Entry Time Effects and Follow on Drug Competition

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Abstract : Pharmaceutical firms have been criticized for concentrating its 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 econometric point of view, possibly because identification of "me-too" is not so obvious. This paper focus on the impact of the entry order on "follow-on" drugs competition in the French market from years 2001 to 2007. The main question that we aim to respond is what are the effects on market share and prices of being the first me-too in the market and how this possible competitive advantage changes over time. First results are coherent with theoretical economic issues concerning the importance of being first. We find evidence that first movers in the follow on drug market are more inclined to set higher prices and have the ability to capture and maintain market share for a long period. The hierarchical market position of follow on drugs seems not to be affected by generic drugs emergence. From a dynamic perspective, preliminary analysis shows that prices of precursors follow on drugs tend to increase over time while market share decreases. Moreover, we can infer that prices of similar drugs are negatively correlated with the number of competitor in each specific market.

Keywords : incremental innovation ; follow on drugs ; entry timing ; fixed effects

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 when the US senate promoted discussions related to market power and pricing strategies of drug companies. Moreover there is no consensus about the exact definition of a 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 segments of authors as regards 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 considerable different of 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. 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 other have focused on more technical and medical characteristics of molecules to class them in the sphere of me-too drugs. These different points of view haven’t brought a consensus about what is really a me-too or follow on drug and their definition has become wider. We then decided to employ the term follow-on drug because, according to certain authors (DiMasi and Paquette, 2004) it has a more neutral-value component instead of 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. Prices of follow-on drugs have become a very sensitive question but given that there is such an empirical gap on this subject we are not able to make conclusions about strategic price positions practiced by firms on the similar drugs market. Some authors such as Hollis (2004) and Chada and Blomqvist (2005) have showed that prices of follow on drugs are often higher than first in class drugs while Dimasi (2000) conducted a study demonstrating that new entrants in a therapeutic class have an average launch prices lower than mean prices of precedent drugs. Hollis (2004) have shown that follow-on drugs not only fail in increasing competitiveness but may actually pull up prices. Wertheimer and Santella (2009) argue that even tough follow on drugs have a similar mechanism of action, chemical composition and biological effects, they still have to undertake extensive clinical trials in order to prove safety and efficacy and hence prices may not be necessarily low. Chada and Blomqvist (2005) apply a model of patent races in a context where there is introduction of follow on drugs in an existing market dominated initially by a breakthrough drug. The authors define it as Bertrand competition but they show that price and demand of me-too drugs are higher than that of first-in-class drugs. The prerogative is based on the fact that if the quality of a me-too drug is sufficiently high it is optimal to sell similar drugs at a higher price than breakthrough drugs. Moreover, as healthcare expenditures are mainly financed by public health insurance, consumers prefer to purchase the high quality drug even if it is more expensive. In fact there are no empirical evidences about the relevance of their theory. One of the main purpose of this paper is en fact to fulfil the existing gap concerning prices on the empirical literature of follow on drugs competition. More than only trying to understand price trends in the French pharmaceutical market we aim more precisely in dissecting prices 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 different forces co existing in the drug segment. 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). Hence there may be cases in which older products may be prescribed even if there is a range of new products available. In the other hand, there is an institutional force coming from firms intending to launch in the market new innovative products with more added value. Since innovation is one of the main drivers in the economy today, more innovative products can increase profits of firms and bring more therapeutic advances to patients. Interest on

innovation comes equally from government institutions that often provide incentives to firms to innovate. Apparently the innovation forces are stronger than patients and physicians attitudes toward medicines but it does not mean that the latter force does not exist. That is why we presume that prices of different follow on drugs may be very different if we take into account when 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.

Thus we can consider that this paper aims at analysing prices of follow on drugs and specially different in prices of follow on drugs in relation to first in class drugs, as well in determining market share of drugs and to see how these variables behave over time in a panel analysis. This research also intends to contribute to the literature concerning incremental innovation on pharmaceutical markets and the definition of follow-on drug was a very important point on the construction of our analysis line and selection of groups. To clarify some aspects on the actual connotation of similar drugs we provide below a table that shows some different definitions of follow on drugs, and we point out the fact that many authors suggested a wild range of different meanings for these pharmaceutical products.

Sams-Dodd, 2007.	Drug discovery today	2007	Follow on is a drug that has the same mode of action (Moa) as an existing drug (first in class) and provides minor, although possibly important therapeutic advances.
Cohen et al.	Journal of clinical pharmacy and therapeutics	2006	Follow on drugs are subsequent class entrants
Hollis, 2004	WHO repport	2004	Me-too drugs are products which largely duplicate the action of existing drugs and wich which have a similar mechanism of action to pre-existing drugs. New molecule similar to the pioneering drug.
DiMasi and Paquette, 2004	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) . Me-too drugs have also been characterized in a more value-neutral way as follow-on drugs.

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

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 classed by molecule entity in a specific ATC class and the entry order is based on the date of commercialization of the molecule on the respective class. If the molecule Lansoprazole is the first follow-on drug in its class then all the presentations of Lansoprazole 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 (ATC) class 5-digit that is to say the molecular level. The Anatomical Therapeutic Chemical Classification system is used for the classification of drugs. 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 5 digit ATC class have similarities in the treatment purpose of a specific conditions and also they have a slightly proximity on the chemical structure. Figure 1 shows an example of different levels in the ATC class.

