System Products).

As DiMasi and Paquete (2004) points out, there may be occasions that a drug in the 4th level ATC class competes with another drug in a different therapeutic class but since we are interested in follow-on drugs we define the market competition field as being the internal perimeter of a four digit ATC class. The data used in our study consist of information on drug sales in the French market for the years 2001- 2007. The Institute for Research and Information on Health Economics (IRDES-Paris) maintains databases containing statistic information on medicines available in France. Amongst the main databases concerning pharmaceutical products stored by Irdes we can mention some of particular relevance for our study such as Sempex (private drug database provided by Vidal which contains prices information), Thesorimed (public drug database which describes drugs characteristics), Medic'Am (sales and reimbursement database from the main national health insurance, Cnamts; this database enables us to calculate market shares) and EPPM (the IMS- Health Permanent Survey on Medical Prescription), which is a private database. Thus, the variables constructed and used in our analysis come from these different sources. Other variables necessary for regrouping drugs in specifically markets such as chemical entity, dosage, package size, and indication were collected on the Thesorimed dataset. Finally, prescription data set EPPM was used to calculate Daily Treatment Costs for each drug.

3. Variables description

Since our goal is to analyse the effects of entry order on market shares, we should include in the right hand side of the econometric model variables that could reflect the characteristics of the chemical entities such as entry order, reimbursement level, indicator of added therapeutic value (ASMR), prices, drug indications and size of the firm commercializing the molecule. These variables could give us an interesting overview of the effects of firm's strategies on the market share over time of follow-on drugs.

Market share is the market share of the follow on drug in a specific 4-digit anatomical therapeutic class (MOL/ATC). We identify the product by its active ingredient (chemical entity). Data in market share is provided by Medicam and is calculated in percentage of the total volume sales of a product in a specific class. This variable is calculated taking into account the presence of generic drugs in the market. Hence, the market share of the follow-on drug is the real market share of the drug in a specific 4th level ATC class.

Entry order of the follow-on drug. This variable is calculated in function of the entry order of similar drugs in a sub-therapeutic class of 5 digits. The first drug commercialised in a sub-ATC class is named "breakthrough drug" and is the reference chemical entity in the class. In this paper we also mention the breakthrough drug as being the «first in class» drug. Subsequent molecules with a similar mechanism of action and chemical structures are the follow-on drugs. Hence, the variable is classed by the date in which the product was effectively marketed en France. Information on this variable is provided by Thesorimed database. In our sample the entry order varies from 1 to 15, which means that, in some groups, we can have a 15th molecule commercialised. It does not mean that we have 15 competitors in a class because maybe intermediary molecules are not commercialized anymore or were excluded because it didn't match our requirements to include the group. The entry order is defined in terms of molecule and not by presentation.

Relative Price per DTC (Daily Treatment Cost) in log is the relative price in log of the "follow-on" drug (expressed in Daily Treatment Cost) in relation to the first in class drug (also in DTC). The price of the drug package is not relevant for our analysis in that packages are not the same within each group. Furthermore, dosages of each drug package are not necessarily comparable. The price per DTC, or cost per day, refers to the cost of taking the drug on a daily basis. This variable is calculated by dividing the price of the drug package by the number of treatment days contained in the package. For each drug, we can obtain the number of treatment days by calculating the ratio between the number of unit doses in the package and the average prescribed dose of a specific drug. The average prescribed dose is obtained from the medical prescriptions database EPPM furnished by IMS health. The price of the individual package is in gross prices and is obtained from the Sempex. The choice of this variable in our regression analysis is based on the fact that prices per DTC represent a very interesting measure of pharmaceutical prices based on real prescriptions for each drug presentation taking into account the period of treatment for each drug. The only problem is that we do not have exhaustive information for this variable and hence we are constrained to reduce the number of observations in our regressions. In average we observe a reduction of 30% of observations for each year as a consequence of lack of information concerning the variable daily treatment cost.

$$Daily\,Treatment\,Cost = \frac{Package\,\Pr ice\,at\,Manufacturer\,Level}{\left(\dfrac{Number\,of\,Units\,in\,the\,Package}{Average\,\Pr escribed\,Dose} \right)}$$

Therapeutic Value (SMR) of the drug. The medical service rendered is a criterion defined by the Transparency Committee for Pharmaceutical Products based on the actual or expected benefit of a medicine. The SMR is a fundamental element in the reimbursement rate decision process of a drug and represent the actual therapeutic value of the product. SMR is defined considering five elements: severity of the disease, efficacy of the drug, side effects, relevance in the therapeutic strategy and the public health relevance. Thus, the SMR can be classified in five categories: 1. Major; 2. Important; 3. Moderate; 4. Low; 5. Insufficient. When the SMR is considered as "insufficient" the drug cannot be reimbursed

by public health insurance. Five dummy variables were created for this variable. The SMR is not used as such in the regressions but is used uniquely to build the therapeutic group value variable.

