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The Impact of Market Entry on Total Class Volumes of Me-too Drugs in France

by

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Abstract

Me-too drugs have been under heated discussion in the economic, public health and pharmaceutical literature for years now. This study investigates the impact the entry of a me-too drug has on the total sold volumes of a class. This aids to determine, whether a me-too drug serves a market of its own, and augments the number of patients to whom there is an acceptable treatment available, or whether it does not increase total volumes and merely redistribute existing market shares. We find that the impact of an entering me-too drug strongly depends on how many drugs exist in the class previous to the entry. According to our estimates, the first me-too drug augments total volumes substantially, while the second will already have hardly an impact on total volumes by less. Depending on the characteristics of the entering drug and those of the drug class, after the first or second me-too drug entry, a new entrant will not increase total volumes. This means, the potential strain for the insurance system is limited, while patients benefit from larger diversity. Drug company's incentives to invest in innovation are potentially threatened, but higher innovation does always significantly pay-off for the pharmaceutical company.

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All errors are mine.

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Introduction

"Critics of Me-Too Drugs need to take a chill pill", goes the provocative title of a recent article[1] by Henry I. Miller, published in the Wall Street Journal in January 2014. A me-too drug is a drug, which treats the same condition as a drug that was already on the market before, but which is not chemically exactly equivalent. The article is a pladoyer for me-too drugs, arguing that the existence of a variety of drugs within the same class is highly beneficial for a public health system. The case is being made, that slightly varying drugs that treat the same condition, increase the number of patients to whom a tolerable treatment is made available. This is because people react differently to the same drug, and what helps one person, does not necessarily help another. Having multiple drugs, one also has multiple side effects, cross-drug reactions and additional indications, such that it may be possible that more patients can actually be treated.

On the same side of defending me-too drugs, a study by DiMasi & Paquette (2005) attempts to clear the bad reputation of me-too drugs as pure imitators of existing drugs, by showing that companies do not intend to develop me-too drugs to begin with, but that multiple pharmaceutical companies often develop drugs for the same illness in parallel time. However, in a process of 10-15 year drug development, there will be one who wins the race for first approval, and some who will enter as me-too drugs.

On the other end of the spectrum of opinions, critics say that me-too drugs are a plain waste of R&D resources by drug companies, and also put a strain on public health systems, because they reimburse drugs despite having no additional benefit, and whose prices are possibly even higher than the original ones (Mihaescu & Rudholm 2013, Bergua et al. 2012).

[1] http://online.wsj.com/news/articles/SB10001424052702303293604579256263038269796

This study shall shed light on the discussion of me-too drugs, from a perspective, that to the best of our knowledge, has not been investigated hitherto. The question is, what happens to total sales volumes, when a me-too drug enters the market? We deliberately focus on volumes sold, not prices, because these change freely with demand, while prices are set fixed in the regulatory framework. Is there demand for a me-too drug, that was not previously satisfied by the existing first-in-class drug? In this case, the entering me-too would cause an increase in total volumes of a class. If on the other hand, the drug is a pure imitation of an existing drug in terms of its efficacy and side effects, then demand should stay the same and the market shares within the existing sales volumes may merely change. The interest of the study is to provide a further "piece of the puzzle", in the quest of evaluating the overall impact of me-too drugs. While it is found that in the long term the existence of me-too drugs can decrease average prices in a class (Lu & Comanor 1998) through competition, showing that total volumes increase through me-too drug entry would compensate this effect. It would therefore weaken the argument in favor of me-too drugs, from a pure public finance perspective. On the other hand, the fact that volumes do increase, can also serve as an indication that there is real demand for the new drug, and it serves many additional patients, who were not treated adequately previously.

The study is conducted on French data within the time frame of 1998 to 2013. We only consider reimbursed prescription drugs. Our results show, that the impact of a me-too drug depends on how many drugs are already existent in a class. While the first me-too drug entering a class increases total class sales volumes substantially, the following entering drugs will hardly increase total volules, depending on their characteristic. After the second or third drug, the market is saturated, and any further entering drug, does not increase total volumes, but will at best redistribute market shares. The impact the incoming me-too drug will have on the class, also depends on its innovative and medical benefit value. The higher the benefit and the greater the innovative level of the drug compared to the existing one(s), the greater the ability of that drug to create its own demand and increase total volumes.

The structure of the study is the following. First, a literature review presents the current debate on me-too drugs in detail, and places the study in its context, in order to identify its added value. Then, a short section sheds light on the regulative framework in France as background information, and clarifies the research question more precisely. Following this, a large section on data and methodology presents the variables and identification strategy employed for the analysis, before turning to the presentation and discussion of the results in the subsequent section. A number of useful possible extensions to the study are pointed out. Finally, section 6 concludes and discusses possible policy implications of our findings.

2

Literature Review

2.1 Overview and Definition

Me-too drugs, whether one approves of them or not, are an inevitable reality on the pharmaceutical market. The speed of competitive market entry of drugs into drug classes has drastically increased. The reasons for this are mainly the increasing mobility of labour and faster diffusion of information as well as technical know-how. Following DiMasi & Paquette (2005), the gap for competitive entries into a drug class has decreased from 10 years in the 1960s, to 0.25 years in the 90s, on average.

The topic of me-too drugs is widely debated and contested. The social welfare implication of having a range of drugs with similar therapeutic and chemical properties has not been clearly established in the literature thus far. Proponents of me-too drugs argue, that multiple drugs in the same class are beneficial to patients, not only because competition should normally lead to price decreases, but particularly because a greater variety increases the probability of finding a tolerable cure for an individual. Opponents on the other hand claim, that me-too drugs waste R&D resources through insufficiently small incremental innovation and are further a strain on public health systems, because they are often reimbursed at a similar level as their first-in-class counterparts. The following part shall shed light upon the literature on this debate in order to place the memoire in its context and to understand its contribution to the existing literature.

It is no surprise that the existing literature does not agree on whether me-too drugs are a good thing or a bad thing, given that it does not even agree on a precise definition. Therefore, a clarification of the terminology appears highly beneficial to begin with. A me-too drug, also commonly called "follow-on" is a drug that is therapeutically equivalent, *i.e.* serves to treat the same illness, without having the exact same chemical

formula as another drug, in which case one would refer to it as a generic. It is therefore common to have multiple patented drugs in one *class* of me-too drugs. Throughout the study, the term class will refer to class of therapeutically equivalent and chemically similar pharmaceuticals, including one *first-in-class* and its me-too drugs. It shall also use the term me-too drug or follow-on drug interchangeably, without the intention of keeping a positive or negative connotation to either term.

Hollis (2004) suggests to define a me-too drug as one that is approved after a pioneering drug and which is the same, in the sense of the US Orphan Drug Act, and is not clinically superior (Milne, Kaitin & Ronchi 2001), where same means comparable or similar. The aspect in which most definitions of me-too drugs differ, is the point of clinical superiority. Some scholars call a me-too a drug, which is strictly not clinically superior compared to other drugs in class, meaning that it brings no therapeutic innovation. Others also call a drug a me-too, even if it bares some clinical improvement, such as an additional indication or less side-effects, as long as it serves to treat the same condition as the first-in-class, despite being better at it. In this study we want to keep the definition of a me-too drug in its widest sense, in that it is a drug that is therapeutically equivalent, but may very well bring some minor improvements. The aim is also to see, what characteristic of an entering me-too drug allows it to create its own market power.

2.2 In favour of me-too drugs

In one of the most frequently cited papers on me-too drugs, DiMasi & Paquette (2005) argue that follow-on drugs are wrongly perceived as pure imitations of existing drugs. Given that the development process of a new drug takes approximately 10-15 years, some laboratories embark on developing a treatment for the same illness roughly around the same time. Drugs that enter after the break-through drug has been approved, have simply lost the race of being the first one approved. DiMasi & Paquette (2005) find, that nearly all drug classes in the late nineties had at least one follow-on drug with phase III testing initiated before the first drug in the class was approved. It is therefore very often a case of parallel development, instead of only pure imitation. Of course, this depends on the time lag, with which the drugs are brought into the " pipeline" *i.e.* start their development. Limiting or restricting market entry for me-too drugs, could therefore discourage laboratories to do research into new drugs to begin with, faced with the risk of losing a race that may take 15 years to run.

The fact that there is parallel development taking place, does not have to be a disadvantage. There is nothing that guarantees, that the first drug approved in a class is necessarily better at treating a particular condition, than its follow-on drug approved

some time later. An example of how parallel development may be beneficial is given by an anti-diabetic drug that was approved as a breakthrough blockbuster in 1997. However, this same drug had to be withdrawn from the market due to its high toxic content shortly after its market entry. By that time, there were two follow-on drugs available, which were less toxic and are today widely used and ease the life of millions of diabetes patients (WSJ 2014) [1]. While this may be a singular example, it does show that in the absence of the me-too drug, patients may have waited a much longer time for treatment.

The strongest argument in favour of me-too drugs, is that they provide patients with a greater diversity of treatment and can therefore improve risk-benefit ratios for available treatments. For example, there may be two drugs that are found to be effective for 50% of patients with a certain condition. However, the two drugs may not be effective for the same 50% of patients. In the best case obviously, they would serve the two non-overlapping patient pools. This way, having two drugs can strongly increase the pool of patients for whom there is an acceptable treatment without too many adverse side effects. It is extremely unlikely that two chemically non-identical drugs would serve the exact same population of patients, and therefore the chance of increasing the patients pool at least a bit, is quite high. Bardey, Jullien & Lozachmeur (2013) argue, that many me-too drugs on the market for one drug class can be strictly beneficial. In a theoretical model that maximises a representative individual's Von-Neuman-Morgenstern expected utility function from health insurance, they relate average risks from side effects to available pharmaceutical product diversity in one class. They create an index of drug diversity. Higher numbers of available products, increase the probability for a patient to find a treatment that he or she can tolerate, or that does not interact adversely with any of the other treatments. They find that "ceteris paribus, the higher the number of drugs available in the therapeutic class, the higher is the perceived utility of the health service as patients benefit from a decrease in the average side effect"(Bardey, Jullien & Lozachmeur 2013, p.6). They even argue, that theoretically, diversity of treatment is an indirect form of insurance that may substitute for or complement monetary insurance, since patients have increased chances of finding an acceptable treatment.