1st Level	ATC 1	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. insulins
4th Level	ATC4	A10BA	Chemical subgroup	Biguanides
5th Level	ATC5	A10BA02	Chemical substance	Metformin

As DiMasi and Paquete (2004) points out, there may be occasions that a drug in the 5th level ATC class competes with another drug in a different therapeutic class but since we're interested in follow-on drugs we define the market field competition as being the internal perimeter of a five digit ATC class. The data used in our study consist of information on drugs 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 (provided by Vidal), Thesorimed, Medica'm and EPPM (the IMS-Health Permanent Survey on Medical Prescription. Thus, the
variables constructed and used in our analysis come from these different sources. Information on sales of reimbursed drugs come from Medica'm in which we are able to calculate market share for each product analysed. Prices of follow on drugs for each year came from the History Prices Dataset on Sempex. Other variables necessary for regrouping drugs in specifically markets such as chemical entity, dosage, package size, and indication were collected on the Thesorimed dataset.

3.Variables description

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 the product was effectively commercialised in the market. Information on this variable is provided by Thesorimed database. In our sample the entry order varies from 1 to 15, which means that some group can have a 15^{th} molecule commercialised which 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.

Relative Price per DTC 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 per DTC, or cost per day, refers to the cost of taking the drug daily. This variable is calculated by

dividing the price of the drug package by the number of treatment days. 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 posology of a specific drug. The posology 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 price history database in 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 constraint to reduce the number of observations in our regressions.

Market share: is the market share of the follow on drug in a specific 5-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.

Medical Service Render (SMR): it 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 of a drug and represent the actual therapeutic value of a drug. Thus, the SMR can be classed in 5 categories : 1. Major ; 2. Important ; 3 ; Moderate ; 4 ; Low; 5. Insufficient. five dummy variables were created for this variable.

Improvement on Medical Service Rendered (ASMR): or added therapeutic value, it 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 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 drug. There are five level of added value: 1. Major improvement; 2. Important improvement; 3. Modest improvement; 4. Minor improvement; 5. No improvement.

Therapeutic relevance class: 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 in a therapeutic class. In France, drugs can be classed 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 co-payment: 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 condition. 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 way of contrast, drugs for dermatology or mucolytic agents are considerably less reimbursed. 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. Thus, we constructed a three level scale variable where:
1= classes with a low therapeutic relevance: 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 relevance: In this class we can mention groups like statins with average reimbursement level of 59% in 2004 and 63% in 2007. 3= classes with a high therapeutic relevance: such as immunosuppressive agents with average reimbursement level of 79% in 2005 and 89% in 2007.

Drug reimbursement rate: it is the percentage rate of reimbursement for the drug. This variable comes 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".

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 Medicam where we can find sales value for each product in a specific year.

Market power: For each follow on drug market (5-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 :

$$MP = \left(Pi \Big/ \frac{1}{n} \sum_{i=1}^{n} pi \right)$$

, where pi 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 than firms have the ability to set higher prices than the average price of all the drugs in the group, and hence the market power would be positive. If the market power is below 1 than market power is negative meaning that the firm had less ability to set an important price for the drug.

An indicator variable was created for the first follow on drug into each market, which has a value of 1 for the first follow-on drug into a given therapeutic class (market) and 0 otherwise. It was also created another dummy variable for the last follow on drug into each market. We group drugs from 10th to 15th enter position as being part of the dummy variable “last” because their number is relatively low.

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. 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 opt 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 Theriaque database its indication does not match with the first drug commercialised in its class.

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 the social security system, 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. 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 then 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 in 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 2.

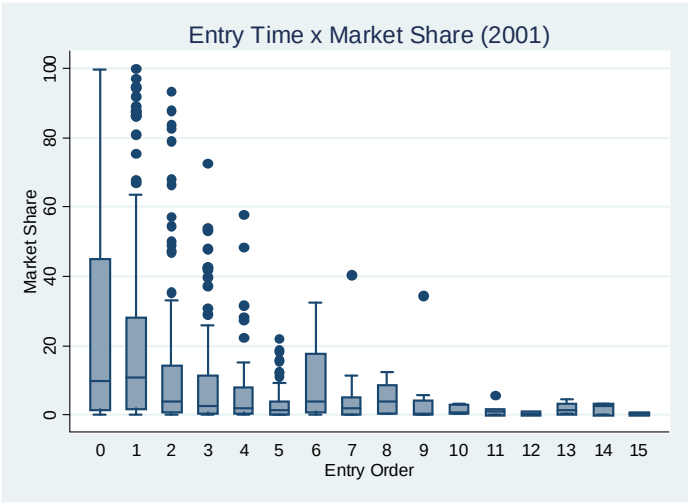
	2001	2002	2003	2004	2005	2006	2007
Average number of follow-on drugs (by presentation)	6.09	6.33	6.46	6.53	6.71	7.57	7.66
Average number of follow-on drugs (by chemical entity)	2.44	2.46	2.48	2.51	2.56	2.52	2.52