Therapeutic group value. This variables accounts for the relevance of the therapeutic class in our sample and is obtained by calculating the arithmetical means of the reimbursement level of all the drugs in a therapeutic class. Our mean value includes also drugs not selected for our econometric analysis because we aim at obtaining a representative value for the whole group. In France, drugs can be ranked in two categories: reimbursed and not reimbursed drugs. If the therapeutic value (SMR) is sufficient the Transparency Commission includes the drug in the reimbursement list and set the level of the reimbursement rate: 15%, 35%, 65% or 100%. Hence, the level of reimbursement is based on the therapeutic value of the product as well on the severity of the disease. For example, drugs for cardiologic diseases or to treat patients suffering from Aids are reimbursed in average from 65% to 100% of the drug price. By contrast, drugs for dermatology or mucolytic agents benefit from a lower reimbursement rate. In our sample, the class of mucolytic agents is classed as having a "low therapeutic relevance" because the average level of reimbursement in this ATC class was 1.25% in year 2007 (in 2001 the average level of reimbursement was 25%). In the latter case the reason for decrease in reimbursement level is linked to policies of delisting medicines with low or moderate medical service rendered, which took place in March 2006. Thus, we constructed a three level scale variable where:

1= classes with a low therapeutic value (average mean of reimbursement level less than 44% and accounting for 15% of our observations): For example the expectorants class in which the average level of reimbursement was 14% in 2001 and 6% in 2007.

2= classes with a medium therapeutic value (average mean of reimbursement level between 44% and 64% and accounting for 47 percent of our observations): In this class we can mention groups like statins with average reimbursement level of 59% in 2004 and 63% in 2007.

3= classes with high therapeutic value (average mean of reimbursement level over 64% and accounting for 37% of our observations): such as immunosuppressive agents with average reimbursement level of 79% in 2005 and 89% in 2007.

The intervals defining each level of therapeutic value were chosen to guarantee a relative homogenous number of observations in each category.

Added Therapeutic Value (ASMR) is also a criterion defined by the Transparency Committee but slightly different from SMR. The ASMR compares the estimated benefit of a new drug in relation to other drugs in the market and in the same class used to treat the same conditions. This criterion is always relative to previous drugs already commercialized and is used in negotiations between pharmaceutical firms and the regulator to set the price of the reimbursable drug. There are five levels of ASMR: 1. Major improvement; 2. Important improvement; 3. Modest improvement; 4. Minor improvement; 5. No improvement. A drug with a ASMR level equal to 1 can benefit from higher prices whereas the price of a level 5 ASMR has to be lower than its comparators.

This variable is important in our analysis because it reflects the actual level of innovation of a drug compared to predecessors. This variable can directly affect prices of drugs and hence, market shares. Moreover we can expect the level of innovation of the drug to be correlated with the speed of entry on the market.

Drug reimbursement rate it is the percentage rate of reimbursement for the drug. This variable is obtained from the Sempex database.

Dummy variables for drug indication. We constructed two dummy variables that measure the level of differentiation of the drug in regard to other follow-on drugs while considering indications. If the follow on drugs have the same main indications that the reference drug and some other different additional indications we class these observations into the category "more indication" while follow-on drugs with less indications than the reference drug is classed on the categorical dummy variable "less indication". More indications could indicate that the drug could capture more market shares because the size of the market is greater. Since drug prices in France are negotiated taking into account the ASMR and predicted sales then more indications could indicate more target population and some effect on prices.

Size of the firm: we constructed also a variable that indicates the size of the pharmaceutical firm for each drug observation. The variable is obtained by calculating the total sales of the pharmaceutical firm in a given period (year) in the French market. Data came from Medic'Am which contains sales value for each product in a specific year. The intuition behind this variable is that large firms could have a more important negotiation power with government institutions that regulates drug markets.

Price of the drug relative to the average price of all the drugs in the class: for each follow on drug market (4-digit anatomical therapeutic class) we calculated the ability of the drug to set prices over the average price of the drugs in the ATC class. This variable is given by:

$$MP = \frac{P_i}{\frac{1}{n}\sum_{i=1}^{n} p_i}$$

where p_i is the price of the drug and n is the number of drugs in the therapeutic class. Hollis (2002) uses the same intuition to calculate the market power of generic drugs in the Canadian market. The rationale for this variable is based on the fact that if a drug has a market power greater than 1, firms have the ability to set higher prices than the average price of all the drugs in the class, and hence the market power would be positive. If the market power is below 1 than market power is negative which means that the firm had less ability to set an important price for the drug. This variable incorporates the concept of monopoly power and the ability of the firm to create a "mark-up" price.

Indicator variable for generics in the group: Dummy variable indicating the presence of generic versions in the ATC class.

4.   Descriptive statistics

We identified 119 therapeutic classes where at least one follow-on drug entered the market and then collected information on these drugs from 2001 to 2007. These 119 ATC classes refer to the total number of ATC class indentified for the whole period analysed but we allow for new ATC class entrants and also there are cases where an ATC class can be dropped out from our sample for not matching our requirements for inclusion. The average number of follow-on drugs per group in 2001 was 6.09 in 2001 and 7.66 in 2007 with a median value of 3 in 2001 and 4 in 2007. We identified each follow-on drug as soon as it presented chemical, anatomical and therapeutic

similarities with the first-in-class drug. We define the competition perimeter of follow on drugs as being the 5 digit ATC class and hence, in each group we have one first-in-class product and its follow on drugs. There may have some occasions where chemical entities in a 5 digit ATC class are aimed to treat totally different conditions of their reference product. We chose to exclude from our sample drugs that do not have the same therapeutic indications of the precursor drug. This choice allows us to have drugs competing in relative homogenous groups where the different drugs have a little degree of differentiation with each other. This degree of differentiation is captured by the dummy variable "more indication" or "less indication". In fact our groups are constituted by drugs that have at least some indications in common and we highlight one more time the fact that there is no drug in a specific group with indications totally different from the other drugs in the class. A simple example of exclusion is the product containing the molecule Bisoprolol. The drug belongs to the group of selective beta blocking agents and is used primarily in cardiovascular diseases. However it is indicated for chronic heart failure and according to Thesorimed database its indication does not match with the first drug commercialised in its class so it was excluded from the sample.

