Biosimilars entry and price development in Europe

Elena Dacheva

Erasmus University Rotterdam
The Netherlands

14th August 2015

Master's Graduation Thesis

International Economics

Abstract

In light of the increasing interest in pricing and entry of biosimilars in Europe, this research has found that the market of *filgrastim* biosimilars is dominated by the entry effect, while that of *epoetins* is driven by the competition effect. The *epoetins* market gets saturated relatively faster in terms of number of local competitors, which can be explained by the molecular complexity of that medicine. For both *filgrastim* and *epoetins*, the effect of biosimilar prices on originator prices is weak. This outcome is amplified by the impossibility of direct substitution for biosimilars in Europe.

1. Introduction

It is a prominent feature of the continuous evolution of science to search for more effective, comprehensive and neater solutions for all fields of human activity. That same zeal for improvement has included the search for more effective cures for ailments and diseases. Yet, while most innovations have been driven by forces favouring shrinkage in size, such as microchips, medicines for human use have surprisingly been moving in the opposite direction: towards increase in size.

The past several decades have seen the pharmaceutical industry make enormous leaps in research, discovery and development, with a particular development of complex biologic medicines. While the first drugs were based on chemical synthesis and represented small, compact pills, the formulations and production techniques of medicines have evolved enormously since then. The molecules which initially revolutionised medicine by providing treatment for some wide-spread diseases were relatively simple in terms of chemical components (Dranitsaris, 2011). Later on, however, with the advent of technical innovation, more efficient, intricate and precise devices were introduced in R&D labs across the developed world. This has allowed the pharmaceutical industry to enter an entirely new phase of its development – that of producing medicines based on living organisms, namely the so-called biologics. Typically, this type of medicines is capable of treating serious, life-threatening or degenerative diseases, such as cancer or multiple sclerosis, and are usually better absorbed by the human body. Thus, doctors and pharmacists have seen the drugs they provide to their patients grow in effectiveness, as well as in size and molecular weight.

While the benefits of all these innovations for patients and society at large are indisputable, the economic and financial considerations open up an arena for competition on part of manufacturers. The problems which define the commercial decisions of producers of biologic medicines are somewhat different from those of producers of simple chemical drugs. Some of the main concerns of biotech companies are how to price their products in a way which allows them to realise earnings (that account also for substantial return on investment), to be reinvested in new biologic medicines, and at the same time keep on providing the products at an affordable price to those who need them most.

Importantly, as soon as the patent on an originator biologic expires, the market is open to the so-called biosimilars, which represent a close approximation of the original molecule. In this sense, a parallel can be drawn with originator pharmaceutical drugs, which, once their patent protection has expired, are similarly exposed to competition by generic drugs. However, from an industry and societal perspective, given the high cost associated with biologics and biosimilars, the price behaviour of that

class of medicines is particularly relevant. In some cases, price erosion of biosimilars may reach up to 72%, as happened in Norway with an *infliximab* biosimilar (GaBI, 2015).

It is the subject of this study to explore exactly what may influence the pricing decisions of biotech and biosimilar companies and how the different local market considerations across Europe may play a role in this process. In order to evaluate the impact of the country-specific regulatory environment and the market access conditions in Europe, a sample of ten countries is considered: Bulgaria, France, Germany, Greece, Hungary, the Netherlands, Norway, Poland, and the UK. Although the biosimilars market has been receiving increasingly more attention, there are relatively few studies which explore the impact of a wide collection of non-numeric variables. What the present research aims to achieve is show how price erosion of biosimilar products cannot be solely ascribed to the number of local competitors as main determinants of price development. Researchers on the topic of biosimilars in Europe are unanimous in recognizing the diversity of regulatory structures (Roediger, 2015; Grabowski et al., 2014). Therefore, it is interesting to see which variables are most potent in determining the pricing decisions of biotech companies. The regulatory and market access environments in Europe are complex and constantly evolving. The purely regulatory elements involve discussions about risk-benefit analyses of new medicines and are typically conducted with regulatory agencies such as the European Medicines Agency (EMA). Market access, in turn, deals with multiple other tasks, and one of them is to achieve the right price and reimbursement (P&R) level of medicines in a certain country. Given that each country has a unique market access environment in terms of procedures and requirements, biotech and biosimilar companies devote special attention to these factors. In that sense, governments often introduce multiple mechanisms for price control (such as mandatory price cuts) or purchasing (such as tenders). Since that environment is constantly evolving, it is important to understand what type of policies may be introduced in certain European markets, based on the success of these very policies in other countries. Thus, the conclusions drawn from this research inform the understanding of the magnitude of impact of certain drivers of biosimilars price erosion in a heterogeneous group of European countries, while also taking heed of regulatory parameters.

In order to provide a clear industry-specific context in which the economic conclusions can be interpreted, it is important that some background information on the considered medicines should be given. The specific terminology used throughout this paper is left to Subsection A in the Appendix. The other characteristics which build up the profile of small molecules and biologics are briefly explained here. Due to the higher molecular complexity of biologic drugs (Table 1), the potential side effects of these products on patients may be more or less severe. This in turn affects physicians' willingness to prescribe biosimilars should such be present on the market at any time. The main reason for this

reluctance is the lack of accumulated medical evidence, for instance gathered as part of pharmacovigilance. Being a type of 'experience goods,' medicines need to build a history of safe and efficacious use. If doctors feel comfortable with the usage of an established originator biologic product, they will not be easily convinced to switch all their patients to a newly-developed biosimilar product, even when the latter has been subjected to strict regulatory review and has met the marketing authorization criteria (Dranitsaris et al., 2011). Hence, the threat of low market uptake may turn out to be an important consideration for manufacturers and limit the number of incumbents.

Since the present research will look into the price erosion of two biosimilars – for *filgrastim* and *epoetins* – it is worthwhile to represent their location on a "molecular complexity" scale, as shown on Figure 1. The reason for this classification is that some product characteristics may define the market uptake of a given drug, and that effect spills over to the pricing decisions of manufacturers. By outlining the obstacles which each next wave of biosimilars may encounter, starting with *filgrastim* and continuing on to *epoetins*, it is possible to derive better-informed conclusions about the next wave of products, or in this case, *monoclonal antibodies* (mAbs). Although *filgrastim* and *epoetin* are not the only biosimilars currently present on the European market, they have been chosen here because they have experienced the highest number of entrants. As of 2014, there are four marketed biosimilars of *epoetins*, and seven of *filgrastim*. That allows for a better investigation of the interplay between number of competitors and price changes. In comparison, there are only two biosimilars of *somatropin*, which is one of the few other marketed biosimilars in general.

Figure 1: General categorisation of biologic products

Increasing level of molecular complexity
Rising number of indications
Rising doctors' reluctance to prescribe

Table 1: Comparative characteristics of some small-molecule drugs and biologics

INN	Molecular size (Da)	Number of indications
Paclitaxel (SM)	854	

Filgrastim biosimilar	18 000	Three
Epoetin biosimilar	34 000	Four
mAbs	145 000 – 160 000	Six (*infliximab*)

Source: Dranitsaris et al. (2011); EMA (2015)

Filgrastim is used for the treatment of cancer, neutropenia (expressed in low levels of a type of white blood cells) and hematopoietic stem cell transplantation (the transplantation of specific stem cells). It is administered by means of an injection under the skin or by direct infusion into a vein. *Epoetin* can be of several subtypes, such as alfa, beta, theta and zeta. The distinct names indicate slight molecular differences. *Epoetins* are used to treat anemia (low levels of red blood cells), cancer, autologous blood transfusion (self-donation of blood prior to surgery) and chronic kidney failure. The medicine is administered with an injection under the skin or into a vein (EMA, 2015).

The main findings of this research are that, on the biosimilars terrain, while for *filgrastim* it is competitors' prices which drive further market entry, for *epoetin* the opposite direction of causality holds. In addition, although the number of biosimilar competitors currently present on the market has an impact on the prices of the incumbent, this is not necessarily the case for both INNs. In other words, beside direct competition, there is a myriad of other factors which exert influence on price erosion of the originator. These regulatory parameters are addressed in due course throughout the present study.