Another prominent argument pro me-too drugs is that there are cases in which the full value of a drug had not been revealed at the time of its approval. Numerous drugs have proved to be very effective in treating a different condition than they were initially marketed for. For example, a drug that was initially approved in the US in 1986 to treat a rare blood condition called hairy cell leukemia, was later found to be extremely effective in treating chronic hepatitis C and myelogeneous leukemia (WSJ 2014). It is now barely used for it original indication. Me-too drugs, while treating the same illness, do not necessarily have the same way of functioning. Therefore, a breakthrough

[1] http://online.wsj.com/news/articles/SB10001424052702303293604579256263038269796

drug, may not turn out to have the same second indication as its seeming imitator. Denying entry to me-too drugs therefore does bare the risk of inhibiting a potentially very beneficial discovery.

For these reasons, any assessment of the value of me-too drugs, must take into account the social rate of return including any clinical and economic benefits it may provide, as DiMasi & Paquette (2005) point out. Drugs in a same class, since they are not clones of each other's chemical formulas can differ in their side effects and efficacy profiles, delivery system or interactions with other drugs.

If the public health system would strictly deny market access to me-too drugs or put in place very strong price controls, pharmaceutical companies may have to cease the production of some drugs, once another company gets a first-in-class drug approved. This would mean, that companies operate with a moving target and increased uncertainty about future revenues, which could discourage them from any attempts of improving an existing drug altogether, or even investing in new drug research. Some drug benefits only become visible at late phases of testing, and may therefore never be known, if the research process was prematurely aborted. Moreover, many drug companies actually use revenues from me-too drugs to finance research into their blockbuster break-through drugs (Hollis 2004).

Another often mentioned argument in favour of me-too drugs is the increased price competition, that should eventually lead to an average price decreases in a class. Lu & Comanor (1998) find, that an extra competitor in a class leads to an average price reduction in the class of 2%. However, various empirical studies from different countries suggest different results on the matter (see below). The price of me-too drugs seems to mainly depend on the added therapeutic value of the entering drug (Bergua et al. 2012), but also on the different price setting mechanisms used in different countries.

Summing up the arguments in favour of new market entry into an existing drug class, me-too drugs increase the variety of available treatments to patients, and therefore increase the chance for a patient to find a suitable pharmaceutical. They may also bring advantages, that are not known ex-ante to their approval, and a strong restriction on me-too drug approval may discourage drug companies from research and development of new drugs all together.

2.3 Contra me-too drugs

As mentioned in the previous section, an often used argument for competitive entries into drugs classes, is that it induces price competition and leads to price decreases. However,

this argument does not generally seem to hold true. The usual economic reasoning that increased competition should lead to decreases in prices does not always apply on the pharmaceutical market, in particular if the latter one is heavily regulated by the state or public health system provider. On the contrary, there are studies that suggest that me-too drugs are marketed at a higher price than their first-in-class counterparts. Following Ekelund & Persson (2003), in Sweden where the pharmaceutical market is rather strongly regulated, drugs of comparable therapeutic value enter at a higher price than the pioneer drug, compared to the US, where they enter at about the same price Lu & Comanor (1998). In a study by the Irdes, Bergua et al. (2012) show that in France, there are significant price gaps between the break-through drug and their follow on drugs. The latter are often sold at elevated prices, even if they only bare minor levels of additional innovation compared to the originator drug. The authors run a random effects panel data model on French pharmaceuticals data of 2001-2009. They find, that added levels of innovation, as measured by the ASMR in France, *l'amélioration du service médical rendu*, the added therapeutic value of a drug compared to other existing drugs in a class (see below for precise definition), is the main driver of the price gap and explains large parts of the higher me-too drug prices. One degree of added innovation is typically associated with a 16 % price increase, while two degrees lead to as much as a 43% increase. Such numbers certainly do not speak in favour of me-too drugs from a public health system and budgetary perspective. The problem of course is, that in the case of reimbursed prescription drugs, (on which we shall focus through-out the study), entry is being subsidized by generous reimbursement rates. Me-too drugs are typically reimbursed at the same rates as their originator drugs. Therefore, this can lead to a situation, where excessive entry of me-too drugs with minor innovation is simply too expensive and not optimal from a social welfare point of view. Ideally, with no additional therapeutic value, a me-too should be sold at the same price. Additional innovation on the other hand, should be rewarded by higher prices. The question to ask at this point certainly is, how much additional innovation is enough, and how little innovation remains a waste of resources both by the state, and by the drug company.

The danger that approving too many drugs with minor innovations on the reimbursed drug market bares, is that it reduces the incentive for pharmaceutical companies, to invest into research for pioneering innovation (Hollis 2004). This is particularly true, if the competitor me-too drug succeeds to capture a large market share from the incumbent drug, without adding any therapeutic value. As is well known in economics, exemplarily from the findings of Dixit & Stiglitz (1977), monopolistic competition can induce too much or too little product diversity. In the case of the pharmaceutical market, one can argue, that there is excessive entry, if the incoming me-too drug is a perfect substitute for the incumbent product with no additional indication, the same side effects and

cross product reaction. In this case, the additional variety only reduces the profits of the pioneer drug and thereby reduces the pioneering drug company's reward for its innovation. It also wastes research and development resources and adds administrative cost for the market approval procedure. The question that arises here is, how, why or if the incoming new drug succeeds to capture a market share *vis-à-vis* the first-in-class at all, and even further, whether it succeeds to increase total sold volumes.

There are numerous studies who emphasise the importance of being first, in particular on the pharmaceutical market. On the generic market for example, Hollis (2002) shows, that the first generic to enter the market after a patent has run out, captures the largest market share, and the later a generic enters, the worse are its chances to "get a part of the pie". The main reasons for this phenomenon are linked to excessive switching costs for patients, doctors and pharmacies. While doctors may be prepared, or even obliged to by their public health system, to prescribe the cheaper generic alternative once its available, they may not be inclined to switch a second time, once they decided for an existing generic. Although theoretically equivalent, generics need not be therapeutically and from a dosage perspective, the exact same as the branded drug. There is therefore always a risk connected to prescribing a new treatment to a patient, in terms of effectiveness, cross-drug reactions and side effects. While the cost saving may outweigh the risks of switching from branded to generic drugs- this may not be true when switching from one generic to another.

Andrade (2012) undertook a study on the French market and tests whether the importance of being first also holds for me-too drugs. He finds that indeed, the more drugs already exist in a drug class, the harder it is for a new me-too drug to capture market shares. Later entrants face greater competitive pressures than the few first ones in class, while they usually enter at lower prices than the first ones in class. One could argue, that to a certain extent, the same reasoning of switching cost applies to me-too drugs. The risk-benefit ratio for a patient to switch to yet another therapy may be extremely high. Unless an existing treatment is not effective for a patient, he probably does not want to switch drugs for no reason, if all is going well. A doctor also has little reason to change her prescription habit for a certain condition, unless the current treatment is not adequate for the patient. The same is probably true for the procurement and stocking decisions of pharmacies.

To sum up the counter arguments, excessive market entry of me-too drugs raises the following issues. Prices of me-too drugs may be higher than that of the pioneer drug, despite only minor innovation. They reduce the incentive for drug companies to invest in strong innovation and reduce the profits of the first-in-class drug. Further, the risk-benefit ratio of new drugs may not be acceptable, given that there is an established

drug on the market treating the same condition. The added therapeutic value of me-too drugs, may be too small to offset the risk and cost of approving a new drug on the market. Lastly, the opportunity costs of resources spent on such minor innovations, may be too high.

This literature review served to elucidate the recent debate on me-too drugs. It becomes clear rather quickly from the discussion, that a verdict on me-too drugs depends on the added value a drug bares. The following part now shall shed light on the research question at play here, and how the literature helps to make hypotheses on the expected results.

3

The research question and background of the study

The research question this study asks is: what happens to total sales volumes of a pharmaceutical drug class when a new drug in this class enters the market? Can this new me-drug create its own market and therefore its own demand, or does it merely redistribute the existing demand and hence take market shares from the first-in-class drug and other me-too drugs already on the market? We deliberately focus on total sales volumes instead of prices or market shares, in order to assess the impact on the class as a whole, on a criterion that can freely change through market forces, not negotiations.

If a me-too drug can indeed raise totals sales volumes instead of just reallocating the existing ones, it has created its own demand. It means that, given that the occurrence of the illness the drug class is treating has not changed, the new me-too is serving a new market of patients, that was not treated by this class before. This would indicate, that the drug is valued in its own right, for example for its improved cross-drug reaction and lesser side effects, not just as an imitation of an existing drug. The clinical improvement of whatever sort, may therefore allow a new part of patients with one condition to be treated, for whom there was no acceptable drug available before this market entry. It is also possible, that the new drug has an additional indication to the ones of the existing drugs, and therefore has created a new market for itself. This all could indicate, that there was a need for the drug in question in the first place.

In terms of the impact for the public health system of a new drug, the question is at what reimbursement rate and what price the drugs is approved for the market. In France, the process of market approval, pricing and reimbursement rate determination is the following. After market authorisation by either the AFSSAPS (*Agence Francaise de*

Sécurité Sanitaire des Produits de Santé), the French Health Products Safety Agency or the European Medicines Agency (EMA), the drug is in a first step evaluated in terms of its medical and economic benefits by the *Commission de la Transparence*, the Commission for pharmaceuticals evaluation, which is a body of the HAS, the high authority for health. This agency fixes the ASMR and the SMR. The ASMR is the measure for the improvement of medical benefit, and is divided into five levels (major innovation, important improvement, significant improvement, minor improvement, no improvement), level 1 being a major improvement and 5 no improvement. The improvement is measured in comparison with the existing drugs in the drug class. The ASMR is then a major determining factor in the price negotiations between the CEPS, the Economic Committee on Health Care Products and the drug manufacturer. The price, once it is fixed, may of course still change during the course of a therapeutic class life cycle with the arrival of generic equivalents, a new molecule or downward price revisions decided by the regulator. The higher the innovation, the higher the set price is likely to be. Tables 3.1 and 3.2 show ASMRs in **the data used for this study**. Table 3.1 shows the ASMRs for all drugs who enter after the first-in-class is already present, while 3.2 the ASMRs for all entering drugs, including the first-in-class. Not surprisingly, as can be seen, the number of drugs with higher degrees of innovations are given for first-in-class drugs.