Methodological issues also raise important criterions of choice to include drugs in our sample. For the purpose of statistical analysis, the prescription drugs in our sample should be sold in France between 2001 and 2007, reimbursed by public health insurance, used in oral dosage forms, available in pharmacies and having only one single molecule. Products administrated uniquely in hospitals are not included in our sample because the pricing process for those drugs is completely different from the one that prevails for drugs available in pharmacies. We first collected observations for year 2001 and we allow for the possibility of new entrants as we move forward in periods. Hence our sample in 2007 contains more observations and groups than in period 2001. Let's say period 1 is equivalent to year 2001, period 2 is equal to period 2002 and so on. We constructed a panel dataset with information for each drug i in each period t. Since we take into account the possibility of new entrants we also have to consider drugs leaving the market and then our panel dataset is from type unbalanced. In period 1 our sample is composed of 773 observations divided in 109 groups and 664 follow-on drugs. The number of observations rises to n=991 at the end of period 7 and it includes 116 5th level ATC classes and 875 similar drugs. If we consider only the number of chemical entities then we can list in average 2,44 follow-on drug molecules per group in 2001 while in 2007 our data presents in average 2,52 similar drugs per ATC class. The average number of follow-on drugs by group for each year is shown in table 3.

Table 3
Average number of follow-on drugs in groups by period

	2001	2002	2003	2004	2005	2006	2007
Average number of follow-on drugs (by presentation)	6.09	6.33	6.46	6.53	6.71	7.57	7.66
Average number of follow-on drugs (by chemical entity)	2.44	2.46	2.48	2.51	2.56	2.52	2.52

Table 3 reports an increasing in the average number of follow on drugs in groups over time. The ATC class in which we observe more follow-on drugs is the ACE inhibitors plain group (ATC class C09AA). The number of similar drugs observations in this class rises from 32 in year 2001 to 64 in year 2007, an increase of 50% in the number of formulations. The ACE inhibitors plain class contains equally the largest number of similar chemical entities (n=11), however this number remains stable in our dataset in the period analysed. The class where the higher evolution in the number of follow-on drug molecules

was observed is the Protease Inhibitors Class (PIs or ATC class J05AE) in which we counted 3 supplemental similar chemical entities between 2001 (n=3) and 2007 (n=6) meaning an increase of 50% in the number of follow-on molecules. According to some authors such as Serrao *et al.* (2009) this is the class of birth of "Me-too HIV-1 integrase inhibitors".

The development of new follow-on drugs appears to be effectively an important issue in pharmaceutical markets today. Our results corroborate the fact that ATC classes where size of the market is relatively more important are more likely to develop follow-on drugs. Another example from our statistics descriptive is the ATC class C10AA (Statins) in which the number of follow-on drugs formulations increased from 13 in 2001 to 40 in 2007 while the number of chemical entities rises from 3 in period 01 to 4 in period 07.

According to DiMasi and Paquette (2004) the increase in the speed of entry in the follow on market is due to more pharmaceutical firms competing in the sector, more rapid dissemination of new technologies and expanding markets. The market share per entry order is shown in graph 1 for 2001 and in graph 2 for 2007.

As we can see in graphs 1 and 2, considering the mean values on each entrant, there is a negative relationship between market share and entry order. First movers have considerable more market share than last incumbents. We calculated the mean values for market share for each entry order and we found that drugs with entry order from 1 to 3 has a slightly decrease on the participation share of follow-on between years 2001 and 2007 while molecules from number 4 to 10 increase systematically their participation on the percentage of follow on drugs. The percentage of subsequent entrants (11th to 15th entrant) does not vary in an important way.