The rest of the paper is organised as follows: Section 2 presents a literature review of the publications which underlie some of the key model assumptions. Section 3 contains a description of the theoretical model. Section 4 is devoted to an overview of the data and methodology. Section 5 presents the empirical results. Section 6 offers a discussion of the outcomes. Lastly, section 7 provides a conclusion.

2. Literature review

In order to obtain a good overview of the existing publications on the economic performance of biosimilars, multiple sources have been utilised. Beside the search into academic open-source journals, the publications released by international agencies and organisations, such as the European Commission (EC) and the European Medicines Agency (EMA), have been used as well. In addition, some opinion papers and short articles from online journals, such as the Generics and Biosimilars Initiative (GaBI) Online, have been taken into account. Keeping in mind the dynamic nature of the biosimilars industry and the correspondingly complex market access environment, one of the main criteria in

selecting appropriate literature has been that it be published after 2006, when the first biosimilars were approved in Europe.

Academic literature which examines the development of biosimilars prices is generally scarce. So far, most of the attention has been devoted to the market for generics. In addition, where scholars have looked into biologics and biosimilars, most of the studies have been performed as qualitative and descriptive analyses of the current market access environment surrounding these products. The quantitative studies which utilise numerical data remain few and they are often limited in scope, focusing on theoretical constructs without reference to real-life pricing data. In this sense, the current study represents a contribution to the existing literature. The most relevant papers are discussed below.

Some publications adopt an approach whereby they draw a rough parallel between generics and biosimilars and attempt at constructing a predictive model on biosimilars entry to the market. One such article on entry and competition of biosimilars is that by Grabowski, Ridley and Schulman (2007), who focus on the USA market. They acknowledge that the biosimilars market is relatively young and it might take a while before enough experience is built up and sufficient pricing data is made available before robust conclusions on price trends can be drawn. Nevertheless, in order to create an informed opinion on how prices of biosimilar products may evolve in time, Grabowski et al. (2007) look at the market dynamics of generics in order to build an understanding of the biosimilars market. In the process, they take into account the differences between these two categories of drugs. Firstly, they estimate the elasticity of entry of biosimilar companies represented in terms of fixed costs. This is done because biologics and biosimilars generally involve very high initial investments and this in turn might be an effective barrier to entry. Secondly, they compare the different costs associated with the two industries – for small-molecule pharmaceuticals and biologics. The importance of this element boils down to highlighting the difference between the R&D costs in these two sectors of the drugs industry. The authors (Grabowski et al., 2007) take three main elements into consideration, namely the cost for clinical trials, the capital costs for manufacturing facilities, and the cost of the manufacturing process itself. Thirdly, they use market size as a variable explaining the number of entrants of generic pharmaceutical manufacturers, and then translate the estimates for the market entry of biosimilars. The model involves representing the natural logarithm of the number of new competitors as a function of the natural logarithm of sales of the originator product up to the period preceding generic entry. This element in the model measures the attractiveness of the market in terms of anticipated revenues by the prospective entrants. Fourthly, Grabowski et al. (2007) determine the relative prices of generics, explained by the number of market participants. Lastly, the same model with the relevant inferences

is used for biosimilars in order to make projections about market entry and pricing behaviour of manufacturers.

The study is informative as it utilises knowledge of the generics market, where a lot of empirical data is available. Importantly, it shows that although generics and biosimilars are significantly different, some of the assumptions on price development are transposable from one market to the other. What is key about the model developed by Grabowski et al. (2007) is that it is fairly simple, using only three control variables: number of competitors, time trend, and therapeutic class. Still, the number of competitors incorporates fixed costs and market size. Some elements of this model will be borrowed for the purposes of the present study on biosimilars entry and price development, namely the expression of the number of market participants as a function of prices, but with a modification: rather than using the prices of the incumbent prior to biosimilars entry, the prices of currently marketed biosimilars will be used in order to see their impact on the entry decision of new biosimilar competitors. In this way, for filgrastim, the attractiveness of the market will again be measured in terms of anticipated revenues, but taking into account the potential price erosion which would have already settled in. Furthermore, for epoetin, the effect of the number of current market participants on the prices of marketed biosimilars will be studied. Thus while Grabowski et al. (2007) control for drugs' therapeutic class by means of dummy variables, the present study performs separate regressions for the two molecules under consideration, in order to account for the differences in market dynamics and causality between the variables in a more complicated way. Next to that, the current paper will explore the European market, thus adding to the paper of Grabowski et al. (2007) by means of an expanded geographical scope of the investigation.

More recently, Rovira et al. (2013) have performed an insightful study into the market dynamics of biosimilars for three INNs in Europe – *somatropin*, *epoetin alfa/zeta*, and *filgrastim* – by looking at the national markets of 24 EU member states, as well as Norway and Switzerland. The time period covers the years 2007 to 2010, reflecting the pricing and market uptake behaviour of biosimilars in their infancy. The scholars (Rovira et al., 2013) employ an econometric linear-regressions model. Beside numerical variables, such as market penetration (in %) and time period between EMA approval and market entry of the biosimilar (in months), they look at many qualitative parameters, mostly in terms of dummy control variables. A downside of their model, however, is that they run predominately bivariate regressions, which fail to evaluate the effect of certain characteristics of the market in their togetherness. The reason pointed out by the authors (Rovira et al., 2013) is that the preliminary multivariate regression had not reported any statistical significance, thus bivariate regression was adopted as a solution. Still, the fact that Rovira et al. (2013) have decided to consider some regulatory

variables (Table 2), beside prices, lends credence to the incorporation of such variables into the present study for the interpretation of the regression results later on. The country-specific characteristics discussed by Rovira et al. (2013) largely fall into the following categories: demographic, economic and pharmaceutical policy variables.

Table 2: Regulatory variables impacting biosimilars' prices

Continuous variables	Dichotomous variables
Pharmaceutical market value	Generics price control
Population size	Use of European Price Referencing (EPR)
Gross national income (GNI)	Tendering
Price level index of medicines	Generics substitution (Pharmacist level)
Total expenditure on health (% of GNI)	International Nonproprietary Name (INN)
Total expenditure on health (absolute)	prescribing
Government expenditure on health	National procedure for P&R
	Use of National Price Referencing (NPR)

Source: Rovira et al. (2013)

Some of the key findings of Rovira et al. (2013) are that generics price controls have a statistically significant influence (with a coefficient of -21,533) on the market penetration of biosimilars, measured in percentages. This is an important finding, as the presence of mandatory price cuts for generics in some European markets indicate an extrapolation of these rules onto the biosimilars market as well. This variable will therefore be taken into account in the discussion section of this paper later on, in order to account for some differences across the European countries in terms of pricing and entry. In addition, Rovira et al. (2013) find that the timing of market entry of biosimilars measured against the moment of EMA market approval is influenced by the gross national income (GNI) (with a coefficient of +0,002), total expenditure on health as % GNI (+1,156), total expenditure on health (+0,002), government expenditure on health (+0,0019), pharmaceutical generics substitution (-3,08), and price level index of medicines (+0,082) (measuring the relative price levels of medicines across countries expressed in terms of purchasing power parities and nominal exchange rates). Still, in light of the present study and the current market environment, substitution is not likely to be impactful on the decision of market entry of biosimilars. The reason is that most countries do not allow biosimilars substitution at the pharmacy level, although the strictness of the controls varies across the countries (Roediger, 2015). Where substitution and switching do occur, this is mainly at the hospital level, where tenders may lead to the switching from an originator biologic to a biosimilar of either all patients or only of new, treatment-naïve patients (Roediger, 2015). An important finding of the study by Rovira et al. (2013) is that, per INN, biosimilars have demonstrated faster uptake on the European market compared to the originator biologics which they reference. This is a compelling insight, as it

demonstrates how the lower prices arguably drive the higher willingness on behalf of doctors and national regulatory bodies to utilise biosimilars, while also building upon the accumulated experience with the reference product.

Given the importance of these variables for the market uptake and the entry decision and pricing behaviour of biosimilars across different European countries, it is important to incorporate these into the present analysis. Moreover, the current study will encompass a broader time period, starting from 2008 and continuing well until the end of 2014. Therefore, some of the latest policy changes in the sample of countries will be incorporated into the interpretation of the regression outcomes. It is important to mention, however, that the current study will look into a smaller number of countries (10 instead of 26). Notwithstanding, the countries selected here are sufficiently heterogeneous and have been selected with consideration of their different national market environment.