TABLE 3.1: **ASMR of entering me-toos**

Item	Number	Per cent
n/a	19	16
1	1	1
2	2	2
3	9	8
4	16	14
5	71	60
Total	118	100

TABLE 3.2: **ASMR of all entering drugs**

Item	Number	Per cent
n/a	24	13
1	2	1
2	7	4
3	17	10
4	30	17
5	98	55
Total	178	100

The second measure determined is the SMR, which is the medical benefit assessment. This is not a comparative measure, it mostly takes into account the drug in its own right in terms of efficacy, safety, the severity of the disease it treats, the type of treatment it offers, its potential public health impact, as well as the position of the medicine in the therapeutic strategy, i.e. whether there exist therapeutic alternatives. This measure will determine the level of reimbursement of the drug, which is then set by a body that unites the main public health insurance funds in France. The SMR also takes values of 1-4, in descending order of medical benefits of major, important, moderate, weak or insufficient to justify a reimbursement.

Me-too drugs are often criticised for being a strain on the public health system, in that they are reimbursed at same levels as the break-through drugs. This is particularly problematic, if they are priced higher than existing drugs, as the Irdes study by Bergua et al. (2012) suggests. However, it is often said, that the existence of me-too drugs will lead to price competition and eventually lead to price reviews and lower average prices in the class in the long term (Lu & Comanor 1998). On the other hand however, if the total volumes rise through the introduction of a new me-too, then this would offset to a certain extent the lower average prices. This study, will therefore help to elucidate the question of how much of a strain for the public health system me-too drugs are. Of course, it cannot be ignored, that if there is a real own demand for the new drug in question, then the fact that it can provide a treatment to patients that were not treated before, may decrease health care costs for the patients in total. For example, patients who can now receive an adequate treatment after the entry of a me-too drug, may need a lot less hospitalisations or doctor visits , which may decrease their total health expenditure. The assessment of such considerations would be a very useful extension of this study.

As already mentioned, the focus of the study are total sales volumes. This is because on the pharmaceutical market, the usual forces of demand and supply, mediated through prices are interrupted by occurrence of an illness, a doctors prescription habits, the patients preferences and what he can tolerate, as well as the pharmacists stocking decisions to a certain extent. Therefore, prices are not necessarily a good predictor of demand, and the price elasticity of demand is likely to be low and even positive. Moreover, prices are not flexible to change in the regulation framework in response to demand. Volumes on the other hand will change in response to demand and therefore serve as an interesting variable to study the impact of the arrival of a new me-too. One drawback of the available data is that they are not retail sales volumes, which would indicate utilisation, but wholesale volumes, *i.e.* what gets sold to pharmacists. This may therefore be an imperfect prediction of demand for a drug. However, it can be assumed that pharmacists

do not want to sit on large amounts of stock and therefore order from the wholesaler on a short-term basis, given their needs on what they sell the most.

To summarize, the questions this memoire will focus on are, what happens to total class sales volumes when a me-too drug enters the market? Does the number of drugs already present in a class at the time of entry matter, does it impact the effect? Are effects immediate or very lagged? What characteristics of the therapeutic class, and what characteristics of the entering drug are useful predictors of what is likely to happen to total sales volumes?

The following section will give an overview of the data used as well as explain the empirical strategy and regression models used.

4

Methodology

This part shall discuss and explain the data that was used for the study, the variables included in the regression and the identification strategy and empirical methodology that is being used in detail. Some descriptive statistics are presented, in order to give a better overview of the data set used. Preparing the data was certainly the most laborious part of the study and took a lot of time, which is why a large part is devoted to this section.

4.1 Data

The data used for this study were kindly made available by the DREES, *Direction de la Recherche, des Études, de l'Évaluation et des Statistiques*, the direction for research, studies, evaluations and statistics attached to the French ministries for health and social affaires. Two data bases where used for the study, namely GERS and Thesorimed. GERS is a database that is delivered to the DREES each quarter and that includes information about wholesale volumes, meaning from wholesalers to pharmacies, as well other information such as wholesale prices, reimbursement rates and turnover. The database by Thesorimed on the other hand includes a wide range of fixed characteristics, such as the ASMRs and SMRs, the type of medicament, its ATC (Anatomical Therapeutic Chemical) code, dosage or presentation, to name a few. These two data bases were merged using the CIP code (*Club inter pharmaceutique*), a seven digit code (or thirteen-digit since 2007) which uniquely identifies each pharmaceutical product, down to its different forms of presentation. For example, a box of 20 and a box of 40 pills of some given drug will be noted as two distinct pharmaceutical products by the CIP code. The time frame of the data is 1998-2013, which is since when the GERS data is available

under the current form. Also, since 1998 the price fixing and reimbursement rate procedure has been largely been the same. The ASMR and SMR systems were exactly introduced then. The GERS data is monthly, meaning we exploit monthly variations of sales volumes from January 1998 to December 2013, which gives 192 month.

A large selection made as to which classes to include in the study. First of all, only prescription drugs were included, meaning that over-the-counter drugs one can buy without a prescription in the pharmacy are excluded. Moreover, the number of classes was reduced significantly through the limits of available information. The used data was drastically reduced by 40%, because only classes were retained, for which at least half of the incoming drugs had an ASMR and SMR attached. The information on ASMR and SMR is extremely badly documented, and is missing in over half of all entering drugs. The reduction of the data base however, seemed a reasonable trade-off given the high variation in monthly data. The final database contains 162 classes, which still gives $162 * 192 = 31104$ observations. Of course the fact that we only keep classes with well documented SMR and ASMR may bias the selected classes to a certain extent, but at the same time at least this allows us to better control for these characteristics.

The following lists and explains all variables used in the analysis.

Total sale volumes

This is the main dependent variable of interest. In the GERS data, volumes sold are presented as number of boxes sold of one drug per CIP code. Boxes of drugs are not a very meaningful measure, given that drugs come in different dosages and there are different numbers of pills in boxes. Therefore, the measure had to be normalized. For this, we used defined daily dosis, as indicated in the Thesorimed data base. The defined daily dosis (DDD) is defined by the WHO as the " assumed average maintenance dose per day for a drug used for its main indication in adults", where an adult is a person of 40 years weighing 70 KG. Total sales volumes were therefore defined as sold defined daily dosis, given by:

$$\text{DDD in box} = \frac{\text{Number of pills in box * dosage}}{\text{DDD}}$$

$$\text{Total DDD sold} = \text{Boxes sold} * \text{DDD in box}$$

This measure of defined daily dosis in one box was then multiplied by total boxes sold of one CIP. Using the defined daily dosis as the measure for normalization is not the perfect measure. The WHO warns, that DDDs do not "necessarily reflect therapeutically equivalent dosis of different drugs"[1]. However, it does seem like an accessible way of

[1] http://www.whocc.no/ddd/definition_and_general_considera

standardization in terms of sales volumes. Since we do not assume that these measures are actual utilization rates, which strongly vary from one patient to another, normalizing total drug sales into how many days of average treatment were sold, is reasonable. Due to large variations in the total sales volumes the natural logarithm of sales is used in the regression model. This smoothes the numbers and also makes the interpretation of the coefficients more convenient, since it gives the semi-elasticities. Percentage changes are a lot more intuitive measure than treatment days sold.

Drug classes

The definition of drug classes is crucial to the study, and was given a lot of thought. Due to limits in time, a criterion that would require a hand by hand selection of drug classes was not viable, and would further require the detailed knowledge of pharmaceutical experts. Further, we found that many definitions of drug classes were too restrictive, because they only included strictly similar drugs with strictly the same indication and way of functioning. However, the aim here was to find a less restrictive definition, and to allow me-too drugs to vary in things such as additional indications or less side effects through a different way of functioning. The main criterion chosen is, that a class of drugs treats the same condition, *i.e.* that they have the same main indication. How can one define therapeutically equivalent pharmaceuticals of from a large database by a simple criterion? We chose to use the ATC Code, which is a code with five levels, which defines a medicament down to its molecule. Tables 4.1 and 4.2 give an overview of the ATC codification. The first level indicates the anatomical main group, down to the fifth level that defines the chemical substance, *i.e.* the molecule. The fourth level defines the therapeutic or chemical subgroup. It is therefore this fourth level of the ATC code we use to define our therapeutic classes, which we call ATC4 from there onwards.

Table 4.1: ATC Code with its 5 levels

Level	**Definition**	**Example**	
1	Anatomical main group	A	Alimentary tract and metabolism
2	Therapeutic main group	A10	Drugs used in diabetes
3	Therap./Pharmacol. subgroup	A10B	Blood glucose lowering drugs, excl. insulin
4	Therap./ Chemical subgroup	A10BA	Biguanides
5	Chemical substance	A10BA02	Metformin

The ATC code is based on the main indication of a drug, in case there are multiple uses for it. It therefore fits the requirements of our class definition. ATC4 is the most narrow subgroup before the molecule, and drugs at this level can be assumed to be therapeutically very similar. The German federal ministry of health actually exactly uses

TABLE 4.2: 14 anatomical main groups

Level 1 Code	Contents
A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito-urinary system and sex hormones
H	Systemic hormonal preparations, excluding sex hormones and insulins
J	Antiinfectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	Antiparasitic products, insecticides and repellents
R	Respiratory system
S	Sensory organs
V	Various

the ATC4 to define their Jumbo-Reference groups[2]. Again the WHO warns again that "substances in the same ATC 4th level cannot be considered pharmacotherapeutically equivalent, since their mode of action, therapeutic effect, drug interactions and adverse drug reaction profile may differ". However, this is not a problem for the definition of a drug class used throughout this study. Our required characteristic is that the drugs inside the class are made to treat the same condition. The fact that they differ in their dosage and adverse affects, does not pose a problem *per se*. Also, we are interested in a drug's main indications, which are exactly used for their ATC classification. If a drug has an additional use, it is likely to be reflected in its reimbursement and price characteristics, which we control for. A paper on the Swedish drug market by Mihaescu & Rudholm (2013) uses a spatial Durbin model in order to determine at which ATC level pharmaceutical products are in competition with one another, by determining the effect of price changes on quantity sold of own and competing products. They find that of course, the closest substitutes at the molecule level are in biggest competition with one another, but that also as of the 3rd ATC level, pharmaceuticals were in competition with one another. At ATC4 level products are clearly in competition with one another. The authors conclude that studies only focusing on the molecule and generic market were not taking into account the whole picture of product competition between drugs. We can be confident that the same is true for France, since ATC levels are an international classification and it is unlikely that the demand drastically differs between Sweden and France. The ATC fourth level therapeutic or chemical subgroup is the "relevant market" for the interest in our study. Some selection on the basis of the ATC level was done, and various groups were excluded from the study. Obviously, any drug without an ATC

[2] https://ppri.goeg.at/Downloads/Presentations/07_DE_Festbetragssystem.pdf

Code was dropped from the database, as well as the entire anatomic class starting by "V" for Various, because this group is a very heterogeneous group of pharmaceuticals that could not be clearly classed.