Graph 1
Market share distribution (in percentage)
within the ATC class as a function of entry order (2001)
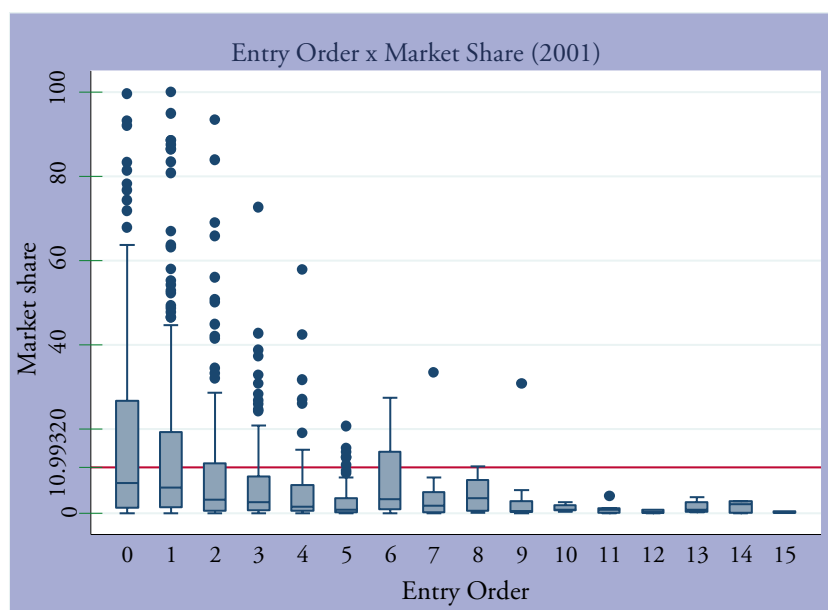
Graph 2
Market share distribution (in percentage)
**within the ATC class as a function of entry order (2007)**
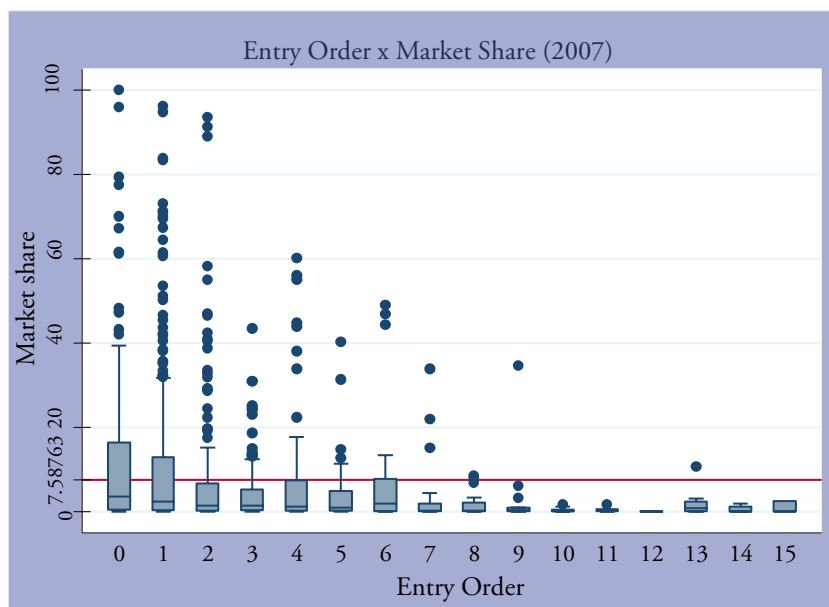
Entry Order equivalent to 0 is relative to first-in-class drugs, and we can observe that breakthrough drugs have larger market share than new entrants with similar mechanisms of action. Despite the fact that we included the values of market shares for first-in-class drugs in our descriptive statistics we do not use information on these drugs in our econometric analysis.

The horizontal line in both graphs represents the average market share of all follow-on drugs. We can observe that, in overall, the mean value of market share in our sample has decreased over time, from 10,9% in 2001 to 7,5% in 2007; this decrease of market share can be explained by the emergence of new entrants in our groups but more precisely we could infer that in this meantime the evolution of generic drugs in France has contributed significantly to the atomicity of market share distribution over time.

The hypothesis of decreasing market share due to generics emergence is based on the fact that this period (2001-2007) coincides with public policies efforts to increase generic drugs consumption in France. In fact, according to Grandfils *et al.* (2004) the development of generics in the French market began to expand in early 2000's and happened later than in other countries such as USA. To give an overview of how generic emergence affected our groups, we computed descriptive statistics concerning the prevalence of groups within generic competition. In year 2001 for example we observed that 57,8% of our selected ATC classes did not have any kind of generic competition while this number decreased systematically over time. At the end of the period analysed the trend has been reversed with the most part of our ATC groups presenting generic versions of follow-on drugs (52,25%).

Graph 3
Percentage of groups with generic versions of follow-on drugs

Percentage of groups with generic presentations
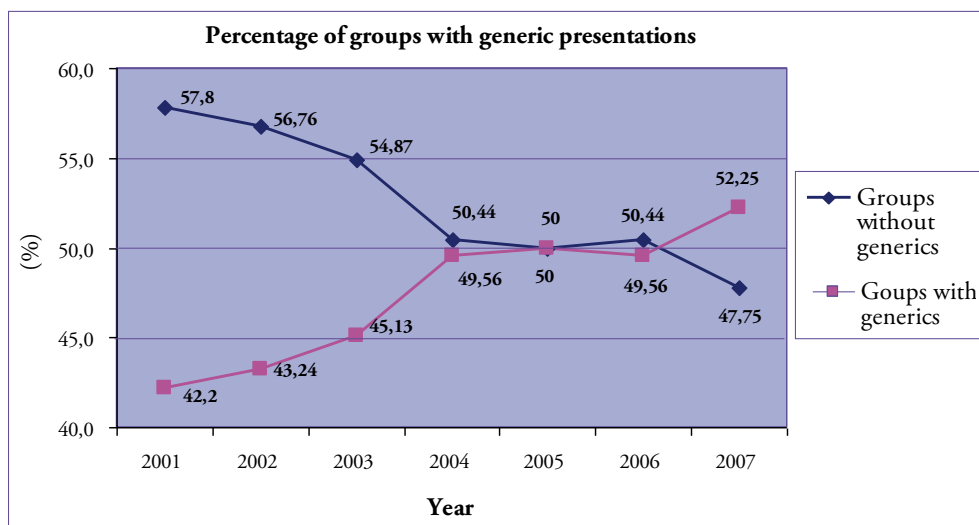
This brief statistical overview allows us to have new insights into dynamics of follow-on drug competition over time. Next section is dedicated to deeper analysis using econometric estimations to better understand trends on market share of follow-on drugs using individual and group variables.