Table2: Average number of follow on drugs in groups by period

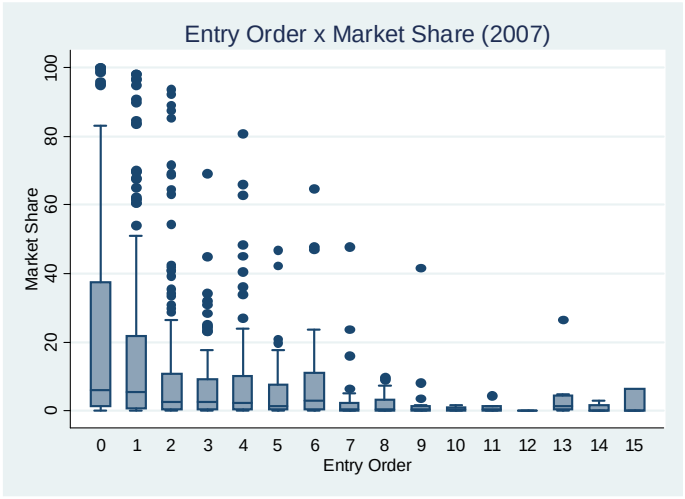
Table 2 reports an increasing in the average number of follow on drugs in groups over time. The ATC class in which we observe more follow-on drugs is the ACE inhibitors plain group (ATC class C09AA). The number of similar drugs observations in this class rises from 32 in year 2001 to 64 in year 2007, 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 we noticed the higher evolution in the number of follow-on drug molecules 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 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 diffusion 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.



Graph1: Distribution in percentage in entry order (2001)



Graph2: Distribution in percentage in entry order (2007)

As we can see in graphs 1 and 2, in general, drugs with entry order from 1 to 3 has a slightly decrease on the participation share of follow on. Molecules from number 4 to 10 increase systematically their participation on the percentage of follow on drugs while percentage of subsequent entrants does not vary in an important way. This seems to be normal since new entrants captures market share from older drugs. In some regulated markets such as Japan and France, initial prices and reimbursement are results of negotiations between the regulator and pharmaceutical firms. The latter are not allowed to set prices higher than the limit stipulated but they are free to set a lower price. According to Danzon and Chao (2000) this mechanism incites manufacturers to cut prices below the limit negotiated in order to capture market shares. However apparently this mechanism may not be the rule in all the regulated markets such as France. Moreover, given that first in class drugs face increasing possibility of generic consumption, than it would be normal to notice a decrease in prices for incumbent products (even if some empirical analysis showed that this is not always the case). Hence, if prices of established drugs tend to decrease over time than prices of new products will have a negative relationship with the number of competitors already in the market. Hence, according to Danzon and Chao, the more products on the market, the less will be the price of successive entrants. Descriptive statistics on average price by entry order of follow on drugs in our sample (tables 9 and 10) support the theory of price breakdown for new entrants in a regulated market. Even if some authors argue that the tendency is to price decreases as new follow-on molecules enter the market, statistical evidence shows us an average increase in prices for follow on drugs and first in class drugs in the period 2001 - 2007.

Statut	Mean DTC 2001	Mean DTC 2002	Mean DTC 2003	Mean DTC 2004	Mean DTC 2005	Mean DTC 2006	Mean DTC 2007
First in class	0,631	0,613	0,645	0,619	0,625	0,728	0,753
Follow on	0,906	0,935	0,971	0,996	1,005	1,018	0,959
Obs	382	417	448	473	475	482	570
Difference (%)	43,58	52,52	50,54	60,90	60,80	39,83	27,22

Table 3: Average price in Daily Treatment Cost for firs in class and follow on drugs

The average price of the referent product in our sample increased by 19,33%, from 0,63€ in 2001 to 0,74€ in 2007, while average prices of follow-on drugs increased by 5,84%. To test whether the increase in prices of first-in class and follow-on drugs are due to new entrants or not, we calculated prices for both categories of drugs in 2007 using the groups of 2001. It's interesting to observe that when we use only the groups of the beginning of analysis the prices of referent products decrease over time, from 0,63€ in 2001 to 0,58€ in 2007 which means that in fact the rise in average prices of referent drugs over time is due to new entrants. However prices of follow-on drugs rise from 0,90€ in 2001 to 0,93€ in 2007 meaning that prices of pre-existing and new entrants similar drugs tend to increase over time.

More precisely, if we look at daily treatment costs for follow-on drugs in relation to their entry order we can observe that, in fact, the price of subsequent entrants decrease with the number of competitors. Table 4 shows average DTC prices for each drug in function of their entry to speed in the market. First in class drugs are in average less expensive than the groups of first, second and third follow on drugs, but prices of similar drugs tend to decrease from the 4^{th} entrant and so on.

Entry Order	Mean DTC 2001	Mean DTC 2007	Evol 01-07 (%)
0	0,631	0,754	19,425
1	1,044	1,053	0,935
2	0,896	1,035	15,476
3	1,109	1,242	12,040
4	0,490	0,924	88,706
5	0,504	0,683	35,545
6	0,571	0,655	14,746
7	0,478	0,667	39,458
8	0,641	0,712	11,048
9	1,079	0,832	-22,841
10	0,395	0,521	31,794
11	0,438	0,449	2,488
12	0,386	0,354	-8,068
13	0,465	0,568	22,132
14	0,458	0,542	18,455
15	0,414	0,396	-4,506

Table 4: Mean DTC of follow-on drugs in years 2001 and 2007.