Molecules and entering drugs

Molecules are the smallest unit of pharmaceuticals in our analysis. The molecule is defined by the ATC5 code, in other words the full length ATC code. Under one ATC code usually there are numerous presentations on the CIP level. Depending on whether there are already generic drugs available for a medicament, there will be all the different generics and its presentations united under one ATC5 code. As in this study we are merely interested in the entry of new molecules into a drug, *i.e.* new me-too drugs that potentially have their own patents, this allows to easily regroup such molecules. The fact that the ultimate data base is one of monthly class volumes meant, that the database had to be collapsed several times. At the CIP level, the 'oldest' CIP representation of a molecule had to be identified and its entry date determined. Also the exit dates were defined, which is the case when an entire molecule at ATC5 level ceases to exist, meaning that there are no sales volumes for the entirety of the remaining data set for this molecule. Then, the data set was collapsed to the molecule level, so that it could be determined, how many molecules were in a class at a point in time, and when and how many enter and exit from a class there were. Finally, the data set was again collapsed to give monthly class data.

Entry

Zntry is the "treatment" variable, to speak in terms of a difference-in-difference framework. To a certain extent, this study is a difference-in-difference regression on the impact of entry on total sales volumes. Entry however is a "treatment intensity', because it takes the value of how many molecules enter or exit. Except for one case, only ever one molecule enters at a time in a month into a class. The variable gives the net entries, i.e. the net of entries and exits into a class. This means that if one molecule enters and one exits at the same time, net entry will still give zero (although such cases are rather rare in the monthly data set). It is an instantaneous variable that only indicates the entering drug at the point in time where the molecule first shows sales volumes. Because we want to account for the fact that the effect of a market entry is not instantaneous, we lag the variable up to 12 month, so that we have a total of 13 month effects. In line with the main interest of our study, entry excludes the "creation" of classes, meaning that entry does not count if it is the first molecule in a class, because this is by definition the first-in-class and not a me-too drug. Table 4.3 shows how many entries and exits there are summed over the years in our dataset. We also include a dummy variables for

strictly positive netentry, meaning only if an actual entry occurs and interact it and the twelve lags with number of molecules in a class.

Number of molecules in class

This variable indicates the number of molecules in a class at time t. Because it would double the effect of entry, number of molecules in class only appear as an interaction with a positive entry dummy and its 12 lags, in order to identify the effect different numbers of molecules have when a drug enters. In the next section of identification strategy, we demonstrate that this allows to identify different levels of number of molecules in class, so that the effect if different when a second or a fifth me-too drug enters into a class. Table 4.4 tabulates the frequencies with which different amounts of molecules in a class are represented. The majority of times this is 1 molecule in a class (40%), up to one eleven molecules.This table represent the number in class variable at any point in time for all classes.

TABLE 4.3: Number of entries by year

Year	Netentries	Entries	Exits
1998	0	0	0
1999	14	16	2
2000	14	16	2
2001	7	14	7
2002	3	14	11
2003	2	7	5
2004	8	13	5
2005	8	15	7
2006	-6	8	14
2007	3	12	9
2008	11	17	6
2009	0	12	12
2010	9	13	4
2011	0	6	6
2012	11	26	15
2013	-2	3	5

Class characteristics

In the regression, time varying characteristics of the drug classes are controlled for. As classes are the cross sectional unit in the panel , we can only consider class averages. The two characteristics which change sufficiently over time, in order not to be absorbed by fixed effects are average prices and the average reimbursement rate. Prices are converted to price per defined daily dosis, meaning that the price of a box is divided by the number of days of treatment it contains. Reimbursement rate is just an unadjusted average of the average reimbursement rate in the class.

TABLE 4.4: **Number of molecules in one class**

Number	Frequency	Per cent
0	8,220	26
1	12,218	39
2	5,251	17
3	2,804	9
4	1,240	4
5	724	2
6	470	2
7	72	0
8	58	0
9	3	0
10	14	0
11	30	0

Entering molecule characteristics

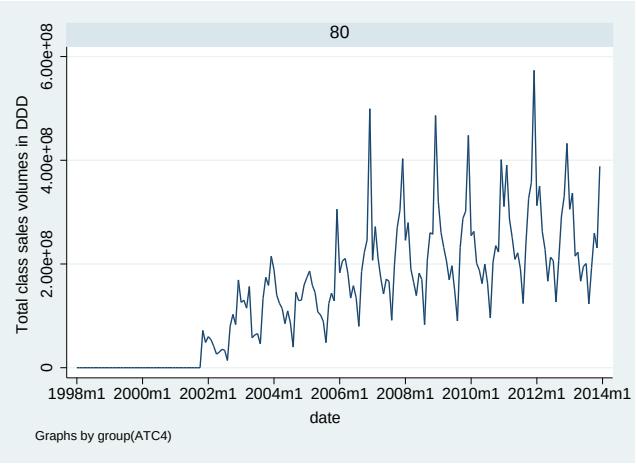
Other than controlling for characteristics of the class, which are merely class averages, we also control for the characteristic of the molecule that enters. The characteristics of the molecules that enter only "show up" at the time the molecule enters, meaning when its first sales volumes are listed. The characteristics are price difference, reimbursement rate, ASMR and SMR. In the rare case when two molecules enter simultaneously, averages are taken. The price difference is difference in cost per defined daily dosis, as defined in the class characteristics between the entering drug and the class average.

Further controls

Moreover, we control for time fixed effects and monthly seasonality. The time fixed effects take the form of year dummies, for each year from 1999 to 2013. We also include monthly variables to control for seasonal effects , by which drug sales are strongly effected, in particular the more common prescription drugs such as antibiotics against strong flues. Figure 4.1 below shows how seasonally varying total volumes for a common antibiotic class are.

Moreover, as we explain below, we control for individual class fixed effects, since a fixed effects panel model is used in the regression. Furthermore, in a second step we add a crisis dummy and interact it with the class and entering drug characteristics. The crisis dummy takes the value of 1 for all month after January 2008. With this, we aim to test whether the recent financial crisis had an impact on how total sales volumes react to drugs with different characteristics, for example with lesser reimbursement rates. Moreover, as a robustness test, lead values of net entry are included in a regression. By including lead variables of entry, we want to ensure, that there are no "anticipatory effects" of a change in volumes. It could also indicate that the observed changes in sales

FIGURE 4.1: Total volumes of class "Combinations of penicillins, incl. beta-lactamase inhibitors"



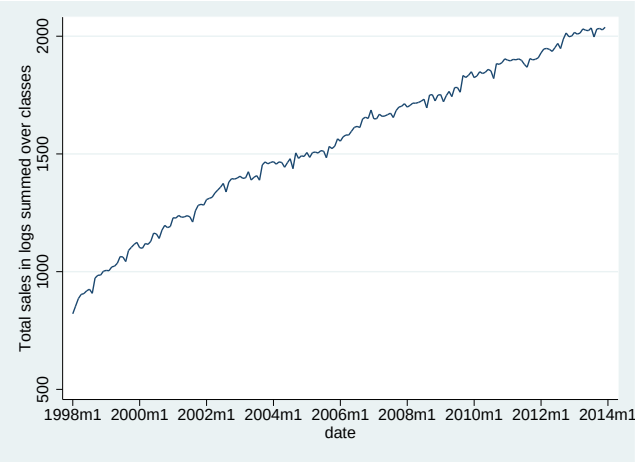
volumes were potentially caused by something else than the entry of the me-too. This method to test for the endogeneity of the "treatment" is used by Autor (2003), who uses it to ensure that there were no anticipatory changes in behaviour before the change of a law.

Below we show some additional graphs describing the evolution of numbers of molecules in class and total volumes sold.

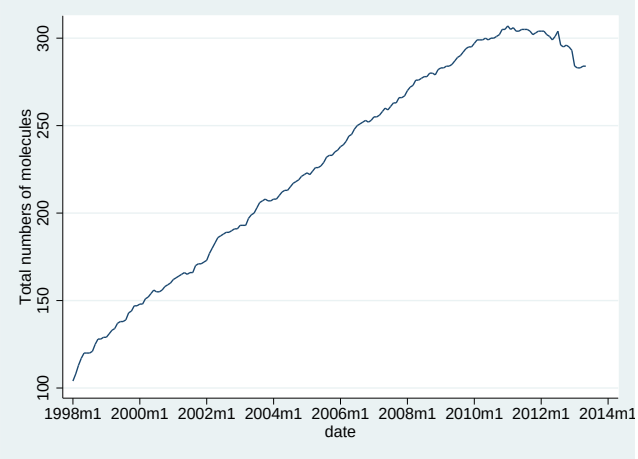
As can be seen in figures 4.3(a) and 4.3(b), the general trend in volumes in slightly upwards sloping, but not as much as the aggregate numbers of molecules in classes. The number of molecules in classes seems to ascend steeply and come to a maximum mid 2012. This must be a particular bias of the selected sample, possibly because of many old classes which slowly "die out" after over 16 years on the market, while maybe the data captures less new class creations. It may also be the case, that exits are wrongly attributed to molecules towards the end of the timeline, since exit is defined when a molecule does not show any more sales for the remaining time. This attributes exit faster towards the end, then at the beginning.

Figures in 4.3 illustrate the case of a classe, in which the entry of a second drug into the class extremely spikes the sales volumes, and which remain high, when one of them leaves the market (with some minor drops). Figure 4.4 on the other hand shows the example of a class with relatively many molecules, in which volumes increase rather smoothly but continuously, and then drop change considerable, with the same number of molecules present. The impacts of the 3 entries cannot be observed as directly as in the previous example. Of course these are but two examples of classes of a total of 162 classes, and each behaves very differently. More examples are shown in Appendix A.