5. Empirical Model

The empirical analysis used in our research is structured to examine certain hypotheses about the effect of entry timing on market shares of follow-on drugs in a dynamic context. Parallel analysis also allows us to better understand the structural determinants of the follow on drugs and to define their characteristics in function of entry timing. Since we have observations for each product by period, then dataset used in the regressions is a "panel data" type. Here we follow the same drugs across a specific period of time. Panel data-also called longitudinal data- is characterized by particular assumptions such as dependence of observations distributed across time. According to Wooldridge (2006), unobserved factors that may affect market shares of drugs (such as perceived quality) in period t will equally affect market shares of drugs in period t+1, t+2, . . . t+N. That is the reason why special estimation methods are employed and the use of panel data has become wider in economics of public policy analysis.

A particular important feature is that we allow for new entrants in the market, and hence the number of observations rises over time. We also take into account drugs that leave the market but in our sample there are more drugs entering the market than exiting, which is the reason why we have more observations as periods move forward. Our dataset is considered as an Unbalanced Panel and most statistic software take into account the unbalanced nature of the panel data. Econometric issues concerning the way in which the error term must be treated is an important preliminary when running regressions for panel data.

Given a model in which regressions with fixed effects estimators would be plausible then the Hausman Test provides information on whether the use of random effects would be almost as good. In case of fixed effects, the Hausman Test is essentially a test of H0: that use of random effects would be more consistent, versus H1 : that random effects would not be consistent. The main conclusion is that if Hausman specification test is large it is better to use fixed effects, otherwise in case of small statistic then it's preferable to perform analysis with random effects. We conducted Hausman test for each model specification and in every case the test rejected the random effects estimation. For market share as dependent variable and a set of explanatory variables the output from Hausman test provides Chi (22)=132.41 with prob>chi2=0.0000. This leads to strong rejection of the null hypothesis that random effects provide consistent estimates.

Another econometric issue is the fact that we use the entry order of follow-on drugs as explanatory variables and these are individual variables that do not change over time. The first follow-on drug in a group will be noted as first in year 2001 and also first in year 2007.   Hence we have an independent variable in a panel dataset that is constant over periods. To control for this particular issue and to capture their effects over time we are constrained to create new variables that would be allow in a panel data specification. The solution is to create interaction variables with the entry order and the binary period variable. According to Wooldridge (2002) it is possible to estimate differences in the partial effects on time constant variables relative to a base period. In this case we can test whether the effects of time-constant variable have changed over time. Hence we can add to the model interactive variables to capture effects of a time constant variable over time. Including interactions between time dummies and another variable Z allows the coefficient on (effect of) Z to vary across periods.

Let d2t, …, dTt denote time period dummies so that dSt =1 if s=t, and 0 otherwise. Let Wit be a vector of time-varying variables and zi a vector of time constant variables. Supposing that Yit is determined by:

$$y_{it} = \theta_1 + \theta_2 d2_t + ... + \theta_t dT_t + z_i \Upsilon_1 + d2_t z_i \Upsilon_2 + \ ... + dT_t z_i \Upsilon_\tau + W_{it}\delta + c_i + u_{it}$$

Using market share as dependent variable in the econometric model above we obtain the following results:

Table 4
Fixed effects coefficients with time interaction variables and market share
of follow-on drugs as dependent variable

Variable name (Market share in volume as dependent variable)	Fixed Effects Coefficients	T Statistics	P>t
Relative prices in relation to the first-in-class drug in Log)	1.47	3.21	0.001
Entry Order x Dummy Year 02	0.279	0.94	0.346
Entry Order x Dummy Year 03	0.584	1.99	0.046
Entry Order x Dummy Year 04	0.897	3.06	0.002
Entry Order x Dummy Year 05	1.24	4.21	0.000
Entry Order x Dummy Year 06	1.30	4.34	0.000
Entry Order x Dummy Year 07	1.46	4.85	0.000
ASMR	-6.48	-2.14	0.032
ASMR Missing	-11.31	-2.32	0.020
ASMR square	0.917	2.15	0.032
Medium size firms	1.86	3.46	0.001
Big size firm	1.01	1.60	0.110
Low Therapeutic Relevance	4.16	5.91	0.000
Medium Therapeutic Relevance	0.177	0.80	0.424
Median age drugs	0.435	1.73	0.083
Old age drugs	0.434	0.90	0.368
Number of generic presentations in the ATC class	-0.011	-2.15	0.032
Chemical entity with generic versions	-2.84	-7.30	0.000
Level of reimbursement	5.87	5.69	0.000
Year 2002	-0.749	-1.26	0.207
Year 2003	-1.62	-2.76	0.006
Year 2004	-2.77	-4.71	0.000
Year 2005	-3.73	-6.28	0.000
Year 2006	-4.14	-6.85	0.000
Year 2007	-4.74	-7.78	0.000
Constant	15.27	3.13	0.002
Sigma_u	13.03		
Sigma_e	3.76		
Rho	0.923		