Another key article on which this research is based on is by Grabowski, Guha and Salgado (2014) who investigate the price erosion of two of biosimilars that represent the first wave of biosimilar approvals in the EU. These medicines are *filgrastim* and *epoetins* (*alpha, beta, theta, zeta*). The authors explore the market uptake of the biosimilar products compared to the originator (reference) products. They find out that there is cross-country, as well as cross-indication, heterogeneity of biosimilars uptake. In order to account for this disparity within a sample of five European countries (Germany, France, Italy, UK, and Sweden), Grabowski et al. (2014) take certain regulatory and cultural parameters into account. For example, countries with traditionally high generics uptake, such as Germany, Sweden and the UK, exhibit higher willingness to utilize biosimilars compared to other countries. At the other end of the spectrum they find France and Italy who have some historically high resistance to generics use. Apparently, such cultural characteristics of the pharmaceutical market can be transposed onto the market of biologic products. For this reason, the present study shall incorporate some of those same factors into the analysis.

Another element of interest from the study by Grabowski et al. (2014) is that the market uptake of biosimilars appears to be relatively promising when agglomerated with the reference 1st-generation product. However, when looking at the market of the respective INN including the 2nd-generation product (usually a long-lasting version), the biosimilars uptake appears almost negligible. In this sense, just as the authors (Grabowski et al., 2014) point out, it would be worthwhile to investigate how this tendency applies to the market of monoclonal antibodies, since these are products with enormous revenue and several patents are expected to expire in the near future. It is expected that by 2020,

biologics which are worth US$54 billion will lose their patent and be exposed to biosimilars competition (GaBI Online, 2011). Although the scope of the present study may not reach so far as to cover the questions posed by Grabowski et al. (2014), it will remain interesting from an industry as well as 'payer' perspective to answer to what extent the threat of 2nd-generation biologic products can be considered a significant threat to the uptake of biosimilar products referencing 1st-generation biologics. In addition, it is interesting whether the same considerations and market dynamics apply to the mAbs market, given the specific characteristics of these products which set them apart from other biologics. Answering these questions is important because they can inform our understanding of whether investors and biotech companies perceive 2nd-generation biologics as a great threat to market share growth of biosimilars referencing 1st-generation products. Also, the conclusions can be used to form anticipations as to whether the industry's willingness to invest in 1st-generation-referencing biosimilars is declining, in light of any pipeline 2nd-generation products. In other words, is the paradigm shifting towards investments in 2nd-generation products or is there still persistent interest in 1st-generation products? It may well be that the current paper does not succeed in answering all these questions, yet some of the conclusions in the later sections may represent a small step on the way of addressing mAb-related topics.

The main factors identified by Grabowski et al. (2014) for the rate of market penetration of biosimilars in Europe are presented in Table 3 below.

Table 3: Factors impacting biosimilars market penetration in Europe

Relevant variables (mostly as dummy)
History of high generics usage
Quotas (for prescriptions)
Reference price system for biosimilars
Mandatory price cuts for biologics
Presence of patient co-payments

Source: Grabowski et al. (2014)

Therefore, some of the variables, e.g. especially reference pricing, which recurs in most of the academic publications on biosimilars pricing, are considered in the interpretation of the estimates of the present study. Once again, similar to other respectable publications, the one by Grabowski et al. (2014) offers a valuable yet limited glimpse into the dynamics of the biosimilars market, since its geographical scope is limited to five countries. The current research offers an extension in that respect.

A report compiled by Roediger (2015) based on a survey by the European Biopharmaceutical Enterprises (EBE) organisation looks at a number of regulatory variables for biosimilars in all 28 EU

member states, as well as Norway, Serbia and Switzerland. Although that publication does not look at any numerical variables, it still examines regulatory parameters which are particularly relevant for the market penetration, hence pricing, of biologic drugs in general. More specifically, the types of tenders conducted in the different European countries are identified in several dimensions. Therefore, the insights provided by the report are used here mainly in terms of the factors which might explain country differences in the final results. Furthermore, the current research provides a more rigorous estimation of the effect of these regulatory variables on biosimilars price erosion by testing them in a regression model, instead of relying on a descriptive account only.

Similar to the EBE report (Roediger, 2015), Tele and Groot (2009) look into a variety of cost containment measures which the authorities in different countries have adopted throughout the years, so as to minimise the healthcare expenditure costs. It is important to note that these measures can set the price development of biosimilars, or any medicines for that matter, on a downward spiral (Table 4).

Table 4: Cost containment measures in Europe

Relevant variables	
Use of positive list	Reference pricing schemes
Use of negative list	Fostering the use of generics
Price controls	Substitution by pharmacists
Profit controls	Economic evaluation
Individual or global budgets for doctors	Monitoring of prescription practices
Delay in Market Authorisation approval	Patient co-payments
Education for health	Financial incentives for physicians
Non-financial incentives for physicians	

Source: Tele and Groot (2009)

Since some of these variables have been considered also by Grabowski et al. (2014) in their analysis of biosimilars market share development, it is worthwhile to consider at least some of them and incorporate them, where possible, in the interpretation of the regression results.

3. Theory

The empirical analysis in this paper rests upon a theoretical model, inspired by Industrial Organisation. It is assumed that the attractiveness of any given market is determined by the anticipated stream of revenues (Brekke et al., 2007). In other words, the entry decision of firms is motivated by whether the prices charged for their products would be sufficiently high in order to recoup the initial investment.

In light of the high R&D costs associated with the pharmaceutical industry as a whole (Grabowski et al., 2007), the value that can be assigned to the medicines bears particular importance. The development costs necessary for small-molecule drugs are much lower compared to those for biologic medicines (Grabowski et al., 2007). The reason for this difference lies, firstly, in the manufacturing process in terms of research and clinical trials, and secondly, in the requirements necessary to obtain marketing authorisation, in terms of evidence on quality, safety and efficacy. Generic pharmaceuticals can be easily replicated by means of standard chemical processes, while for biosimilars a separate and uniquely engineered cell line must be developed. Furthermore, unlike small-molecule producers, who need not demonstrate bioequivalence via clinical trials, manufacturers of biosimilars must show comparable pharmacokinetic and pharmacodynamics properties as proof of quality, and conduct costly Phase III clinical trials as proof of efficacy and safety (Barosi et al., 2011). Some of the associated differences in terms of costs and duration are summarized in Table 5 below.

Table 5: Costs and timeline for development of generics and biosimilars

Drug type	Clinical trial costs	Development time
Generic pharmaceuticals	$ 1 – 2 million	2 – 3 years
Biosimilars	$ 10 – 40 million	5 – 8 years

Sources: Grabowski et al. (2007); Grabowski et al. (2006); Declerck and Simoens (2012)

Table 5 shows that biosimilars prices need to be sufficiently high in order to make the R&D investments worthwhile. Furthermore, there are other significant costs associated with commercialisation activities for biosimilars. Typically, these expenditures involve the sales representatives, medical science liaison officers (taking care of medical affairs and providing educational services), and key participants in marketing activities. Furthermore, post-approval safety studies may be necessitated as well, and their costs can be substantial too. Therefore, it has been assumed that the price premium offered by biosimilars upon launch and for a period afterwards would be smaller than the one for generics. An additional factor fostering the maintenance of high prices for biologics are the incentives of innovator companies. The R&D costs which they have accumulated prior to launch of a biologic are in the range of $100 million (Dalgaard, 2013). These include the development of a cell line, but also the performance of a full round of clinical trials, i.e. from Phase I to Phase III. In this sense, it is in their interest to continue to reap large enough profits even beyond the patent protection period of about 20 years. Moreover, originators would not like to see their blockbuster products devalue quickly, but would rather sustain the profitability of the therapeutic-area-specific market.

The interplay of potential revenues, pricing behaviour and entry decisions is complemented by the interests of governments and P&R agencies, who largely represent 'the payers'. Not only do national

authorities try to curb launch prices of medicines, including biosimilars, but they also attempt to put downward pressure on prices throughout product lifecycle. Thus, given the high regulation of the drugs market in general, price erosion typically ensues much quicker, can be much more severe and driven by forces other than competitive pressure alone.