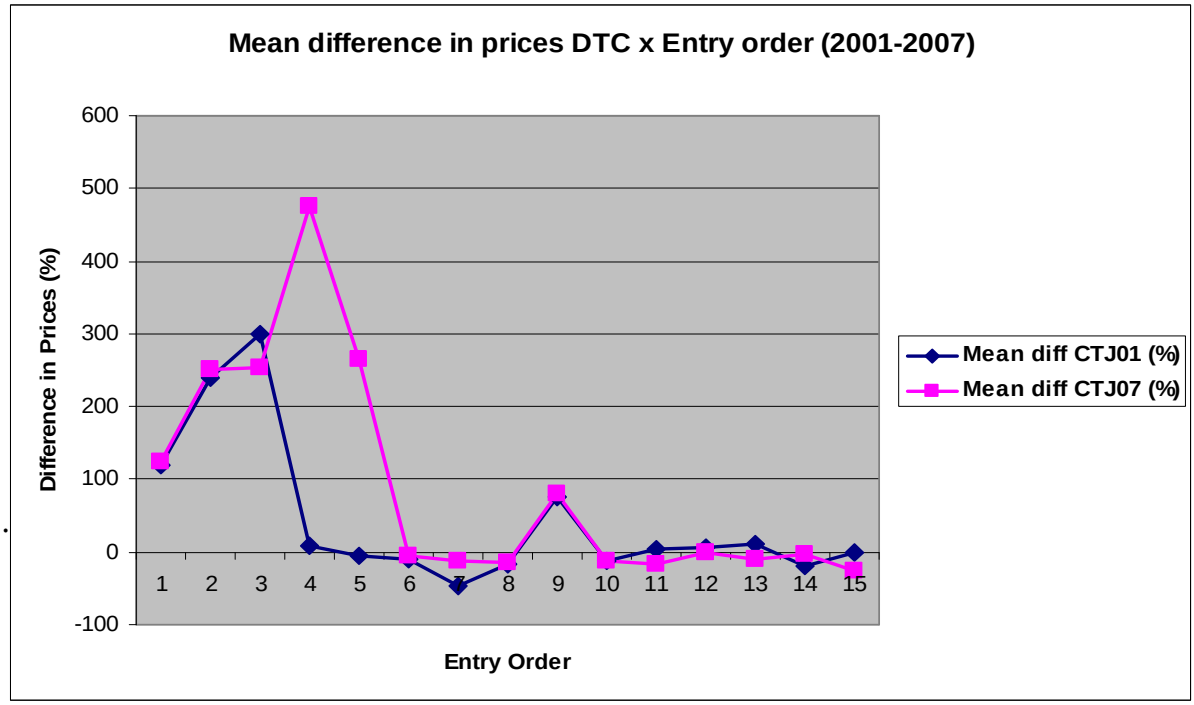
The French pharmaceutical market is an interesting field for research in pharmaeconomics because regulation implies several tools used by governments to negotiate prices and to measure level of innovation and medical benefits of new drugs. This specific regulation in France guarantees important reimbursement rates for drugs adding important medical value to patients (Naudin and Sermet, 2003). The purpose of this specific system is to reduce government expenditures with drugs that do not add substantial benefits to patients and somehow to provide incentives for firms to produce more innovative products in order to get into the reimbursement list. An indicator of therapeutic advance over already existing products is the Improvement in Medical Service Rendered (ASMR). The level of ASMR varies from I (high added therapeutic value) to V (no added therapeutic value). We don't have exhaustive information for this variable but it gives a subtly outline of the average degree of innovation for different follow-on drugs.

Table 5 shows average ASMR level by follow on drug entry order. The 0 entry order refers to first in class drugs and it is clear to observe that first movers in a therapeutic class are characterized by being more innovative. Last follow on drugs appears to be to less innovative in relation to pre existing drugs since ASMR level for last ones are close to 5.

Entry Order	Mean ASMR 2001	Mean ASMR 2007
0	2,29	3,06
1	3,41	3,85
2	3,25	3,32
3	4,33	4,28
4	4,56	4,63
5	4,77	4,30
6	2,33	4,16
7	4,00	3,67
8	5,00	5,00
9	4,00	4,88
10	N/C	5,00
11	5,00	5,00
12	N/C	N/C
13	3,00	3,67
14	5,00	5,00
15	5,00	5,00

Table 5: Mean ASMR by entry order (2001-2007)

Another important variable that we created for the purpose of our analysis is the relative difference in prices of the follow-on drug with respect to the first-in-class drug. Based on the average price that we calculated previously we are able to see that difference in prices of first follow-on drugs are relatively more important than last incumbents. Indeed the difference in prices becomes negative for last entrants because their prices are lower than first in class drugs. We constructed a graphic where we can see means for the variable difference in prices in relation to the entry order of the molecule for years 2001-2007



Graph 3: Mean difference in prices DTC x Entry order (2001-2007)

As we can see in graph 3, difference in prices for follow-on drugs in 2001 with entry order 1, 2, 3 and 4 are positive and relatively high but these gap prices become less important as new products enter the market. In 2007 the difference in prices for all the molecules after the 10th position are negative meaning that their prices are lower than the product of reference in the class.

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 and prices of follow-on drugs using individual and group variables.