The fixed effects coefficients with market share as dependent variable are shown in table 4. The observation of coefficients for the first variable, which corresponds to relative prices of follow-on drugs in relation to the first-in-class drug, supports the presence of a positive relationship between prices and market share. Classical economic theory suggests prices to be negatively correlated with demand and we should expect more expensive drugs to be negatively correlated with volume sales. However it is exactly the opposite result that we have found in the regression above. It is important here to highlight the fact that we use information on drugs with slightly level of differentiation and we can consider that inside an ATC class we have products that are imperfect substitutes. Hence even if they have similarities in the chemical, anatomical and therapeutic levels they still possess some differential element (ASMR) that could give some strategic advantage over other products. Moreover the literature on market

power and prices has been assuming that firms with an important bargaining force are more likely to negotiate higher prices when there is negotiation. As we pointed out earlier, the price of ethical drugs in France is the result of a bilateral negotiation between the regulator and the firms. A higher price may also be related to the possibility of higher quality. Our model also suggests a positive relationship between market share and innovation (Added Therapeutic Value). In the French system the higher is the ASMR the less innovative is the drug. (For example if ASMR is equal to five there is no therapeutic added value while ASMR is equal to 1 there is a very important level of innovation). That is the reason why the coefficient between market share and ASMR is negative in our regressions. If we consider that this variable is a measure of quality then we can infer that pharmaceutical demand in France is linked to high quality drugs. And hence higher quality is positively related to prices. It is possible that pharmaceutical firms concentrate their efforts and bargaining power on high quality products than negotiating lower prices. It may be also that demand function for pharmaceutical products in France could be more inelastic because of full insurance coverage and generous level of reimbursement for some products (even if the cost-containment policies have increased gradually the patient co-payment).

The main goal of this paper is to analyse the effects of entry order on market share. The interacted variables on entry order versus time dummies can give us an interesting overview on these effects. The time base period in the regression above is year 2001 and coefficients for the interaction variables are relative to this year. As we can see in Table 4 there is a systematically increase in coefficients for the interacted variables. These coefficients can be interpreted by correcting them with the time dummies, which means that, after correction, the coefficients still remain negatives because later entrants have less market share. However as time goes on it becomes more and more negative meaning that even later entrants have difficulties to capture market shares over time. For example, in year 2007 the corrected value for the entry order would be -4.74 +1.46 = -3,27. This coefficient is negative and corroborates the negative relationship between market share and entry order. If we dress a rapid overview looking at drugs by entry order that conquered market share over time we noticed that only groups of 13th and 15th follow-on drug entrants were able to capture market shares in the period analysed. This result suggests also that older drugs maintain a little competitive advantage over time but gradually this better position becomes less important as new entrants arrive and patents of first in class drugs fall in the public domain (generics). Moreover one may wonder what would happen to new follow-on drugs entering the market long time after the first-in-class drug and our results corroborates the fact that later entrants face important barriers to expand their market influence.

The graph 4 below shows the dynamics of the corrected coefficient for the entry time variable.

Our results suggest equally a negative relationship between market share and level of ASMR. The closest is the ASMR to the value of 1 the more is the added therapeutic value of the product and hence the more is the market share. We introduced the square value of ASMR and we can observe that the coefficient for this variable is positive and statistically significant (0.917), while for the absolute value of ASMR we have a negative coefficient (-6.48). This result suggests a convex impact of ASMR on market share, implying a U-shape pattern with declining left hand side greater than the rising section in the right hand side of the curve. The optimum level of ASMR to maximize market share would be the highest quality one (ASMR=1), confirming our hypothesis of quality competition.

Graph 4
Corrected coefficients for entry order effects on market share
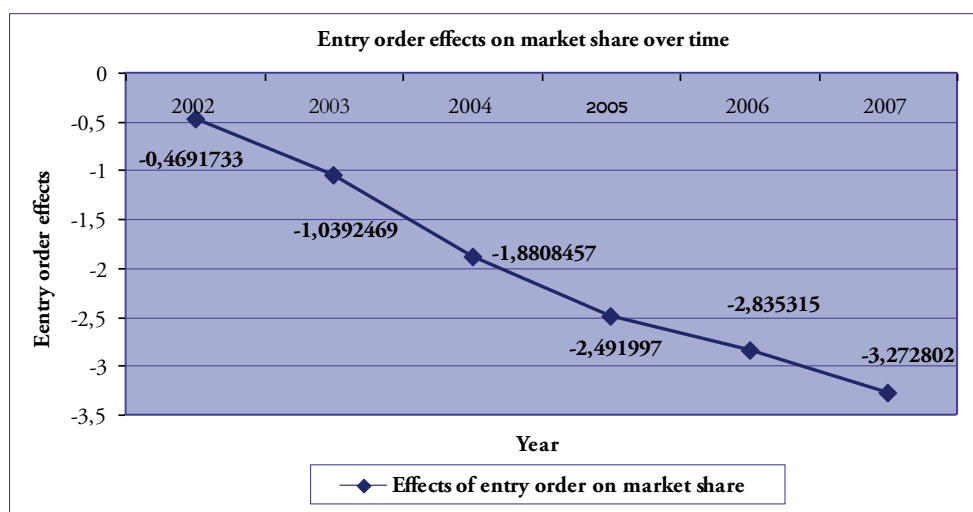
We included in our regressions variables indicating the size of the firm. The dummy variable excluded in regressions is the one relative to small firms. We found that pharmaceutical firms of medium size have larger market share than smallest ones but we found no significant relationship between the largest ones and market share. However when we excluded the largest firm dummy variable as the omitted category (the base group) we found statistically significant negative coefficients for the variable "Small Firms" which indicates that small companies have less participation in drug sales than big laboratories. We also tested the model without the relative prices of drugs (because the exclusion of this variable could capture other interesting effects) and we found that larger and medium firms have more volume sales than small firms (both coefficients are significant), confirming the fact that volume sales are concentrated amongst the largest firms.