In their attempt to make savings and manage the progressively shrinking budgets, European payers have implemented a series of cost containment measures (CCMs). Within the EU, where each national government has the autonomy of creating its own market conditions, on the one hand, there is much heterogeneity in terms of measures used, and on the other hand, there are quite a few elements in common. Given that the biosimilars market is relatively young and evidence on price development is sparse (Rovira et al., 2013), it could be argued that a large number of the cost containment measures have been directly borrowed or generally inspired by the generic pharmaceuticals market. In addition, European nations often look at their 'neighbor' to borrow ideas on how to reduce healthcare costs. Table 6 gives a thorough overview of the cost containment measures which are most commonly implemented in Europe, as well as some of the parameters with greatest impact on biosimilars entry and pricing.

Table 6: Some commonly used cost containment measures and regulatory parameters impacting entry

Cost containment measures in Europe			Other regulatory variables
Use of positive list	Substitution of biosimilars	Use of EPR for biologics	Availability of national legislation on biologics
Use of negative list	Mandatory discounts for pharmaceutical originators	Use of NPR for biologics	Average duration of P&R for biosimilars (in months)
Profit control	Mandatory discounts for biologic originators	Type of NPR for biologics (generic or therapeutic reference)	Delays in biosimilars Marketing Authorisation approval
Cost containment measures in Europe (cont.)			Other regulatory variables (cont.)
Presence of budgets (for doctors)	Mandatory discounts for generic entrants	Tenders for biologics	Level at which substitution is prohibited
Financial incentives for doctors	Mandatory discounts for biosimilar entrants	Type of tenders (single or multiple win)	

| Information campaign on generics / biosimilars use | Monitoring of prescription patterns | Fostering the use of generics / historically high use |

Another characteristic which may determine the attractiveness of a given market is price volatility. It can be measured by the variance, or standard deviation, of the prices of a particular drug throughout time. In principle, it is assumed that markets where prices fluctuate less are more attractive, since the stream of revenues is more stable, secure and, arguably, predictable. Because most EU markets are highly regulated, it is difficult to speak of frequent and unexpected price changes. Where price changes do occur, they are mostly downward adjustments in response to competitive pressure or as a result of strategic action. This is largely due to the binding contracts or other trade agreements which manufacturers make with retailers or hospitals, thus price increases are basically not observed. Still, these are the conditions which apply to price management throughout product lifecycle. At launch, the possibilities for price responses are different for originators and biosimilars.

When bringing a product to the market, originators set the price more or less freely, as in most cases there is no specific price ceiling or price tunnel for innovative products. Nevertheless, this free-price period may last only for a while, until the negotiations with the national authorities have been finalised. The duration of this process is not standardized, and may vary per country and per product. It has been estimated that for oncology products, for example, the negotiations in the period after obtaining marketing authorisation may last from 6 to 32 months, depending on the country and the respective medicine (Swilling, 2014). However, even if some price fluctuation and possibly increases are observed in the period up till a price agreement has been reached, originator prices are not revised too frequently. Except for some instances where originator prices were increased upon entry of the first biosimilar on the local market, there is an overarching tendency for downward price evolution. For biosimilars, on the contrary, certain price cuts may be applied already upon launch. Such measures successfully push prices down and cause price erosion to occur even absent immediate competitive pressure. Mandatory price cuts for biosimilars exist in Hungary, Italy, Poland, while non-mandatory cuts are applied in France. In one of these markets, Hungary, there is a meticulous regulation on price cuts of consecutive generics entrants and, interestingly, there also exists a similar step-wise approach to biosimilars pricing upon launch. Still, the regulation explicitly stipulates the mandatory reductions up to the 7th generic entrant, while for biosimilars the list stops at the 4th entrant. This is an important insight, as it suggests that national authorities implicitly recognize the relatively smaller number of biosimilar market participants compared to the generics market. As a result of mandatory price cuts, biosimilars price erosion may ensue much quicker, and be more severe, than if left to competition

alone. It is even more challenging to achieve a sustainable price at launch as well as to maintain that price throughout the years afterwards in the countries where European Price Referencing (EPR) is used. Within the sample of countries considered here, EPR is used in Bulgaria, France (only for highly innovative medicines), Greece, Hungary (only for originators), the Netherlands, Norway and Poland.

Undoubtedly, all forces which may trigger a reduction of biosimilars prices exert a pull-effect on originator prices, since the two types of products enter direct competition. Competitive pressure is a potent mechanism leading to price reduction despite the fact that the two types of products are considered comparable (Barosi et al., 2011), but are not perfect substitutes (EC, 2013). Therefore, the prices of marketed biosimilars directly impact the price of originators.

From the above theory and description of real-life market access conditions, the following predictions can be made from the model:

1. Prices of the currently marketed biosimilars determine the attractiveness of the market and impact the entry decisions of other manufacturers.
2. A measure of the price volatility must provide additional insights into the attractiveness of the biosimilars market for potential entrants, over and above the currently charged prices by the other competitors.
3. The prices of originators are directly affected by the prices of biosimilar entrants.
4. Price volatility of biosimilar prices may influence the prices of originators.

These predictions are tested by means of econometric regressions, as described in the next section.

4. Data and methodology

a. Data and resources

For the empirical model, the sample includes 10 European countries: Bulgaria, France, Germany, Greece, Hungary, Italy, the Netherlands, Norway, Poland, and the UK. Only one of them, Norway, is not a member of the European Union (EU). Yet, due to the country's advanced economy and healthcare sector, Norway is not anticipated to exhibit significantly different market environment based on non-EU membership alone.

The insights needed for the analysis are collected from semi-structured interviews within Teva Pharmaceuticals Europe, one of the largest pharmaceutical manufacturers in Europe. In addition, a

survey focusing on regulatory and pricing information has been dispatched to country affiliates. This input is used in order to obtain an understanding of the market access conditions in each country and is complemented by literature findings from desk research, as outlined in the previous section.

The econometric model utilizes average manufacturer selling prices per product from the IMS MIDAS database. A key feature of this source is the regular and mostly intermittent frequency of the observations. The reason why this category of prices is preferred is that they reflect the *public* price level, since in most cases the negotiations between manufacturers and national authorities are over prices which are eventually to be made available on official price lists. Moreover, as is confirmed by the semi-structured interviews, practically in all countries it is exactly the published price which is used for EPR, at least for generics. This is why it is considered appropriate to determine entry decisions and track price development with respect to public prices. Still, it should be taken into account that there are numerous types of undisclosed agreements and discounts between manufacturers and other participants in the distribution channel. Thus, the reader is invited to factor that element of price erosion into the picture prior to drawing any deterministic conclusions about biosimilars pricing.

b. Econometric model design

The econometric model adopted here is Ordinary Least Squares (OLS) regression with country fixed effects. The reason for this choice lies in the intrinsic differences displayed by the countries in the sample, which may account for the unexplained variation in the estimates. The model specification is tested with the Granger causality test.

The methodology can be summarized as follows. Firstly, the number of biosimilar entrants (N) is represented as a function of the prices of other marketed biosimilars (CP for 'competitor prices') – current as well as with one period lag, and the number of competitors in the previous period. The equation takes the following form:

$$\Delta N = \beta_0 + \beta_1 \Delta LCP + \beta_2 N(-1) + \beta_3 LCP(-1) \tag{1}$$

In order to obtain the estimates in percentages, the competitor prices in equation (1) are expressed in logarithms (LCP). In addition, first differences of that independent variable are taken (ΔLCP) so as to measure the effect of the growth rate of the variable on the number of competitors. In addition, the first differences remove any time invariant omitted variables. This is applied to the dependent variable as well. Equation (1) corresponds to the underlying assumption in this study, namely that the prices of

currently marketed biosimilars define the attractiveness of the market and impact the entry decision of further competitors.