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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 and prices 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 price and market share of drugs (such as perceived quality) in period t will equally affect price and 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 Ho : that use of random effects would be more consistent, versus H1 : that random effects would not be consistent. When performing the test we obtain a vector with dimension k (dim(b)) with distribution chi-square (k). 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)=201.73 with prob>chi2=0.0000. This lead to strong rejection of the null hypothesis that random effects provide consistent estimates. The variable entry order does not change over time and hence we have an independent variable in a panel dataset that is constant over periods. To control for this particular variable and to capture their effects over time we are constrained to create new variables by interacting the entry order variable with a 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 of time-varying variables and zi a vector of time constant variables. Supposing that yit is determined by

$$y_{it} = \theta_1 + \theta_2 d2_t + ... + \theta_t dT_t + z_i\gamma_1 + d2_t z_i\gamma_2 + ... + dT_t z_i\gamma_t + W_{it}\delta + c_i + \mu_{it}$$

and using market share as dependent variable we obtain :

Variable name (Market share in volume as dependent variable)	Fixed Effects Coefficients	T Statistics	P>t
Difference in prices (Log)	2.89**	7.40	0.000
Entry Order x Dummy Year 02	.298	0.98	0.329
Entry Order x Dummy Year 03	.720*	2.37	0.018
Entry Order x Dummy Year 04	.805**	2.67	0.008
Entry Order x Dummy Year 05	1.16**	3.84	0.000
Entry Order x Dummy Year 06	1.24**	4.17	0.000
Entry Order x Dummy Year 07	1.24**	4.15	0.000
ASMR 02	1.29	0.97	0.330
ASMR 03	-.081	-0.02	0.981
ASMR 04	.208	0.21	0.835
ASMR 05	2.25*	2.89	0.004
Medium firm	1.63*	2.92	0.004
Big firm	1.13	1.71	0.087
Low Therapeutic Relevance	2.00*	2.95	0.003
Medium Therapeutic Relevance	-.031	-0.14	0.890
Less Old Drug	.312	1.19	0.234
Old Drug	-.027	-0.06	0.956
Year 2002	-.837	-1.36	0.173
Year 2003	-2.16**	-3.53	0.000
Year 2004	-2.73**	-4.47	0.000
Year 2005	-3.70**	-6.00	0.000
Year 2006	-4.23**	-6.84	0.000
Year 2007	-4.37**	-7.00	0.000
_cons	6.89**	14.00	0.000

Table 6: Fixed effects coefficients with time interaction variables and market share of follow-on drugs as dependent variable

The time dummy variables Year 2001- Year 2007 capture the effects of market share over time and we can observe that coefficients are significant from 2003. 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 on 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 than there could exist market forces exerting pressures on the follow on drug market. The main plausible explanation for lower market share of follow on over time is, as said before, the emergence of generic drugs in the period analysed. These dummy variables capture the effects of market share over time independently of the follow on entry order effect. For the purpose of our analysis the coefficients for the interaction variables reflect better the impact of entry order over time.

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 6 there is a systematically increasing in coefficients for the interacted variables. This coefficients can be interpreted by correcting them with the time dummies of the time, which means that, after correction, the coefficients remain negatives because later entrants have less market share but as time goes on it becomes more and more negative meaning that even later entrants have difficult to capture market shares over time. However, if we dress a rapid overview regarding drugs by entry order that conquered market share over time we noticed that only groups of 13^{th} and 15^{th} follow-on drug entrants were able to capture market shares in the period analysed. This result suggests also that older drugs maintain a 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.

We included in regressions variable indicating the size of the firm. The dummy variable excluded in regressions is the one relative to big firms. We can observe in the regression table that the coefficient for small firm is negative and statistically significant suggesting that small firms have less market share than bigger pharmaceutical industry. The therapeutically relevance of an ATC class has also an important impact in market share. This variable 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. Regressions show that less important classes have more market shares then very important ATC classes. These results can be interpreted in the sense that drugs integrally reimbursed have more added value than medicines with a lower level of co-payment, and hence they aim to treat more particular conditions where size of the market is not so relevant. The expansion of follow on drugs seem to occur in therapeutic classes where size of the market is relevant and medical conditions are not too severe. Another interesting result is that difference in prices are positively related to market share suggesting that more expensive drugs are supposed to have higher market shares. If we consider follow on drugs as imperfect substitutes then the theoretical result should be a negative correlation between market share and difference in prices. Concerning innovation aspects, the regression shows that less innovative products (ASMRV) are more likely to have important market shares than more innovative follow on drugs. This result seems to be normal since products adding high therapeutic value are often very specific drugs aims to treat some particular diseases that may not affect an important part of the population. It seems that follow on drugs are designated to capture high market share because they treat often some very common conditions and pharmaceuticals strategy may be behind this intuition. We used the same model to estimate the effects of entry order on price of follow on drugs. More precisely we aim to analyse difference in prices of the follow on drug in relation to the first in class drug. Descriptive statistics have shown that first follow on drugs are more likely to have higher prices than first in class drugs but prices fall down for subsequent entrants. Prices used are in DTC and reflect the real cost of medicines used by patients on the period analyzed. Results are shown in the table below.