The therapeutic relevance of an ATC class seems also to have an important impact on market share. This variable is a group indicator that takes into account the average level of reimbursement for all drugs in the class. Drugs reimbursed at 100% are considered as being very relevant from a therapeutic point of view. Our regressions show that less important classes have drugs with high market shares. Considering the group's characteristics, two distinct conclusions can be drawn from this result: first we can assume that a drug with high market share belongs to a group with fewer competitors and hence their market sales are larger. The second hypothesis for observations with high market share is that the therapeutic class in question (group) is relatively new with fewer generic versions of follow-on drugs what would imply high market share of drugs. Therefore, less important ATC classes would have fewer competitors or less generic versions of follow-on drugs. That would be another argument favourable to our hypothesis of quality competition in the French market with competitors concentrating their efforts on very important ATC classes where the level of reimbursement is high. We added a variable that corresponds to the level of reimbursement of the drug in year t and not surprisingly this variable has a positive and significant coefficient implying more volume sales for drugs with a lower patients' co-payment (higher reimbursement rate).

The age of drugs does not seem to affect market share. On the other hand the fact that the chemical entity has generic versions available and the number of generics versions in the class contributes significantly for a reduction in market share.

Our regression includes also time dummy variables to capture the effect of market share of follow-on drugs over time. The base period uses here is year 2001 and we can observe that coefficients are significant from year 2003 (t=3). That means that over time there was a significant decrease in market shares for follow on drugs. Since we allow for new entrants in our dataset then it is normal that market shares decrease over time because new products will directly compete with older drugs. Not all the ATC class in sample contain new entrants and this decrease in coefficients for the time dummies could indicate some classes where market share falls down because of exogenous factors such as generic competition. Moreover, our descriptive statistics show that later entrants do not conquer considerable market share and then there could exist market forces exerting pressures on the follow-on drug market. The main plausible explanation for lower market share of follow-on drugs over time is, as said before, the emergence of generic competition in the period analysed. These dummy variables capture the effects of market share over time independently of the follow-on entry order effect.

Amongst all the variables analysed, we retain the ASMR as one of the most crucial elements that may affect drug sales in the French pharmaceutical market. As we said before the convex relationship between market share and ASMR implies a maximal level of drug sales when the level of innovation is maximal (quality competition). We can calculate the level of ASMR that minimises the market share and hence deduce the one that maximises the market share :

$$Y_{it} = C - 6,48 ASMR + 0,917 ASMR^2$$

$$\frac{\partial Y_{it}}{\partial ASMR} = -6,48 + 1,834 ASMR = 0$$

$$ASMR = 3,53$$

The inflection point in the ASMR curve as a function of market share is when the level of innovation is equal to 3,53, which is the point that minimises the market share (in a scale of 1 to 5). When ASMR=1 the optimal market share level corresponds to Y_{it} =15,27 − 6,48(1) + $ASMR$.917(1)^2 => Y_{it} +9,70. It is possible to observe the relationship between ASMR and market share in Graph 5 below.

We also tested our model with a different measure of prices as independent variable, which corresponds to the variable that we called MP (MP= Market Power) corresponding to the price of the drug relative to the average price of all the drugs in the class. In summary the results are the same with slightly difference in coefficients but the behaviour patterns of all variables remains essentially the same.

Graph 5
Optimum level of ASMR to maximize market share

Optimal level of innovation to maximize market share

Yit=15,27-6,48ASMR+0,917ASMR^2
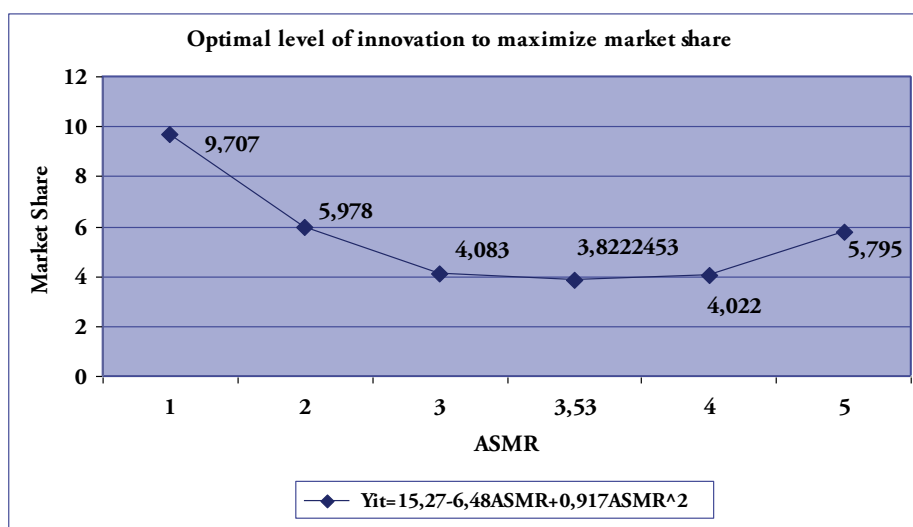
6. Conclusion

Incremental innovation is supposed to be an important driver for drug discovery and it brings important profits for firms to make possible constant investments in research and development. Emergence of follow-on drugs must be seen as well having some limitations in the contribution to improve the health status of patients. Arising questions concerning the low level of innovation in the pharmaceutical firms have raised an important amount of discussion in the literature about social benefits eventually provided by pharmaceutical firms and the aim of this paper is to contribute to assess the actual relevance of development in incremental innovation in France. Moreover this paper has broached the follow on drugs subject with an industrial organisation point of view and empirical analysis of the dynamics of this market segment. Moreover competition can be analysed with a global overview or by going deeper on the comprehension of some important aspects of market structure such as the impact of first incumbents in our case. The importance of being first has been largely discussed in the economic theory and our results have shown that first entrants in the follow-on drug market have an important competitive advantage in relation to posterior incumbents.