Secondly, equation (1) is extended by adding a measure of price dispersion or volatility. A log of the standard deviation of competitor prices (LSTD) is used and it is represented by the first differences and a one-period lag, as follows:

$$\Delta N = \beta_0 + \beta_1 \Delta LCP + \beta_2 N(-1) + \beta_3 LCP(-1) + \beta_4 \Delta LSTD + \beta_5 LSTD(-1) \qquad (2)$$

Once again, in equation (2), the first difference in the log of the standard deviation is used, in order to measure the effect of the growth rate of the variable on the number of competitors.

Thirdly, the prices of originators are represented as a function of the number of biosimilar competitors on the market – current and with one period lag (LOP, for log of 'originator prices'), and the originator prices in the previous period:

$$\Delta LOP = \beta_0 + \beta_1 \Delta LN + \beta_2 LOP(-1) + \beta_3 LN(-1) \qquad (3)$$

Lastly, equation (3) is extended by adding price volatility (LSTD) in order to improve the estimates by controlling for the attractiveness of the market for originators, given the presence of biosimilar entrants:

$$\Delta LOP = \beta_0 + \beta_1 \Delta LN + \beta_2 LOP(-1) + \beta_3 LN(-1) + \beta_4 \Delta LSTD + \beta_5 LSTD(-1) \qquad (4)$$

For all estimation equations, cross-section and period fixed effects are used. The single exception is equation (2) for *filgrastim*, where fixed effects are applied only for the cross-sections, but not for the periods. The initial attempt to use fixed effects for both parameters has not rendered a feasible outcome, which is why the fixed effects for the periods have been removed.

Each regression, from (1) to (4), which constitutes part of the model, is run separately for the two molecules. This is necessary because of the different nature of the medicines in terms of uptake, ease of manufacturing, doctors' willingness to prescribe them, and overall pricing strategy. In their togetherness, these factors define the different dynamics on each product's market. Therefore, it is anticipated that different results may be obtained for the two molecules. Indeed, market research on the rate of biosimilars entry across Europe has indicated that it differs per INN. For example, there are

generally many more competitors of *filgrastim* than there are for *epoetins* (Grabowski et al., 2014). In addition, the same trend is observed for the uptake of these medicines, where the molecular complexity and the relative manufacturing ease of *filgrastim* biosimilars compared to *epoetin* biosimilars may have facilitated their wider usage in clinical practice.

5. Empirical results

The following section demonstrates the empirical findings from the analysis. More specifically, the interconnection between the number of biosimilar competitors and their prices on the one hand, and between the number of biosimilar competitors and the prices of originator biologics on the other hand, is displayed.

a. Effect of competitor prices on biosimilars entry decision

Table 7 presents the estimates obtained for the effect of marketed biosimilar prices on the entry decision of further competitors, based on equation (1).

Table 7:
Estimation of equation (1): $\Delta N = \beta_0 + \beta_1 \Delta LCP + \beta_2 N(-1) + \beta_3 LCP(-1).$
Dependent variable: ΔN, the first-difference of the number of biosimilar competitors.

Filgrastim:

```
Dependent Variable: D(N)
Method: Panel Least Squares
Date: 06/15/15   Time: 13:21
Sample: 1 830
Periods included: 74
Cross-sections included: 10
Total panel (unbalanced) observations: 680
```

Variable	Coefficient	Std. Error	t-Statistic	Prob.
D(LCP)	0.434884	0.123094	3.532952	0.0004
C	-0.803050	0.395831	-2.028769	0.0429
N(-1)	-0.315796	0.029667	-10.64469	0.0000
LCP(-1)	0.344576	0.082634	4.169922	0.0000

Effects Specification

```
Cross-section fixed (dummy variables)
Period fixed (dummy variables)
```

R-squared	0.267131	Mean dependent var	0.038235
Adjusted R-squared	0.162260	S.D. dependent var	0.435883
S.E. of regression	0.398956	Akaike info criterion	1.117795
Sum squared resid	94.54437	Schwarz criterion	1.689706
Log likelihood	-294.0502	Hannan-Quinn criter.	1.339168
F-statistic	2.547218	Durbin-Watson stat	2.424302
Prob(F-statistic)	0.000000		

Epoetins:

```
Dependent Variable: D(N)
Method: Panel Least Squares
Date: 06/19/15   Time: 12:26
Sample: 1 817
Periods included: 82
Cross-sections included: 10
Total panel (unbalanced) observations: 807
```

Variable	Coefficient	Std. Error	t-Statistic	Prob.
D(LCP)	-0.191875	0.076350	-2.513094	0.0122
C	2.013168	0.395479	5.090459	0.0000
N(-1)	-0.276448	0.025252	-10.94774	0.0000
LCP(-1)	-0.206970	0.070295	-2.944312	0.0033

Effects Specification

```
Cross-section fixed (dummy variables)
Period fixed (dummy variables)
```

R-squared	0.268942	Mean dependent var	0.029740
Adjusted R-squared	0.173587	S.D. dependent var	0.436098
S.E. of regression	0.396445	Akaike info criterion	1.096559
Sum squared resid	112.0611	Schwarz criterion	1.643241
Log likelihood	-348.4617	Hannan-Quinn criter.	1.306483
F-statistic	2.820421	Durbin-Watson stat	2.483752
Prob(F-statistic)	0.000000		

Unlike the estimates for *filgrastim*, which show satisfactory statistical significance for all independent variables except for the constant, those for *epoetin* render p-values of 0,0122 and 0,0033 for ΔLCP and LCP(-1), respectively. These values indicate that the equation may not have been defined in the most appropriate way. In order to avoid any misconstruction of the direction of causality, it is important that the equation specification should be examined. For that purpose, a sensitivity test is performed and reported in the next section. Nevertheless, the outcomes for *filgrastim* merit a brief discussion. The coefficient for ΔLCP indicates, in combination with the intercept value, that 1% increase in competitor prices will lead to $\beta_{\Delta LCP}$ = 0,435% increase in the growth rate of biosimilar entrants. Last period's

competitor prices have a positive effect on the number of competitors today. This suggests that although the overall effect is not too strong, a potential rise in prices would attract more competitors. If prices were to increase by 1%, the rate at which competitors will enter the market would increase by 0,435%. Still, increases in biosimilar prices are hardly ever observed throughout product lifecycle. The number of competitors in the last period has a negative effect on this period's number, so that if there were one more competitor in the last period, this would lead to 100•(-0,316)%, or 31,6%, fewer competitors this period. Clearly, the market cannot tolerate an indefinite increase in the number of competitors. While a potential price increase attracts entrants, this is counterbalanced by the fact that too many current competitors disincentivize further entry.

In order to obtain a clearer picture of the trend, the effect is represented by means of (three-month) moving averages of the period fixed effects (Figure 2). The advantage of this method is that it smoothens out the fluctuations which may arise in each month, thus clearing "the noise". The left-hand axis on Figure 2 is only used in order to visualise the evolution of the effect, thus the actual intervals of the scale do not have meaningful interpretation. Clearly, in the first periods the effect of the price increases of biosimilars on the number of further entrants is stronger, but eventually the number of firms on the market converges to equilibrium. Throughout this paper, the formula for the calculation of the three-month moving average is the following:

$$Moving\ Average = \frac{m_{t-1} + m_t + m_{t+1}}{3}\ , \qquad\qquad (5)$$

where 'm' stands for a 'month' with observations.

Figure 2: Period fixed effects: LCP on N (*filgrastim*)

b. Sensitivity analysis – Granger causality test

Given the results obtained for *epoetin* where competitors' prices turn out to be insignificant, a Granger causality test is performed. An additional motive for the test is that the results for the two molecules suggest different causality between the variables under consideration. Admittedly, in both situations, there are two effects at play – the entry effect, where higher prices attract more competitors by means of higher anticipated profits, and the competition effect, where an increase in the number of firms triggers a price reduction. What is of interest here is the relative strength of these effects for *filgrastim* and *epoetins*.

The Granger test provides inconclusive results for *filgrastim* and no evidence for reverse causality has been rendered. The relatively high p-values suggest that the regressors in the equation are significant. Thus, the standard hypothesis for the Granger test whereby the two variables – ΔN and ΔLCP – are unrelated, could not be rejected. For *epoetin*, on the contrary, there is strong evidence that the number of firms, N, affects the market prices, LCP, while there is no such evidence for the reverse. Consequently, it is necessary to switch the dependent variable and the main independent one, since the interplay of the two variables in *epoetin* is better explained by reverse causality. Importantly, the trend for that molecule cannot be explained by competition alone.