Variable name (Difference in Prices in Log as dependent variable)	Fixed Effects Coefficients	T Statistics	P>t
Market Share Volume	.0042**	7.40	0.000
Entry Order x Dummy Year 02	-.0129	-1.11	0.268
Entry Order x Dummy Year 03	-.0314*	-2.71	0.007
Entry Order x Dummy Year 04	-.0106	-0.92	0.356
Entry Order x Dummy Year 05	-.0263*	-2.27	0.023
Entry Order x Dummy Year 06	-.0296*	-2.61	0.009
Entry Order x Dummy Year 07	-.0313*	-2.74	0.006
ASMR 02	-.1138*	-2.24	0.025
ASMR 03	.0350	0.28	0.783
ASMR 04	.2083**	5.47	0.000
ASMR 05	-.1477**	-4.96	0.000
Medium firm	.0963**	4.49	0.000
Big firm	.1316**	5.24	0.000
Low Therapeutic Relevance	-.0634*	-2.44	0.015
Medium Therapeutic Relevance	-.0221*	-2.58	0.010
Less Old Drug	-.0188	-1.88	0.060
Old Drug	-.0100	-0.52	0.605
Year 2002	.0344	1.47	0.142
Year 2003	.0591*	2.53	0.011
Year 2004	.0530*	2.27	0.023
Year 2005	.0950**	4.03	0.000
Year 2006	.1088**	4.60	0.000
Year 2007	.1270**	5.31	0.000
_cons	-.004	-0.21	0.830

Table 7: Fixed effects coefficients with time interaction variables and difference in prices in log of follow-on drugs with respect to first-in class drugs as dependent variable.

Table 7 shows fixed effects regression using difference in prices (log) as dependent variable and a set of independent variables grouping individual characteristics of follow on drugs. We can observe that coefficients for the time dummy variables increase over time. From year 2003 coefficients are statistically significant which means that differences in prices of follow on drugs in relation to the first in class drug are constantly increasing as years go by. This result is coherent with descriptive statistics concerning the average difference in price evolution from 2001 to 2007. We have shown that within this period the mean difference in prices increased from 43,58% in 2001 to 60,80% in 2005 with a slightly decrease in years 2006 and 2007. Here is important to highlight the fact that one may argue that this increase in gap prices is due to a decrease in the prices of the first in class drugs and the emergence of generic competition. This can be true since we described that prices of older first-in-class drugs tend to decrease over time while new first-in-class components appear to be marketed at

high prices. Indeed the increase in the average price of all first-in-class drugs is in fact due to new entrants. But it's important also to notice that follow-on drug prices tend to increase over time even for older follow-on products and we can drawn the conclusion that price gaps increase at some period not only because referent products become less expensive but also because prices of similar drugs in average increased in the period analysed. The interactive variables for entry order versus time dummies give us a slightly preview of evolution of difference in prices relative to entry timing. Coefficients are negative and significant for almost every observation year except 2002 and 2004 and statistically decreasing over time. It means that evolution of difference in prices over time is negatively correlated with entry order and that this correlation is even more negative as time moves forward. Differences in prices are even more important for first in class drugs and this relation gets more intense over time. This model captures the fact that first follow on drugs enter the market with a relative higher price than first in class drugs and that theses prices get higher in time, despite of last entrants.

Concerning market share, it is interesting to observe that difference in prices is positively correlated with this variable. This result shows the importance of being first in the follow on drug market and could indicate that subsequent entrants face a stricter regulation from health authorities. In fact, we can observe that prices are negatively correlated with the number of follow on drugs in each market. The level of innovation is also an important variable that may affect prices over time. Results shown in table 7 gives an interesting overview of the relationship between prices and level of innovation for follow on drugs in the period analysed. Coefficients are negative and statistically significant for drugs with ASMR V which means that follow on drugs adding no therapeutic value over existing drugs have less difference in prices than those more innovative (here the base innovation level is ASMR I). However follow on drugs with ASMR IV (little therapeutic added value over existing drugs) have coefficients positive and significant comparing to very innovative products. Here it is possible to conclude that intermediary innovative drugs may have higher prices than follow on drugs with ASMR I meaning that the relation here is not linear.

Variables concerning the size of the firm were also added to capture the possible market power of firms producing follow on drugs. As we might expect, the difference in prices is positively correlated with the size of the firm. This relative price advantage over first in class drugs shows that big pharmaceutical industries have more ability to set higher prices than small or medium industries. This result seems to be normal since R&D is relatively more important in the big pharmaceutical companies than small firms leading to a more innovative

output in the former case. We can notice moreover that medium therapeutic relevance medicines are more inclined to have important difference in prices in relation to first in class drugs than high therapeutic relevance drugs. The next econometric model allow us to better understand the overall relationship of market share and prices over time for some specific variables such as ASMR and general entry order. The difference in relation to the previous model is that we don't construct interaction variables and hence the interpretation for coefficients is for the whole period analysed. Moreover in this model we consider the entry timing as an individual fixed effect and hence we add to the model the dummies related to the follow on entry order without interaction (as we have done in the first model for time dummies). In summary this model is different in the sense that despite of adding dummy variables related to the periods we add dummies related to the entry order. We specify the model to take into account the entry timing as the individual fixed effects.
Hence our model becomes,

$$y_{ti} = \theta_1 + \theta_2 d2_i + ... + \theta_i dI_i + W_{ti}\delta + c_t + \mu_{ti}$$

Where $d2_i,...,dI_i$ denote dummy variables for the entry order (before we have used dummy variables denoting time).

Entry order here takes the values:

$d2_i$ =1 if entries order vary between 1 and 2; and zero else.
$d3_i$ =1 if entries order vary between 3 and 10; and zero else.
$d4_i$ =1 if entries order vary between 11 and15; and zero else.
W_{ti} is a vector of time-varying variables

We'll let the referent dummy be the one that represents first follow-on drugs and comparisons will be in relation to this ones.