FIGURE 4.2: Volumes and numbers of molecules over all classes



(a) Aggregate volumes over classes



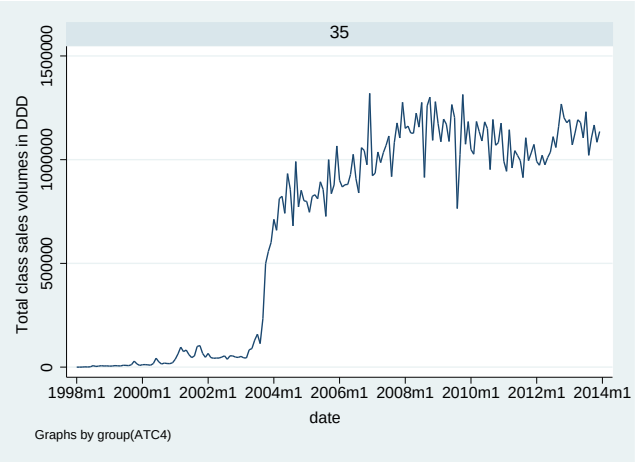
(b) Aggregate numbers of molecules

4.2 Identification strategy

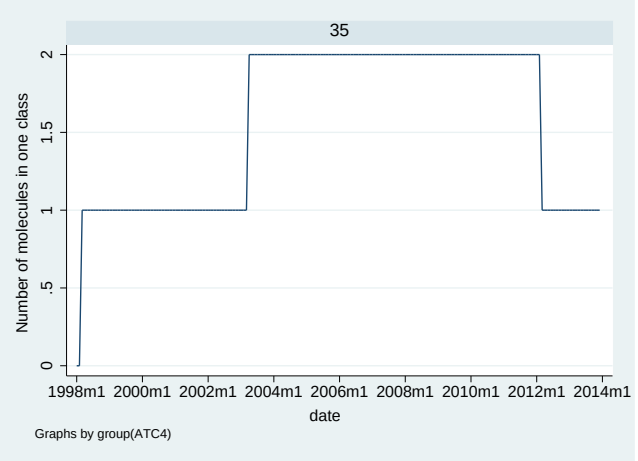
This section shall explain the regression model and identification strategy employed in the study. As mentioned above, the data is monthly data from January 1998 to December 2013 and the dependent variable are log total sales volumes in a class in defined daily dosis. The estimated regression model is the following:

$$y_{it} = \alpha_i + \gamma_t + \gamma_m + \sum_{\tau=0}^{12}[\delta_\tau \mathrm{e}_{it-\tau}] + \sum_{\tau=0}^{12}[\beta_\tau \mathbb{1}_{(\text{if net entry in t}-\tau)} * \mathrm{n}_{it}] + \theta_1 \overline{X}_{it} + \theta_2 X_{jt} + \epsilon_{it} \tag{4.1}$$

FIGURE 4.3: Example: Class 35 evolution



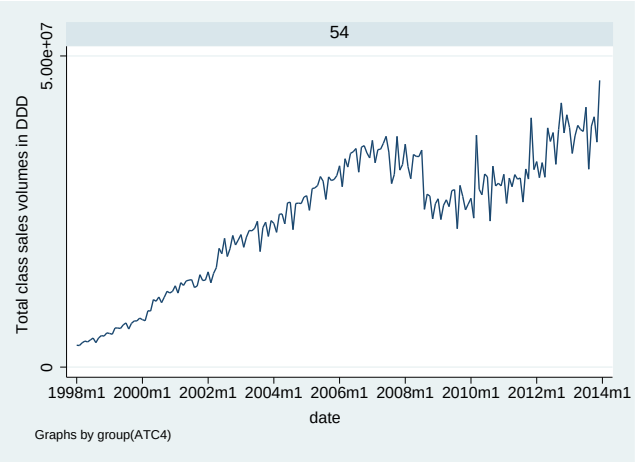
(a) Volumes in class 35



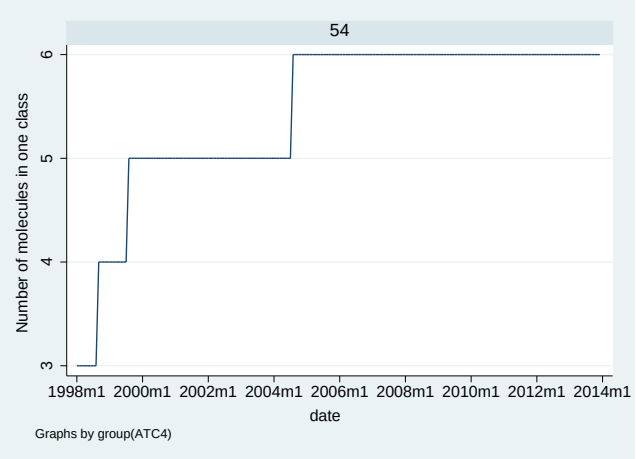
(b) Number of molecules in class 35

where α_i are the individual class effect, γ_t are year fixed effects, γ_m are monthly fixed effects, n_{it} are the number of molecules in class, $e_{i\tau}$ the entry variable, indicating how many variables entered or exited the class, which mostly takes the value of -1 for one exit or 1 one for entry. Entry is lagged up to twelve month. $\mathbb{1}_{(\text{net entry in t}-\tau)}$ an indicator function which is equal to one if there was a net entry at time t. This is equally lagged, where τ is the length of the lag, up to twelve month. The next term is the interaction with the entry indicator and its lags with the number in class variable. $\overline{X}_{it}$ are average class variables and X_{jt} are the entering drug's j characteristics. ϵ_{it} is the error term, which is clustered on class level, in order to exclude problem of serial correlation, within classes. Clustering the errors on class level, means that the errors are allowed to be correlated within classes, but are independent across classes. A fixed effects estimator is used, meaning that we only take into account the deviations from the means that vary with time. The fixed effect estimator only takes into account the variation within the individual unit, which erases the class fixed effects. For this fixed effects estimator

FIGURE 4.4: Evolution of class 54



(a) Volumes in class 54



(b) Number of molecules in class 54

to be unbiased and efficient, the class fixed effects need not be orthogonal with the explanatory variables (Wooldridge 2002). It seems very unlikely, that the characteristics of the classes are uncorrelated with the class fixed effects. Conducting the Hausman test, indeed we reject the H_0 of no systematic difference in the coefficients, i.e. that a random effects model would be more efficient, is rejected. The fixed effects estimator also makes sense from a conceptual perspective in line with the interest of the study. It would be nonsensical to compare the classes between each other, we merely care about what happens within a classes in response to a me-too entry. As the classes are extremely heterogeneous, the fixed effects solve a large part of possible omitted variable bias.

The interaction of numbers of molecules in a class with the entry indicator and lagged entry indicator up to twelve month allows to identify the impact of varying numbers of molecules in the class at different points in time. The following example shall serve to illustrate, of how thank to this specification, the counterfactual is identified, *i.e.* the

case when there was no entry. Let us suppose there is a class i, with four molecules present. In 2005, there are two entries of molecules, one in January, one in September. We want to evaluate the impact of the last entry of September, in November 2005. At this point, there are six molecules in the class. That means we have :

$$\begin{aligned} y_{it} = \alpha_i + \gamma_{2005} + \gamma_{Nov} + \delta_{t-2} + \delta_{t-11} + \\ 6 * \beta_{t-2} + 6 * \beta_{t-11} + \overline{X}_{it} + X_{jt} + \epsilon_{it} \end{aligned} \tag{4.2}$$

The counterfactual situation, without the last entry in September would give:

$$y_{it} = \alpha_i + \gamma_{2005} + \gamma_{Nov} + \delta_{t-11} + 5 * \beta_{t-11} + \overline{X}_{it} + X_{jt} + \epsilon_{it} \tag{4.3}$$

Subtracting the second from the first and neglegting for now the impact of different characteristics, this leaves with us with the causal effect of the last entry of $\Delta = \delta_{t-2} + 6 * \beta_{t-2} + \beta_{t-11}$. Therefore, the impact of the numbers of molecules in the class is identifiable, even at a time after the event of entry. This helps to contribute in explaining the variation in volumes, because we hypothesize that later entries have different impacts than earlier entries. The Δ in this example therefore gives us the total impact of the entry of a molecule two month ago, which now has 6 molecules in the class, and which already had an entry 11 month prior to the time at evaluation. Taking into account the number of molecules in the class as well as entry itself is crucial, because the effect of entry in not the same if a molecule enters second in class as when it enters seventh in class. We thereby control for that fact.

If we were interested in the immediate effect of an entry and assume that there was no entry in the twelve month before, the effect of the entry is given by the addition of the coefficients δ_{it} and $\beta_{it} * n_{it}$. Since entry indicates only entries as of the second drug that enter, the minimum effect of $\delta_{it} + \beta_{it} * 2$, with a greater (or smaller impact depending on the sign of β_{it}) for each additional molecule in a class. n_{it} is the number of molecules in the class once the new drug has entered.

5

Results and Discussion

5.1 The Results

We shall now turn to the presentation and discussion of the regression results. The most basic regression is presented in Table 5.1 model (1): Here the natural logarithm of total volumes is simply regressed on the entry variable, and all its lagged effects, controlling for year, class and month fixed effects. The model suggests that as such, the entry of a me-too drug, meaning the entry as of the second drug in a class, has an instantaneous impact on total sales of increasing them by 93%, other things being equal. All coefficients are highly significant, including almost all year and monthly effects. The monthly effects are indeed strongest on sales volumes during the fourth quarter of the year, the typical time when people tend to get sick. Strikingly in this specification, the coefficients of the lags increase with the length of the lag. Clearly, this specification cannot be correct, because it omits many variables, such as the fact that it must make a difference whether a molecule enters as the second or fifth molecule. A later entrant faces greater competitive pressure and is not as likely to create its own market. It also appears very implausible, that the twelve month lagged effect of an entry be 30 percentage points larger than the immediate effect. We therefore augment the model by taking into account the number of medicaments in a class. The second specification in model (2) Table 5.1, already comes very close to our "final" and best model in terms of coefficient magnitude, sign and significance. Here, the immediate impact of an entry at time t is the coefficient of entry, plus the coefficient of the entry dummy multiplied by the number of molecules now in the class. As the minimum number of molecules in class which is captured by the coefficient of the entry and number interacted term is two, given that entry of first-in-class drugs is by definition excluded, the coefficient of $\mathbb{1}_{(\text{entry at t})}$*$n_{it}$ has to be at least doubled. This means, that the maximum effect of a me-too entry in this specification