There may be an additional justification for the results obtained from the Granger test. The direction of causality running from the number of competitors to prices is consistent with economic logic, because as more competitors enter the market, the cohort of patients, or 'customers', who are potential candidates for the medicinal product, remains largely unchanged (abstracting from any possible change in disease incidence rates). In this way, in order to serve the same patient population

for a certain disease, companies may need to differentiate their medicines based on price. It is important to note that biosimilars, unlike generic pharmaceuticals, are not considered direct substitutes. While in some cases doctors may be reluctant to prescribe a generic, this is largely due to brand loyalty, rather than any clinical consideration. Conversely, many physicians are very cautious about treating their patients with biosimilars out of fear that some adverse reactions may be provoked or the treatment may overall not be as efficacious as that delivered by the originator product. This particularity is due to two main reasons: first, biosimilars do exhibit molecular variability, even within the same batch (European Commission, 2013), and second, stakeholders have accumulated relatively little experience with biosimilars, given that the first such product was approved in Europe in 2006 (EMA, 2014). In this sense, *epoetins* biosimilar prices may be more susceptible to change as a result of competitor entry. Thus, the very nature of the products may be the reason why on the *epoetins* market it is the number of competitors which influences the currently charged prices for biosimilars and not the other way round. The revised equation for *epoetins* is the following:

$$\Delta(LCP) = \beta_0 + \beta_1 \Delta N + \beta_2 N(-1) + \beta_3 LCP(-1) + \beta_4 \Delta LSTD + \beta_5 LSTD(-1) \qquad (6)$$

Similarly to the previous equations, cross-section and period fixed effects have been used for equation (6).

c. Effect of price volatility on entry and competitor prices

In order to strengthen the results and check to what extent price volatility may be an impactful factor in biosimilars entry, the regression equation is extended with the edition of standard deviation (Table 8). The new regression reflects the modification for *epoetins*, in response to the outcomes of the Granger test. By including standard deviation, the results have been improved, as is seen by the increase in R^2.

Table 8: Estimation of equations (2) and (6)

Filgrastim:

Estimation of equation (2):
$$\Delta N = \beta_0 + \beta_1 \Delta LCP + \beta_2 N(-1) + \beta_3 LCP(-1) + \beta_4 \Delta LSTD + \beta_5 LSTD(-1)$$
Dependant variable: ΔN, the first-difference of the number of biosimilar competitors.

```
Dependent Variable: D(N)
Method: Panel Least Squares
Date: 06/15/15   Time: 13:25
Sample: 1 830
Periods included: 74
Cross-sections included: 10
Total panel (unbalanced) observations: 680
```

Variable	Coefficient	Std. Error	t-Statistic	Prob.
D(LCP)	0.384806	0.107865	3.567485	0.0004
D(LSTD)	0.245086	0.018298	13.39428	0.0000
C	-0.656090	0.346878	-1.891415	0.0591
N(-1)	-0.285966	0.028233	-10.12863	0.0000
LCP(-1)	0.265768	0.072539	3.663768	0.0003
LSTD(-1)	0.054556	0.016419	3.322757	0.0009

Effects Specification

```
Cross-section fixed (dummy variables)
Period fixed (dummy variables)
```

R-squared	0.440775	Mean dependent var	0.038235
Adjusted R-squared	0.358591	S.D. dependent var	0.435883
S.E. of regression	0.349090	Akaike info criterion	0.853263
Sum squared resid	72.14337	Schwarz criterion	1.438475
Log likelihood	-202.1095	Hannan-Quinn criter.	1.079784
F-statistic	5.363300	Durbin-Watson stat	2.430747
Prob(F-statistic)	0.000000		

Long-run effects	
LCP(-1)	0,929
LSTD(-1)	0,191

Epoetins:

Estimation of equation (6):
$$\Delta(LCP) = \beta_0 + \beta_1 \Delta N + \beta_2 N(-1) + \beta_3 LCP(-1) + \beta_4 \Delta LSTD + \beta_5 LSTD(-1)$$

Dependant variable: ΔLCP, the first-difference of the log of competitor prices.

```
Dependent Variable: D(LCP)
Method: Panel Least Squares
Date: 06/19/15   Time: 14:02
Sample: 1 817
Periods included: 82
Cross-sections included: 10
Total panel (unbalanced) observations: 807
```

Variable	Coefficient	Std. Error	t-Statistic	Prob.
D(N)	-0.071733	0.018707	-3.834524	0.0001
D(LSTD)	0.054499	0.010662	5.111581	0.0000
C	2.315450	0.178768	12.95230	0.0000
N(-1)	-0.018684	0.013941	-1.340151	0.1806
LCP(-1)	-0.418332	0.030966	-13.50949	0.0000
LSTD(-1)	-0.024888	0.007878	-3.159166	0.0016

Effects Specification

```
Cross-section fixed (dummy variables)
Period fixed (dummy variables)
```

R-squared	0.335431	Mean dependent var		-0.004794
Adjusted R-squared	0.246635	S.D. dependent var		0.214519
S.E. of regression	0.186195	Akaike info criterion		-0.412774
Sum squared resid	24.64944	Schwarz criterion		0.145540
Log likelihood	262.5543	Hannan-Quinn criter.		-0.198383
F-statistic	3.777537	Durbin-Watson stat		2.491971
Prob(F-statistic)	0.000000			

Long-run effects	
LCP(-1)	-0,045
LSTD(-1)	-0,059

From the results, it can be concluded that for *filgrastim*, a 1% increase in last-month's growth rate of competitors' prices leads to approximately 38,5% increase in the number of competitors this month. This suggests that the entry effect dominates the *filgrastim* market, so that an increase in the current prices attracts more entrants. The outcome is consistent with the fact that there are more approved biosimilars of *filgrastim* in Europe, namely seven (EMA, 2014). Obviously, at least in the initial periods when only a few products had been granted marketing authorisation, the anticipated revenues remained sufficiently high, hence attractive, for future entrants. In other words, it had taken more time until the market for *filgrastim* got saturated. Indeed, it would be difficult to predict when exactly, if ever, profits on that market would decline so as to preclude further entry. In some countries, for example, local regulations in the recent years have led to such a severe price decrease and curbed profits to such an extent that it has led some manufacturers to actually exit the market. This is confirmed by the long-term effect of biosimilars prices on number of competitors, where a sustained increase in prices would lead to approximately 93% increase in the number of competitors, which is more than what the market can reasonably sustain.

For *epoetins*, where the causality runs in the opposite direction, that is, the number of competitors influences biosimilar prices, each next entrant in the current month leads to a 7% decrease in the price growth rate next month. In the long run, the sustained effect is of 4%. Price volatility does not seem to have too high an impact on price growth rate, yet in the long run, last-period's increase in price volatility rate by 1 unit may lead to almost 6% decrease in biosimilars price growth rate in this period. It is clear that for *epoetin*, the competition effect predominates, whereby each consecutive entrant has the power to drive prices down. This suggests that the *epoetins* market gets saturated much faster, compared to the *filgrastim* market, and this is confirmed by real-world facts: although seven products of the *epoetins* class have been granted marketing authorisation in Europe (EMA, 2015), most markets have fewer competitors locally, namely up to 4, whereas for *filgrastim* the number can reach 7. The faster market saturation for *epoetin* generally means that an optimal point of market participants has been reached sooner than it has been for *filgrastim*.

It is important to have obtained an insight into the strength of the effect in the longer term, spanning years rather than months, because this is a way to capture the persistence of a given control variable's influence. The long-run effects have been calculated from the following formulas:

For *filgrastim:*

$$Long-run\ LCP(-1) = -\frac{Short-run\ LCP(-1)}{Short-run\ N(-1)} \qquad (7)$$

$$Long-run\ LSTD = -\frac{Short-run\ LSTD(-1)}{Short-run\ N(-1)} \qquad (8)$$

For *epoetins:*

$$Long-run\ N(-1) = -\frac{short-run\ N(-1)}{Short-run\ LCP(-1)} \qquad (9)$$

$$Long-run\ LSTD(-1) = -\frac{Short-run\ LSTD(-1)}{Short-run\ LCP(-1)} \qquad (10)$$

At this stage, it is possible to picture the effect of the number of firms on biosimilars prices for *epoetins* (Figure 3), with period fixed effects. There is no definite trend and except for some minor fluctuations, which remain despite the use of the moving averages method, the impact of the number of firms remains relatively stable.