Using fixed effects and market share as dependent variable we obtain the following results:

Variable name (Market share in volume as dependent variable)	Fixed Effects Coefficients	T Statistics	P>t
Difference in prices (Log)	1.39	3.28	0.001
Entry Order 2	-8.58	-11.91	0.000
Entry Order 3	-12.1	-13.09	0.000
ASMR	10.7	3.53	0.000
$ASMR^2$	-1.58	-3.54	0.000
ASMR missing	14.20	3.15	0.002
Low Therapeutic Relevance	1.65	0.79	0.429
Medium Therapeutic Relevance	-2.32	-2.36	0.018
Less Old Drug	2.15	2.82	0.005
Old Drug	1.93	1.92	0.055
Ratio price/group prices	.968	2.41	0.016
_cons	2.27	0.50	0.618

Table 8: Time Fixed effects coefficients with market share of follow-on drugs as dependent variable

We included here dummies grouping the entry order of follow on drugs and we can observe that coefficients for this variable are significant and negative as we might expect. Given that we have 3 categories we should have (3-1) dummy variables and we choose the first entrants as base group. Hence coefficients are interpreted in relation to the first follow on drugs in the market, and not surprisingly last entrants have considerable less market share than first incumbents. Moreover we can observe that the strength of the negative correlation gets more powerful for last entrants compared to intermediary incumbents. The level of innovation represented by the variable ASMR are also significant at 1% level and it is interesting to observe that here we have a concave relationship between market share and level of innovation. The first regression with interactive variables (table 6) shows a negative relationship between market share and less innovative follow on drugs. Unfortunately coefficients for the other levels of innovation were not significant for the first specification model. Here we have added the variable representing the value of ASMR squared and surprisingly we obtained a negative and significant correlation for this variable, while for absolute value of ASMR the relationship is negative. In a first moment one might argue that level of innovation is negatively correlated with market share but here we can observe that this relation is not linear. The same interpretation can be drawn for therapeutic relevance classes since low therapeutic relevant follow on drug have more market share than drugs belonging to high reimbursed classes, while medium therapeutic relevant drugs capture less market share than the base group. Regression also included the individual variable market

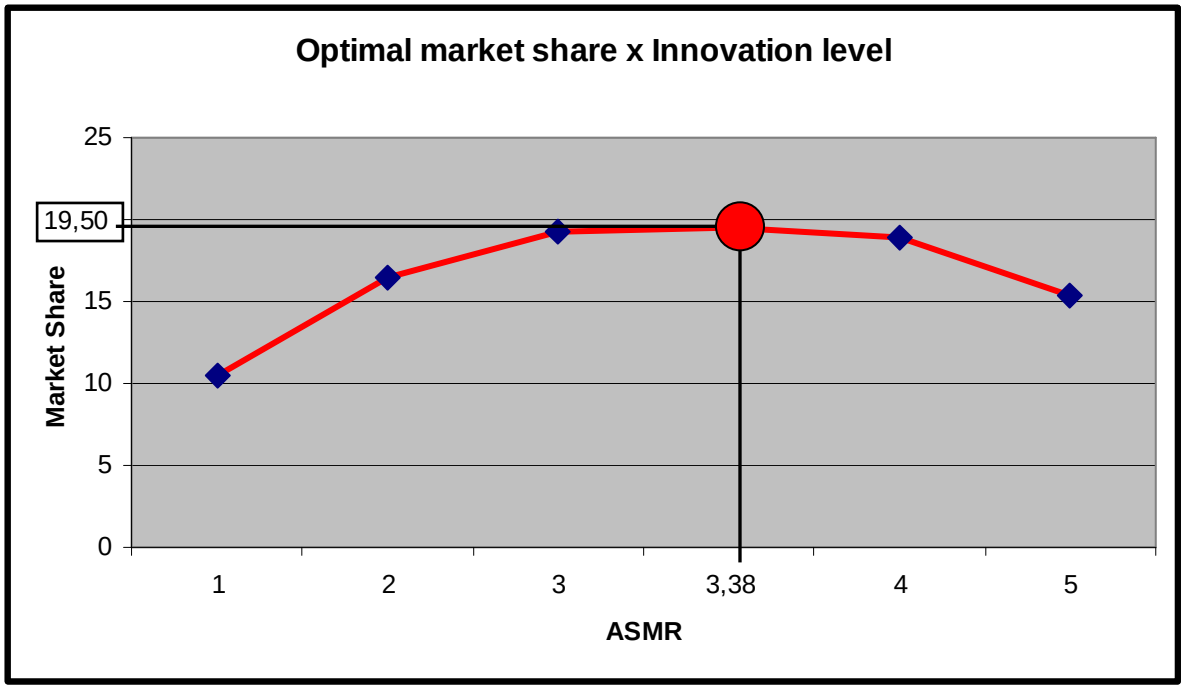
power that represents simply the price in DTC of the drug divided by the average mean DTC price of all the drugs within the ATC class. This variable could indicate a certain level of market power since we consider that follow on drugs are imperfect substitutes. Hence if a specific drug have the ability to set prices over the average group price than this drug could contain some specific characteristics that would be fundamentally important for its own differentiation. Not surprisingly the relationship between market power and market share are significantly positive in the period analysed.

We used the same model but included difference in prices (log) as dependent variable. Results are shown in the table below.