The paper has shown that later entrants face large competition and exhibit more problems in conquering market shares. However prices are lower for last incumbents meaning that even in a regulated market such as France, regulatory mechanisms are able to create a favourable environment to induce competition.

Some papers have shown that in pharmaceutical markets, physicians are more likely to prescribe drugs already used by patients and that patients are more reluctant to switch to new products. The same conclusion can be drawn in our analysis of follow-on drugs since market share is positively correlated with prices and negatively correlated with the entry order of follow-on drugs. In fact, the standard result should be for prices being

negatively correlated with market share but our results show the inverse tendency in the follow-on market. We remember that the prices are expressed in relation to the first-in-class drug. We still emphasize that this conclusion can be interpreted in the sense that patients and physicians are loyal to follow-on drugs that already showed to be effective and hence they are more reticent to change habits. The French structure of social security and reimbursement of listed drugs could be also a reason why patients consume relatively more expensive drugs. Since consumers do not pay integrally the price of the drug they are insensitive to less expensive drugs and hence prefer to continue with the conventional treatment.

The size of the firm seems to play also an important role in the development and competition of incremental innovation for pharmaceuticals. Not surprisingly, firms possessing ability to capture important market shares are the big ones. Actually this result is interesting since some authors such as Angell (2004) have argued that proliferation of me-too drugs is unproductive and unnecessary and the author argues in her book that incremental innovation is symptomatic of "Big Pharma's intellectual bankruptcy". Our results allow us to infer that this incremental innovation is in fact a characteristic of not small firms and that follow-on drugs are targeted to treat more common diseases where size of the market is important. Descriptive statistics highlighted this evidence by showing that therapeutic classes where the number of follow on drug formulations have increased the most in the period analysed are beta blockers and statins. These are markets where number of patients has been largely growing in the last years and consequently incremental innovation to treat theses conditions has also known an important improvement.

It seems that the French pharmaceutical market regulation induces a natural competition environment where firms producing more innovative products enjoy a certain level of monopoly and a level of reimbursement more attractive, while last incumbents face severe barriers to capture market shares and to set high prices. Moreover, we have shown that the optimal level of innovation to maximize market shares in a specific ATC class is the highest one.

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Entry Time Effects and Follow-on Drugs Competition

Luiz Flavio Andrade (Gate-Groupe d'analyse théorique et économique, Irdes)

Pharmaceutical firms have been criticized for concentrating their efforts of R&D on the so called "me-too" or "follow-on" drugs. There have been many comments against and favourable to the dissemination of these incremental innovations but few papers have broached the subject from an empirical point of view, possibly because identification of "me-too" is not so obvious. This paper focuses on the impact of entry order on "follow-on" drugs competition in the French market between years 2001 and 2007. More precisely, this study examines the effects on market share of first entrants in the follow-on drug market and how this possible competitive advantage changes over time. Our results are coherent with theoretical microeconomic issues concerning the importance of being first. We find evidence that first movers in the follow-on drug market have the ability to capture and maintain greater market share for a long period of time. The hierarchical market position of follow on drugs does not seem to be affected by generic drugs emergence. From a dynamic perspective, our analysis shows that market share is positively correlated with the ability of follow-on drugs to set prices higher than the average follow-on drug price in a specific therapeutic class (ATC) which means that market power remains considerably important for first movers. Finally we found that the optimum level of innovation to maximize market share is the highest one.

L'effet du délai d'entrée sur la concurrence des médicaments *follow-on*

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Les critiques auxquelles fait face l'industrie pharmaceutique sont axées notamment sur sa capacité à innover. La concentration des efforts de recherche et développement sur la production et dissémination des médicaments du type *me-too* ou *follow-on* est une préoccupation majeure des institutions responsables de la régulation du marché pharmaceutique. Le débat autour de cette problématique s'est considérablement répandu ces dernières années mais très peu d'études empiriques sur le sujet ont vu le jour, probablement en raison de la difficulté à établir un consensus sur la « vraie » définition de ces produits.

Cet article propose une analyse empirique de l'impact du délai d'entrée sur la concurrence des médicaments *follow-on* en France entre 2001 et 2007. Plus précisément, nous cherchons à mettre en évidence la relation entre ordre d'entrée dans une classe thérapeutique et parts de marché et comment l'avantage compétitif des premiers entrants évolue dans le temps. Les premiers résultats sont cohérents avec les prédictions de la théorie économique selon laquelle les premiers *follow-on* détiennent d'importantes parts de marché sur longue période. La position hiérarchique sur le marché des *follow-on* semble ne pas être affectée par l'émergence des médicaments génériques et les leaders de l'innovation incrémentale ont un pouvoir de marché relativement fort. Nous constatons également que le niveau optimal d'innovation pour maximiser les parts de marché est le plus élevé.

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