Figure 3: Period fixed effects: N on LCP (*epoetin*)

d. Effect of number of biosimilar competitors on incumbent's prices

Once the relationship between the number of biosimilar competitors and the market prices has been established, the next step is to find out how the number of competitors influences prices of the incumbent manufacturer. This is important in order to understand to what extent the originator may expect to sustain its market share by downward price adjustment, rather than by any other type of product differentiation. In some geographies, the prices of originators may be subjected to a regulation, for instance via mandatory price cuts upon biosimilars entry, or explicit EPR referencing.

Table 9:
Estimation of equation (3): $\Delta LOP = \beta_0 + \beta_1 \Delta LN + \beta_2 LOP(-1) + \beta_3 LN(-1)$
Dependent variable: ΔLN, the first difference of the log of number of marketed biosimilars.

Filgrastim:

```
Dependent Variable: D(LOP)
Method: Panel Least Squares
Date: 06/15/15   Time: 13:23
Sample: 1 830
Periods included: 74
Cross-sections included: 10
Total panel (unbalanced) observations: 653
```

Variable	Coefficient	Std. Error	t-Statistic	Prob.
D(LN)	-0.034765	0.019807	-1.755177	0.0797
C	1.341885	0.139359	9.628978	0.0000
LOP(-1)	-0.242229	0.025141	-9.634784	0.0000
LN(-1)	-0.036490	0.008588	-4.248922	0.0000

Effects Specification				

Cross-section fixed (dummy variables)

R-squared	0.133913	Mean dependent var	-0.002672
Adjusted R-squared	0.117674	S.D. dependent var	0.087721
S.E. of regression	0.082398	Akaike info criterion	-2.134793
Sum squared resid	4.345282	Schwarz criterion	-2.045573
Log likelihood	710.0100	Hannan-Quinn criter.	-2.100194
F-statistic	8.246349	Durbin-Watson stat	2.569596
Prob(F-statistic)	0.000000		

Epoetin:

```
Dependent Variable: D(LOP)
Method: Panel Least Squares
Date: 06/19/15   Time: 12:41
Sample: 1 817
Periods included: 82
Cross-sections included: 10
Total panel (unbalanced) observations: 791
```

Variable	Coefficient	Std. Error	t-Statistic	Prob.
D(LN)	-0.043292	0.043549	-0.994101	0.3205
C	2.372045	0.165526	14.33037	0.0000
LOP(-1)	-0.470939	0.032433	-14.52023	0.0000
LN(-1)	-0.015560	0.027178	-0.572518	0.5672

Effects Specification				

Cross-section fixed (dummy variables)
Period fixed (dummy variables)

R-squared	0.337574	Mean dependent var	-0.006863
Adjusted R-squared	0.249187	S.D. dependent var	0.195664
S.E. of regression	0.169542	Akaike info criterion	-0.600271
Sum squared resid	20.03490	Schwarz criterion	-0.044911
Log likelihood	331.4073	Hannan-Quinn criter.	-0.386813
F-statistic	3.819278	Durbin-Watson stat	2.191309
Prob(F-statistic)	0.000000		

Although for both molecules the estimated effect is found to be considerably weak, the results for *epoetin* are even insignificant (Table 9). This has been partially anticipated given the specificity of *epoetin* in terms of physicians' lower willingness to use biosimilars in place of the originator's product. In this sense, regardless of how many market entrants there are, the incumbent can afford more sustainable pricing given a certain number of competitors, ceteris paribus on other factors.

The outcomes of this regression become more meaningful once the measure of price volatility has been added, which is why the interpretation is postponed to the next sub-section.

e. Effect of price volatility on incumbent's prices

In an attempt to improve on the rigorousness of the results, as well as to control for an additional variable, the regression is extended by the addition of price volatility (Table 10). Arguably, that parameter did improve the outcomes with respect to the p-values and the coefficient estimates for *filgrastim*, yet it failed to lend credence to the *epoetin* estimates, which remained insignificant.

Table 10:
Estimation of equation (4):
$$\Delta LOP = \beta_0 + \beta_1 \Delta LN + \beta_2 LOP(-1) + \beta_3 LN(-1) + \beta_4 \Delta LSTD + \beta_5 LSTD(-1).$$
Dependent variable: ΔLOP, the first difference of the log of the originator prices.

Filgrastim:

Dependent Variable: D(LOP)
Method: Panel Least Squares
Date: 06/19/15   Time: 13:56
Sample: 1 830
Periods included: 74
Cross-sections included: 10
Total panel (unbalanced) observations: 653

Variable	Coefficient	Std. Error	t-Statistic	Prob.
D(LN)	-0.047111	0.023795	-1.979863	0.0481
D(LSTD)	0.004812	0.005057	0.951517	0.3417
C	1.343436	0.143162	9.384011	0.0000
LOP(-1)	-0.242431	0.025782	-9.403207	0.0000
LN(-1)	-0.031376	0.013671	-2.295032	0.0221
LSTD(-1)	-0.001868	0.004166	-0.448382	0.6540

Effects Specification

Cross-section fixed (dummy variables)

R-squared	0.136365	Mean dependent var	-0.002672
Adjusted R-squared	0.117413	S.D. dependent var	0.087721
S.E. of regression	0.082411	Akaike info criterion	-2.131502
Sum squared resid	4.332985	Schwarz criterion	-2.028556
Log likelihood	710.9353	Hannan-Quinn criter.	-2.091580
F-statistic	7.195547	Durbin-Watson stat	2.570266
Prob(F-statistic)	0.000000		

Long-run effects	
LN(-1)	-0,129
LSTD(-1)	-0,008

Epoetins:

```
Dependent Variable: D(LOP)
Method: Panel Least Squares
Date: 06/19/15   Time: 14:04
Sample: 1 817
Periods included: 82
Cross-sections included: 10
Total panel (unbalanced) observations: 791
```

Variable	Coefficient	Std. Error	t-Statistic	Prob.
D(LN)	-0.069892	0.053867	-1.297490	0.1949
D(LSTD)	0.010190	0.010965	0.929362	0.3530
C	2.367083	0.166792	14.19179	0.0000
LOP(-1)	-0.470166	0.032645	-14.40261	0.0000
LN(-1)	-0.001467	0.038243	-0.038356	0.9694
LSTD(-1)	-0.004063	0.008772	-0.463173	0.6434

Effects Specification

Cross-section fixed (dummy variables)
Period fixed (dummy variables)

R-squared	0.339204	Mean dependent var		-0.006863
Adjusted R-squared	0.248880	S.D. dependent var		0.195664
S.E. of regression	0.169577	Akaike info criterion		-0.597678
Sum squared resid	19.98559	Schwarz criterion		-0.030502
Log likelihood	332.3818	Hannan-Quinn criter.		-0.379679
F-statistic	3.755390	Durbin-Watson stat		2.189749
Prob(F-statistic)	0.000000			

Long-run effects	
LN(-1)	-0,003
LSTD(-1)	-0,009

The long run effects have been calculated according to following formulas:

For both molecules:

$$LN(-1) = -\frac{LN(-1)}{LOP(-1)} \qquad\qquad (11)$$

$$LSTD(-1) = -\frac{LSTD(-1)}{LOP(-1)} \qquad\qquad (12)$$

The results indicate that for *filgrastim*, an increase by 1 in the log of the number of competitors (that is, an increase by 2,78 times), leads to about 10% decrease in originator prices in the long run. Thus, strictly speaking, in order to bring about a 10% change in the prices, competitors need to almost triple in number. Naturally, prices across Europe have eroded by more than 10% even prior to the entry of three biosimilar competitors. While in some cases originator prices have decreased indeed, for example in anticipation of biosimilar entries or right afterwards, in other instances biologic originators have managed to sustain high prices even after biosimilars were marketed. Arguably, this strategy is more successful in cases where either the brand loyalty in the country is high, or when the molecular profile of the medicine compels physicians to abstain from prescribing it.