TABLE 5.1: Regression Results without characteristics

dep var: ln(vol)	(1)		(2)	
	Coef.	p-value	Coef.	p-value
$\text{entry}_{i,t}$	.936	.000	2.435	.000
$\mathbb{1}_{(\text{entry at t})}$*$\text{n}_{it}$			–.449	.002
$\text{entry}_{i,t-1}$	1.078	.000	1.206	.000
$\text{entry}_{i,t-2}$	1.158	.000	1.235	.000
$\text{entry}_{i,t-3}$	1.191	.000	1.321	.000
$\text{entry}_{i,t-4}$	1.169	.000	1.285	.000
$\text{entry}_{i,t-5}$	1.132	.000	1.277	.000
$\text{entry}_{i,t-6}$	1.111	.000	1.244	.000
$\text{entry}_{i,t-7}$	1.125	.000	1.310	.000
$\text{entry}_{i,t-8}$	1.189	.000	1.371	.000
$\text{entry}_{i,t-9}$	1.228	.000	1.419	.000
$\text{entry}_{i,t-10}$	1.266	.000	1.488	.000
$\text{entry}_{i,t-11}$	1.231	.000	1.407	.000
$\text{entry}_{i,t-12}$	1.238	.000	1.486	.000
$\mathbb{1}_{(\text{entry at t-1})}$*$\text{n}_{it}$			–.079	.253
$\mathbb{1}_{(\text{entry at t-2})}$*$\text{n}_{it}$			–.058	.432
$\mathbb{1}_{(\text{entry at t-3})}$*$\text{n}_{it}$			–.085	.260
$\mathbb{1}_{(\text{entry at t-4})}$*$\text{n}_{it}$			–.085	.243
$\mathbb{1}_{(\text{entry at t-5})}$*$\text{n}_{it}$			–.086	.235
$\mathbb{1}_{(\text{entry at t-6})}$*$\text{n}_{it}$			–.091	.204
$\mathbb{1}_{(\text{entry at t-7})}$*$\text{n}_{it}$			–.109	.125
$\mathbb{1}_{(\text{entry at t-8})}$*$\text{n}_{it}$			–.117	.120
$\mathbb{1}_{(\text{entry at t-9})}$*$\text{n}_{it}$			–.122	.112
$\mathbb{1}_{(\text{entry at t-10})}$*$\text{n}_{it}$			–.145	.048
$\mathbb{1}_{(\text{entry at t-11})}$*$\text{n}_{it}$			–.115	.129
$\mathbb{1}_{(\text{entry at t-12})}$*$\text{n}_{it}$			–.139	.086
Year fixed effects	Yes		Yes	
Class fixed effects	Yes		Yes	
Month fixed effects	Yes		Yes	
Adj. R^2	.241		.242	
No. of cases	31104		31104	
σ_u	5.059		5.068	
σ_e	3.615		3.614	
ρ	.662		.663	

is suggested to be 154%, which is the case when a class goes from one to two drugs, meaning when the first me-too drug enters: $2.435 + [2 * (-0.449)] = 1.537$.

While this looks like a very large increase indeed, it does not seem unthinkable that doubling the number of molecules sold in a drug class from one to two, would more than double total volumes sold. With the entry of the third molecule, the aggregate impact

of entry is 109%, with the fourth molecule it is 63%, with the fifth molecule merely 19% and as of the entry of the 6th molecule the impact is zero or negative. While of course the first four me-too entries (*i.e.* up to the fifth entry in total) increase the total volumes very strongly with fading impact, the impact does fade completely as of the fifth me-too drug. One can say, that is the point at which the market is saturated with follow-on drugs and where a new entry does not create its own market and at best redistributes the existing market shares. The Adjusted- R^2 indicates, that this model explains a slightly larger share of all variation in total volumes than the first model, namely 24%, despite 13 added variables or less degrees of freedom. The lags of entry and the lags of the interaction of entry and number of molecules in the class still indicate an unintuitive pattern of increasing impact. According to this model, the impact is larger for the twelfth lag than for the first one for both set of lagged variables.

We therefore turn to the subsequent specification – results of which are represented in table 5.2 model (3). This specification includes the time varying average characteristics of classes, namely the average reimbursement rate and the price of a defined daily dosis. The impact of a new molecule in a class diminishes a lot faster in this model with increasing numbers of drugs already in the drug class. While the first me-too drug increases volumes by 119% $(2.321 - (2 * -0.564) = 1.193)$, the third one already only increases total volumes by 6.7%, other things being equal. If this model is true, the market is saturated by the before fourth me-too drug enters. The behaviour of the lags is more meaningful in this specification. The coefficients decrease in size and significance almost continuously, the greater the lag becomes. Four month after the entry of a first me-too drug, volumes are "only" 23.% higher than they would be in the counterfactual case with only one molecule in class. However it should be noted as of the fourth lag, the coefficients on lagged entry cease to be significant. This can be explained by the fact that at this point, the potential counterfactual, becomes very hard to track back, meaning how average volumes would have developed if there had not been an entry five month prior. The actual impacts of the two characteristics can be interpreted as follow. The larger the average reimbursement rate, the larger the volumes on average: more precisely, all other things being equal, increasing the average reimbursement rate by one percentage point, would increase total class volumes by 1.7%. The impact of average defined daily treatment cost is very small and not significant on the other hand.

Let us finally turn to the "preferred" specification in model (4) Table 5.2, which implements exactly what the regression equation in 4.1 the identification strategy section describes. This is the full model, including both average class characteristics and entering molecule characteristics. As the characteristics of entrant drugs now tell part of the story, the effect of an entry is composed of even more elements. The impact of the difference in price of defined daily dosis is extremely small, though significantly positive. This

TABLE 5.2: Regression results including characteristics

dep var: ln(vol)	(3)		(4)	
	Coef.	p-value	Coef.	p-value
$\text{entry}_{i,t}$	2.321	.000	2.713	.000
$\mathbb{1}_{(\text{entry at t})}$*$\text{n}_{it}$	–.564	.001	–.557	.001
$\text{entry}_{i,t-1}$	.653	.015	.633	.017
$\text{entry}_{i,t-2}$	.554	.031	.551	.034
$\text{entry}_{i,t-3}$	.527	.036	.533	.035
$\text{entry}_{i,t-4}$	.415	.080	.407	.087
$\text{entry}_{i,t-5}$	.293	.125	.287	.133
$\text{entry}_{i,t-6}$	.237	.217	.226	.238
$\text{entry}_{i,t-7}$	.191	.301	.198	.285
$\text{entry}_{i,t-8}$	.156	.403	.159	.396
$\text{entry}_{i,t-9}$	.149	.422	.140	.454
$\text{entry}_{i,t-10}$	.061	.687	.058	.709
$\text{entry}_{i,t-11}$	–.238	.036	–.258	.028
$\text{entry}_{i,t-12}$	–.165	.187	–.188	.136
$\mathbb{1}_{(\text{entry at t-1})}$*$\text{n}_{it}$	–.109	.209	–.111	.198
$\mathbb{1}_{(\text{entry at t-2})}$*$\text{n}_{it}$	–.064	.436	–.064	.447
$\mathbb{1}_{(\text{entry at t-3})}$*$\text{n}_{it}$	–.054	.488	–.056	.467
$\mathbb{1}_{(\text{entry at t-4})}$*$\text{n}_{it}$	–.028	.709	–.032	.669
$\mathbb{1}_{(\text{entry at t-5})}$*$\text{n}_{it}$	.002	.974	.000	.999
$\mathbb{1}_{(\text{entry at t-6})}$*$\text{n}_{it}$	.007	.921	.008	.907
$\mathbb{1}_{(\text{entry at t-7})}$*$\text{n}_{it}$	.018	.783	.012	.863
$\mathbb{1}_{(\text{entry at t-8})}$*$\text{n}_{it}$	.034	.611	.034	.610
$\mathbb{1}_{(\text{entry at t-9})}$*$\text{n}_{it}$	.044	.502	.043	.513
$\mathbb{1}_{(\text{entry at t-10})}$*$\text{n}_{it}$	.066	.250	.066	.256
$\mathbb{1}_{(\text{entry at t-11})}$*$\text{n}_{it}$	.142	.007	.148	.006
$\mathbb{1}_{(\text{entry at t-12})}$*$\text{n}_{it}$	.125	.016	.145	.006
$\overline{\text{reimbrate}}$	.017	.063	.016	.065
$\overline{\text{price}}$	–.000	.135	–.000	.131
SMR-entrant			–.127	.246
ASMR-entrant			–.105	.124
reimb-entrant			–.010	.003
price-diff			.001	.000
Year fixed effects	Yes		Yes	
Class fixed effects	Yes		Yes	
Month fixed effects	Yes		Yes	
Adj. R^2	.117		.121	
No. of cases	20750		20750	
σ_u	3.762		3.757	
σ_e	1.485		1.482	
ρ	.865		.865	

suggests that *ceteris paribus* and average other entry characteristics, the more expensive the new drug, the more it is able to create its own demand. This is in line with the negative sign of ASMR entrant, which after all is the main determinant for price. The composite total effect of a me-too entry can be obtained as follows: Let us assume that the entrant is the first me-too, i.e. it is the second molecule in class, and that further this drug has the following characteristics: the reimbursement rate is 35%, the SMR is 3 and the ASMR is 5- meaning that this drug is a "real" me-too according to the more restrictive definitions, since it holds no innovation compared to the other drug. This drug has the total effect of: $2.713-(2*0.557)-(35*0.01+3*0.127+5*0.105)=0.343$. The first me-too drug in a class with the given characteristics will increase total volumes by 34.3%. The second me-too on the other hand, if it has the same characteristics, not increase total volumes anymore. Supposing that the impact is unlikely to be negative, as the coefficient for three molecules would strictly speaking suggest, we can assume that it just does not increase total volumes. By using the full specification, the impact of me-too entry gets relativised through its characteristics. As it was expected, a more innovative drug with a lower ASMR, for example one or two, will increase total volumes more than an ASMR 5. More precisely, a first entrant with the same characteristics as the above example but with an ASMR of 4, will increase total volumes by 44.8%, with ASMR3 55.3% and ASMR 2 65.8%. Moreover, other things being equal, the impact gets diminished by 10%, for each level of lower innovation in an incoming me-too.