Variable name (Difference in Prices in Log as dependent variable)	**Fixed Effects Coefficients**	**T Statistics**	**P>t**
Market Share Volume	.0029	3.28	0.001
Entry Order 2	-.019	-0.56	0.572
Entry Order 3	-.279	-6.47	0.000
ASMR	2.06	15.43	0.000
$ASMR^2$	-.316	-16.19	0.000
ASMR missing	2.49	12.47	0.000
Low Therapeutic Relevance	-.163	-1.71	0.088
Medium Therapeutic Relevance	-.165	-3.70	0.000
Less Old Drug	-.144	-4.16	0.000
Old Drug	-.468	-10.36	0.000
Ratio price/group prices	.198	11.03	0.000
_cons	-2.02	-9.88	0.000

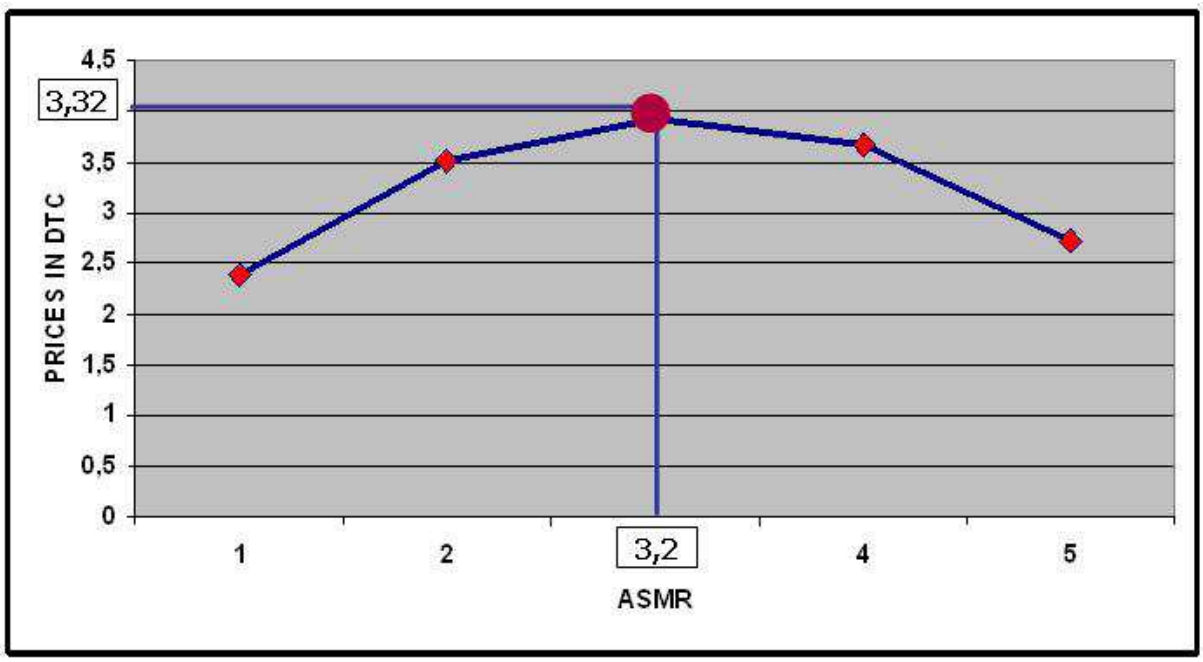
Table 9: Time Fixed effects coefficients with differences in prices of follow-on drugs with relation to first- in-class drugs as dependent variable

The interesting analysis that we can draw from results in table 9 are that, in the period analysed, difference in prices are negatively correlated with last entrants and have a concave correlation with the level of innovation of the products (based on the variable ASMR). Moreover new drugs are more likely to have higher prices than older drug formulations or older molecules. The concave relationship between market share and difference in prices with the level of innovation in the follow on drug market may help us to better understand which point would be optimal for profit maximisation in the pharmaceutical market for imperfect substitutes. Considering ASMR and holding constant the other variables for market share we have the following relationship:



In our dataset and considering the period analysed, we can argue that the optimal innovation level in a scale representing innovative follow on drug output ranging from 1 to 5 is equal to 3,38.We remember that ASMR= 1 represents very innovative drugs in relation to pre existing products and ASMR=5 means no therapeutic advance. Hence we obtain the following graph with the optimal innovation point to maximize market share in the follow on drug market.

Reasoning in the same way we could undertake the same rationale to find the optimal innovation level to maximise difference in prices. However we used the same model but we include the variable related to the absolute value of prices in Daily Treatment Cost. Holding constant all the other variables and derivating the result equation with respect to ASMR we obtain the following graph with the optimal level of innovation to maximize prices.



The graphs above with optimum level of innovation to maximize prices and market share should not be considered as a negative conclusion in relation to the policies undertaken in France to regulate the pharmaceutical market. Since our research purpose is to undertake analysis in a market characterized by concurrency with a relative slightly level of differentiation than it might be normal that level of innovation to maximize market share and prices is not the maximum one.

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 concurrence 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 concurrence 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 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 still emphasize that this conclusion can be interpreted in the sense that patients and physicians are loyal to 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 they prefer to continue with the conventional treatment.

The size of the firm seems to play also an important role in the development and concurrence of incremental innovation for pharmaceuticals. Not surprisingly, firms possessing ability to set high prices and 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 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.

This paper also contributed to the comprehension of prices behaviour as a function of entry order of chemical entities in the pharmaceutical market for similar products, and is interesting to observe that prices increase for first follow-on drugs but those prices decrease as new entrants comes to the market. It seems that the French pharmaceutical market regulation induces a natural concurrence 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.

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