In a next step, the impact of the recent financial or solvency crisis is being analysed. There is reason to believe, that the crisis would cause a structural break in the data, in the way total volumes react to certain characteristics. Even though private drug expenditure is likely to be highly elastic, the purchasing and stocking behaviour of pharmacists may have changed after 2008, to minimize financial risk. In order to test for a structural break in the data, we include interactions of a crisis dummy with the six characteristics average price, price difference, average reimbursement rate, ASMR and SMR of entrants, as well as the characteristics on their own. Subsequently, the coefficients are tested for equality, with the $H_0 : crise * x - x = 0$, where x is the characteristic, and crise is the crisis dummy. The p-value of all tests for structural breaks, *i.e.* for parameter equality, are reported at the bottom of Table 5.3. The results suggest, that the there is a significant difference between the crisis interacted variables and the normal variables for the average price, the price difference and SMR of the entering drug, while the remaining coefficients are not significantly different from one another. Curiously, despite the very small impact, the sign of the two price variables is inverse when interacted with crisis, from negative to positive: This implied that greater average prices as well as entry prices now tend to lead to a higher over impact of an entry on sales volumes. A possible explanation for this phenomenon could be, that given

Table 5.3: Crisis structural break

dep var: ln(vol)	(5)	
	Coef.	p-value
$\text{entry}_{i,t}$	2.39	.000
$\mathbb{1}_{(\text{entry at t})}$*$\text{n}_{it}$	-.492	.049
$\text{entry}_{i,t-1}$	.248	.064
$\text{entry}_{i,t-2}$	.250	.059
$\text{entry}_{i,t-3}$	.186	.163
$\text{entry}_{i,t-4}$	.150	.235
$\text{entry}_{i,t-5}$	.128	.277
$\text{entry}_{i,t-6}$	.102	.388
$\text{entry}_{i,t-7}$	.058	.609
$\text{entry}_{i,t-8}$	.072	.541
$\text{entry}_{i,t-9}$	.076	.504
$\text{entry}_{i,t-10}$	.027	.779
$\text{entry}_{i,t-11}$	–.192	.103
$\text{entry}_{i,t-12}$	–.206	.137
crise*price	.000	.000
crisep*pricediff	.003	.028
crise*reimbrate	.009	.220
crise*reimb-entrant	–.004	.409
crise*ASMRentrant	–.121	.227
crise*SMRentrant	.721	.001
price	–.000	.000
price-diff	–.000	.000
reimbrate	.008	.355
reimb-entrant	–.008	.059
SMR-entrant	–.366	.020
ASMR-entrant	–.074	.285
test price crise		.000
test pricediff crise		.014
test reimb crise		.954
test reimb-entrandt crise		.705
test ASMR-entrant crise		.746
test SMR-entrant crise		.002

the crisis, people are now prepared to only spend money on “high quality” drugs and innovative drugs, for which they use price as a proxy. In other words, the requirements of for new drugs have increased since 2008, if they want to create their own demand.

When one analyses market entry in which ever industry, one has to take into account the possibility that entry in itself is not exogenous, meaning that it cannot be seen as a “random treatment”. This would be the case if the timing of entry was anticipated, so that the drug enters just in a moment when there is a general upward trend for a drug

class for example. Another possibility would be that the competitor drugs change their sales strategy, knowing that a market entry is about to occur, and that in fact that is the reason why sales volumes increase. In order to rule out the possibility of such effects, we include twelve month leads to net entry in the regression, in addition to the lags. We borrow this strategy from Autor (2003), who includes "placebo" treatment variables, in order to see, whether they are significant. The author includes lead dummies of his treatment variable, which indicated the change of a law. By doing this, he wants to exclude the possibility, that people changed their behaviour in anticipation of the change, instead of after the law passed. We use the same technique and use lead entry dummies, to pretend "as if" there occurred an entry before the actual entry. Table 5.3 shows the results. We find, that all lead entry dummies are insignificant, up to the 9 month lead. These are however negative, hence if anything this would be an indication that the entering drug is being put on the market, because total class volumes are low nine month before. However, one has to bear in mind, that we are still dealing with mostly patented drugs here. They take around 15 years to develop and test, and even more if one adds the administrative process of approval, pricing, reimbursement determination and patenting. It is extremely unlikely, that a company can plan and anticipate this long process. It is more likely that a company would want to market a drug as quickly as possible regarding this long procedure, regardless of the sales in the other classes, 9 or 5 month before entry.

5.2 Discussion

Considering the results of our analysis, in particular those from the fully specified model in (4), we can conclude a number of things about me-too drugs. First of all, me-too drugs do undoubtedly increase total sold volumes of a class, when they are among the first me-to drugs to enter after the break-throug drug.

It is remarkable, that according to our estimates, a me-too drug without additional innovative value (ASMR=5) that enters a market, in which already one drug exists that treats the same condition, increases total volumes by 34.4%. It is remarkable for two reasons. First, this means that at equal reimbursement rates, the entry of a first me-too drug in a class will increase public expenditure, and all me-too drugs taken together, can therefore present a serious strain on the public health system. The other reason it is remarkable for, is that the entering me-too drug creates its own demand, on a market that was supposedly already served. This supports the hypothesis, that drug diversity allows to treat more people, because more people have access to a drug with an acceptable risk-benefit ratio to them. It must mean, that it serves an almost distinct

TABLE 5.4: Placebo Entry Testing with Lead Entry

dep var: ln(vol)	(6)	
	Coef.	p-value
$\text{entry}_{i,t-1}$	2.691	.000
$\mathbb{1}_{(\text{entry at t})}$*$\text{n}_{it}$	–.550	.001
$\text{entry}_{i,t-1}$	.482	.008
$\text{entry}_{i,t-2}$	.460	.010
$\text{entry}_{i,t-3}$	.449	.008
$\text{entry}_{i,t-4}$	.352	.024
$\text{entry}_{i,t-5}$	.288	.023
$\text{entry}_{i,t-6}$	.233	.070
$\text{entry}_{i,t-7}$	.206	.089
$\text{entry}_{i,t-8}$	.213	.082
$\text{entry}_{i,t-9}$	.201	.096
$\text{entry}_{i,t-10}$	.171	.095
$\text{entry}_{i,t-11}$	–.001	.993
$\text{entry}_{i,t-12}$	.081	.388
$\text{entry}_{i,t+1}$	–.026	.790
$\text{entry}_{i,t+2}$	.016	.896
$\text{entry}_{i,t+3}$	.039	.744
$\text{entry}_{i,t+4}$	–.006	.964
$\text{entry}_{i,t+5}$	.055	.698
$\text{entry}_{i,t+6}$	–.119	.210
$\text{entry}_{i,t+7}$	–.069	.543
$\text{entry}_{i,t+8}$	–.157	.119
$\text{entry}_{i,t+9}$	–.177	.020
$\text{entry}_{i,t+10}$	–.209	.006
$\text{entry}_{i,t+11}$	–.240	.003
$\text{entry}_{i,t+12}$	–.249	.003
$\overline{\text{reimbrate}}$	.017	.064
$\overline{\text{price}}$	–.000	.137
SMR-entrant	–.123	.262
ASMR-entrant	–.109	.120
reimb-entrant	–.010	.005
price diff	.000	.000
Adj. R^2	.121	
No. of cases	20750	
sigma-u	3.758	
sigma-e	1.482	
rho	.865	

patient pool, assuming that people do not take the break-through and the me-too at the same time. To evaluate the overall impact on the public health system, one would need to conduct a cost-benefit analysis of having the patients treated with the new available drug and the potential saved expenditures versus the cost of reimbursing this new drug. This would be a very interesting extension at this point.

On the other hand, the results also show, that the market in a drug class is on average very quickly saturated. With each additional number of molecules more in a class after entry, the impact becomes dramatically smaller. Depending on its characteristics, an entering drug will not increase total demand, if it is the second or third me-too drug to enter the class. After the third me-too drug at the latest, total volumes do not increase and the new drug either fails to create its own market, or redistributes the market shares of the existing drugs in a class. This fact has two implications. On the one hand, the direct competition may lead to total average price decreases in the class. On the other hand, this may strongly diminish profits of patented drugs, and in particular that of the first-in-class and breakthrough drug. This means, that the break-through drug does not get its full profit in reward for the initial innovation, which may have a discouraging effect on drug companies to invest in innovation. If drug companies know that after the introduction of a break-through drug five more me-too drugs can enter the market with whom they may have to share their profits, the incentive to invest in large blockbuster drugs becomes smaller. At the same time, the more innovative the break-through drug, the smaller are the chances that there are many imitations of me-too drugs in the pipelines of other companies already. The results also show, that the higher the level of innovation of a me-too drug compared to the existing drugs, the greater is its ability to increase total volumes. This means that, the market does reward incremental innovation, because not only do they increase total sold volumes, but also are they sold for higher prices according to Bergua et al. (2012). Of course it can be debated, whether the reward for very small additional innovations is too large, as the authors of the Irdes study suggest. However, as long as a me-too drug increases total volumes, it is an indication for the fact that there are now more treated people than before.

Of course our study has numerous limitations; and the exact magnitude of the coefficients should not be taken as definitive. The definition of our classes is very general, and it is possible that we include ATC4 groups, which cannot strictly be compared. For that matter, rerunning the estimates using the drug classes as defined for example by Bergua et al. (2012), who carefully consulted with a pharmacist and health practitioner for choosing each class, would be a useful extension. Another possibility to define classes would be to consult the catalogue of jumbo groups used for reference pricing in Germany for example: the jumbo groups are used as an extension to generic groups for drug

pricing, meaning that equivalent me-too drug prices are taken into account in the pricing decision of a new entering drug.

This limitation of a quite general definition of drug classes may lead to an overestimation of the impact of a new me-too drug. The true average impact of the first entering me-too drug is likely to be a lot smaller, but also more pertinent for later entering drugs, meaning it does likely not fade away as quickly with increasing numbers of molecules, as the estimates suggest.

From a conceptual perspective, the logical extension to this study would be to combine the approach used here and that used by Andrade (2012), who determined me-too drugs' ability to capture market shares. His findings are that the first entering me-too capture the largest market shares, and the later entrants facing increased competition, only obtain smaller shares. It would be interesting to combine the impact of changes of total volumes and the dynamics of how they are distributed within in the class itself.

6

Conclusion

In conclusion, the impact of a me-too drug on a class is ambiguous. The results from the fully specified model suggest, that a me-too drug that enters into a class where there is only the break-through on the market so far, increases total volumes by 34.4%, assuming it has an ASMR 5 and an SMR of 3. The second me-too drug with the same characteristics on the other hand, will not increase total volules anymore and merely repartition the existing market shares. There are many things to be said about this result. First, of course the impact of the first me-too drug is quite large. However, the fact that total volumes increase with the first me-too drug indicates, that the drug serves a distinct market, because it create some demand for itself, not just diminish the profits of the existing break-through drug. This means that the drug can treat a new distinct pool of patients, who may not have had adequate treatment available before. From a patient utility perspective, the increasing total class volumes is a good sign. On the other hand of course, it can pose a serious problem for the health insurance system, which reimburse those drugs, because their expenditure increase with total increasing volumes. However, it would have to further be determined, if it does not actually save money in the long run to have the adequate medicine available for a larger part of the population.

On the other hand, the results show, that indeed volumes do not rise with any arbitrarily large amount of added me-toos. Our estimates indicate, that the market is saturated as of the second or third me-too, depending on their characteristics. The consequence is, that increasing expenditures for the health insurance funds in terms of reimbursement are capped to a limited amounts of me-too entries. The possible "damage" caused by me-toos to the health insurers, is therefore limited. As of the second or third entry, total sale volumes do not increase, and so they do not pose a direct problem for the public health system, rather the market now benefits from higher diversity and price competition.

However, it is still likely that market shares between existing and incoming drugs are redistributed and therefore profits are shared between the incumbent and entering drugs. This is problematic, in that it potentially decreases the incentive for the pharmaceutical companies to invest in large innovations, because their patent is not protected against therapeutically similar drugs.

The issue of the best policy for me-too drugs largely comes down to the question who one wants to protect: the insurers, the insured, or the supplying companies. In terms of patient benefits, there is no doubt that a larger diversity of drugs is beneficial, because it increases the amounts of patients, for whom effective drugs are available. As Bardey, Jullien & Lozachmeur (2013) explains, it decreases the average disutility from side effects, because patients can find the treatment with the least adverse effects, when there is a larger diversity.

In terms of insurers, me-too drugs pose a problem, because they increase reimbursement expenditures for the same treatment, at least in the short term. To strictly protect insurers one could utilise several policies already used in other countries. In New Zealand for example, me-too drug reimbursement is strictly restricted to such drugs, whose price is systematically inferior to the existing drugs (Hollis 2004). Another possible policy is to adopt a pricing system, that includes me-too drug classes, as the German Federal Ministry of Health does. In a first step, they define drug classes, based on the ATC4 code, and then price new entering drugs by comparing them to the drug in those so called "Jumbo Groups" [1]. A classical reference pricing system would only take into account strictly chemically equivalent substances, and therefore mainly apply to generic entries.

If on the other hand one is interested in the protection of pharmaceutical companies in order to keep the incentive for innovation as high as possible (which ultimately serves the patients too), one could apply a policy as it is already applied in the United States for Orphan Drugs; drugs treating rare diseases which are extremely costly to develop. The US Orphan Drug Act states that during seven years, a drug has marketing exclusivity, and a "me-too Orphan Drug" will not be approved unless it presents substantial clinical benefits over the existing drug. A legislation of this type on me-too drugs is not unthinkable – drugs which are strictly superior would still be able to enter the market, while protecting the drug company's patent profits and keeping up the incentive to innovate.

The optimal policy of course would strike a balance between the three stakeholders and provide protection to patients, insurers and suppliers at the same time. To a certain extent, the regulative framework and the market forces already achieve this goal in

[1] https://ppri.goeg.at/Downloads/Presentations/07_DE_Festbetragssystem.pdf

France: treatment diversity is ensured, because there are no large restrictions on me-too drugs. The adverse impact for the insurance funds of rising volumes is capped to a limited amount of drugs, so that insurers do not need fear ever rising demand and reimbursement expenditures. Lastly, for the pharmaceutical companies, the first entrants in drug classes, still keep the largest market shares. This is because they capture the largest part of the market, and subsequent switching cost for patients are high. Therefore, the first few companies to win the race, will enjoy quite substantial profits.

Bibliography

Andrade, Luiz Flavio. 2012. "Entry Time Effects and Follow-on Drugs Competition." Irdes WP 49.

Autor, David. 2003. "Outsourcing at Will: The Contribution of Unjust Dismissal Doctrine to the Growth of Employment Outsourcing." *Journal of Labour Economics*, 21(1).

Bardey, David, Bruno Jullien, and Jean-Marie Lozachmeur. 2013. "Health Insurance and Diversity of Treatment: A Policy Mix Perspective."

Bergua, Cartier, Clant, Pichetti, Sermet, and Sorasith. 2012. "Comment expliquer les carts de prix des mdicaments similaires ? Une analyse en donnes de panel 2001-2009." *Questions d'conomie de la sant Irdes*, 178.

DiMasi, Joseph A., and Cherie Paquette. 2005. "The Economics of Follow-On Drug Research and Development: Trends in Entry Rates and the Timing of Development - The Authors' Reply." *PharmacoEconomics*, 23(12): 1193–1202.

Dixit, Avinash K, and Joseph E Stiglitz. 1977. "Monopolistic Competition and Optimum Product Diversity." *American Economic Review*, 67(3): 297–308.

Ekelund, Mats, and Björn Persson. 2003. "Pharmaceutical Pricing in a Regulated Market." *Review of Economics and Statistics*, 85(2): 298–306.

Hollis, Aidan. 2002. "The importance of being first: evidence from Canadian generic pharmaceuticals." *Health Economics*, 11(8): 723–734.

Hollis, Aidan. 2004. "Me-too drugs– Is there a problem?" WHO Report.

Lu, Z.J., and W.S. Comanor. 1998. "Strategic Pricing of New Pharmaceuticlas." *Review of Economics and Statistics*, 80(1): 108–118.

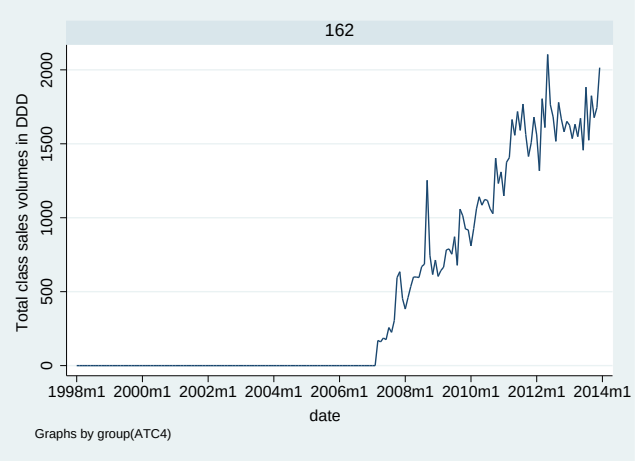
Mihaescu, Oana, and Niklas Rudholm. 2013. "Defining Relevant Product Markets for Pharmaceuticals." HUI Research HUI Working Papers 96.

Milne, Kaitin, and Ronchi. 2001. "Orphan drug laws in Europe and the US: incentives for the research and development of medicines for the diseases of poverty." Geneva: Commission on Macroeconomics and Health.

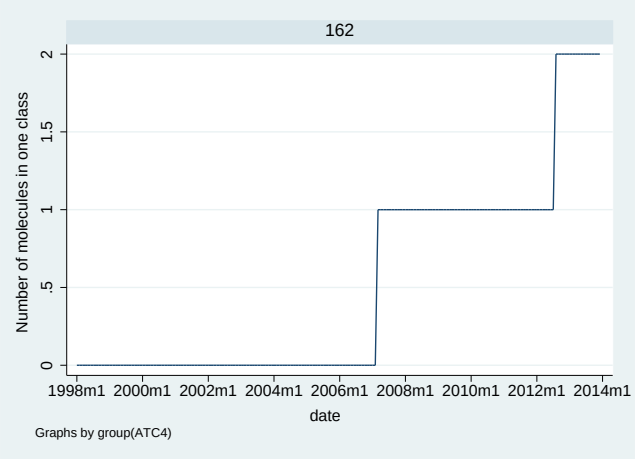
Wooldridge, J.M. 2002. *Econometric Analysis of Cross Section and Panel Data. Econometric Analysis of Cross Section and Panel Data*, MIT Press.

Appendix A: Additional Descriptive Statistics

FIGURE 1: Evolution of class 162

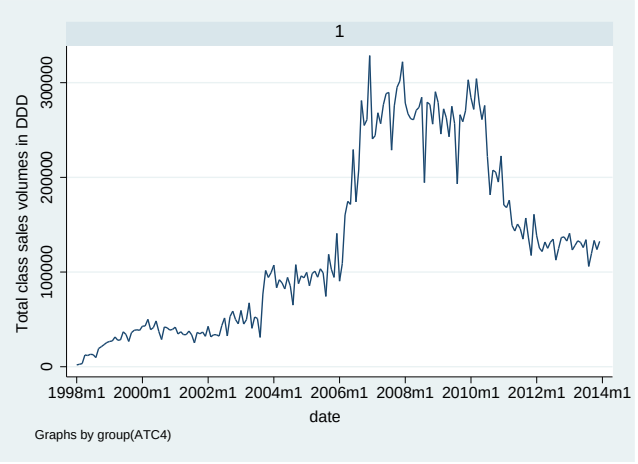


(a) Volumes in class 54

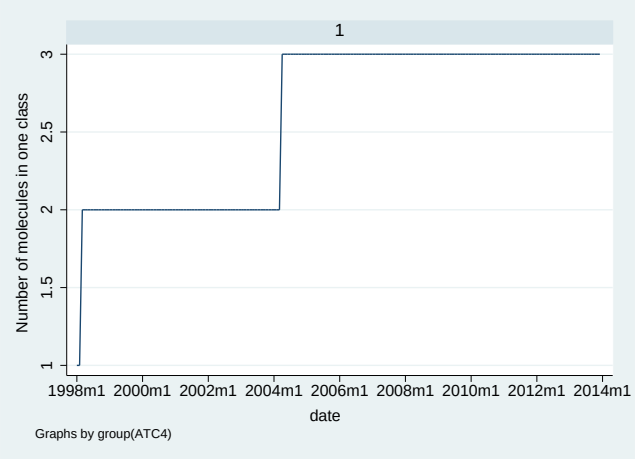


(b) Number of molecules in class 162

FIGURE 2: Evolution of class 1



(a) Volumes in class 1



(b) Number of molecules in class 1