A visualisation of the results demonstrates that the effect of the number of firms on the incumbents' prices is relatively stable throughout time (Figure 4). The trend for *epoetins* can be defined as stable, although the line exhibits a slight downward bend. It is not possible to represent the effects for *filgrastim* in a similar fashion, since for equation (4) the period effects are not fixed.

Figure 4: Period fixed effects: LN on LOP (*epoetin*)

6. Discussion

The attempt to provide insightful conclusions about the entry decisions and price erosion of biosimilars in Europe should always be complemented by the specific regulatory environment in each country. Despite the overall general tendency of biosimilar prices to be influenced by the number of local competitors (*epoetin*), or for the number of competitors to be driven by anticipated profits (*filgrastim*), there still exists cross-country heterogeneity. The estimates derived from the model allow for a somewhat deeper discussion.

The per-country fixed effect of the regression for *filgrastim* – where competitor prices influence the number of entrants – demonstrates that the dependent variables are highest in Poland and Bulgaria, while they are lowest in the Netherlands and Norway (Appendix, Table 11). Interestingly, the highest values are observed in two countries in Central-Eastern Europe, while the lowest are in the North-Western part of the continent. This indicates that price erosion is more severe in North-Western Europe. While this result is surprising given the higher economic strength of countries in that area, it correspond to the use of tenders for biologics (Roediger, 2015). One striking example of the effect of tendering practices in Norway is the 72% discount provided for biosimilar infliximab in early 2015

(GaBI, 2015). At the same time, the fact that multiple cost containment measures have been adopted in the less affluent Central and Eastern European countries and have not led to such a substantial price erosion suggests that those markets hold high enough potential for biosimilars revenues. Naturally, this effect is attenuated by the smaller population size of those nations.

In the regression describing how the number of competitors impacts biosimilars prices for *epoetin*, the highest values are observed in Norway and France, while the lowest are in Italy and Bulgaria. In this case, the geographical division is less clear-cut; still, it is interesting to note that the highest values are found in Western Europe, while the lowest – in Southern. It can be concluded that the number of competitors in Norway and France is relatively higher than that in Bulgaria and Italy, as respective outliers. At first glance, this seems to contradict the results obtained for *filgrastim*, however, given the different nature of the two categories of biosimilar products, it can be anticipated that the observed distribution will be similarly distinct. As Grabowski et al. (2014) have established, Italy has a relatively lower biosimilars uptake as there is persistent reluctance on behalf of physicians to prescribe these products. Possibly, the situation in Bulgaria is similar. As far as the two Western countries are concerned, the results are inconclusive and somewhat contradictory – although France is known for its brand loyalty (Grabowski et al., 2014), it nevertheless has a higher number of competitors in relative terms. This leads to the conclusion that other factors, such as the regulatory environment, can serve to explain why the local market tolerates a higher number of manufacturers.

For the examination of the effect of the number of competitors on originator prices, for *filgrastim*, the highest values of the numbers are observed in Greece and Hungary, while the lowest are in Bulgaria and Poland (Appendix, Table 12). For *epoetin*, despite the insignificance of the regression estimates, the highest numbers occur in Hungary and the UK, while the lowest are encountered in Bulgaria and Italy. Thus, Hungary appears twice in the category of highest values, while Bulgaria – twice in the category of the lowest ones. The differences between the countries with the highest and the lowest values are not substantial. Rather, they demonstrate the country-specific characteristics which do not vary in time with the main dependent variables.

It should be noted that what influences the entry decision of firms is not only the prices of currently marketed biosimilars but also whether the market access environment in a certain country allows for the easy coexistence of multiple competitors. In this sense, if national authorities strictly regulate the prices of each consecutive biosimilar entrant, for instance via mandatory price cuts, EPR or tendering, some markets may have a limited number of competitors. Furthermore, for instance in the Netherlands, although currently biologics are not subjected to tendering, there is a perceived high

likelihood of its introduction in the future. From among the sample of countries, there is a historically high use of generics in Germany, Hungary, the Netherlands, Norway and the UK. Still, campaigns encouraging generics use are taking place in France, as well as in Greece and Italy, although in the latter two countries the success of the campaigns has not been very high. Explicit campaigns encouraging biosimilars uptake are taking place in Norway and Italy, but in the latter they are again evaluated as coming short of achieving truly successful results. In some other countries, such as Greece and Hungary, the undertaken campaigns for biosimilars are not initiated by the national authorities. Another interesting market that is anticipating more stringent regulations is Bulgaria: mandatory price cuts are currently under discussion for all four sub-categories of manufacturers, i.e. pharmaceutical originators, generic entrants, biologic originators and biosimilar entrants. Therefore, when evaluating the attractiveness of the market for a biotech company, the decision to enter is inevitably motivated by the regulatory environment, beside the already predominant prices of competitors.

Admittedly, there are some limitations in the present study. The research has used average manufacturer prices which exhibit some variation throughout time. The fact that the averages contain several products of the same brand and those are sold in different formulations, may occasionally cause additional fluctuation in the average prices due to the corresponding sales volumes. Another element which would add value to the findings is the inclusion of a regulatory parameter in the regression. More specifically, this can be a (national) policy which has been introduced in the recent years, such as the adoption of EPR for biologics, the implementation of a mandatory price cut for originators or biosimilar entrants, the establishment of tendering as a standard means of procurement of biologics, or another type of cost containment measure. The evaluation of the total impact of such a policy on market share, uptake, and price evolution can be informative for payers as well as for biotech companies. Leopold[1] et al. (2014) have prepared such a list of the cost containment measures introduced in eight European countries in the period 2008 to 2011. They reach the conclusion that countries can be divided into two categories: more economically stable and less economically stable. Not surprisingly, the authors (Leopold[1] et al., 2014) have found that less economically stable countries had implemented more policy changes (10 to 22 each), compared to more stable ones (2 to 7 each). Furthermore, the policy measures had positively impacted the sales volumes, while the effect on medicine prices was negative. In a following study, Leopold[2] et al. (2014) have delved deeper into the actual impact of certain policy measures, focusing on Portugal and Finland as representatives of each category of countries according to economic stability. By means of segmented regression analysis of interrupted time series, the authors (Leopold[2] et al., 2014) have been able to measure the effect of introducing EPR system in Finland, and of harmonization of reimbursement rates, radio and TV campaigns for generics promotion and a flat reduction on maximum retail price in Portugal. The

measurements have been made in terms of change of slope in the established sales volumes for certain medicines, and change of level of sales following the policy phase-in period. In order to perform such an evaluation in the context of the present research, specific policies which bear direct impact on biosimilars prices and market entry would have to be identified. Given the current heterogeneity of the regulatory environments in each European country, it would be worthwhile to estimate the effect of policies which have already been implemented. In this way, should a certain cost containment measure gain popularity and be adopted by more than one country, it is important to be aware of the magnitude of its impact within the geographies where it has been in place for at least some years. Consequently, the outcomes of such a research could provide a substantial arsenal of arguments in the hands of the government and the industry, who may argue in favour or against the adoption of such a policy, respectively.

Given the different direction of causality between biosimilar prices and the number of competitors, it is difficult to make predictions about the market behaviour of new biosimilars which are to enter the market in the future. Arguably, the next wave of entrants referencing mAbs might resemble the market of *epoetin*, rather than the one for *filgrastim*. The reason lies in the molecular complexity and the potential uptake. On the other hand, exactly as a result of the low willingness to prescribe these biosimilars, lower prices might be needed in order to incentivise doctors to adopt them and payers to undertake campaigns favouring them. Thus, steeper and faster price erosion may be anticipated. Ultimately, manufacturers should be cognizant of the constant interplay between doctors' inelastic demand, which pulls prices upwards or at least makes them more sustainable, and payers' insistence on making savings, which generally drives medicinal prices down.

7. Conclusion

The results from the present study have informed the understanding of the causality of price erosion and market entry decisions for two INNs in Europe. In addition, there have been convincing indications for cross-country differences with respect to number of biosimilar competitors. Since the regression results for *filgrastim* and *epoetin* indicate a different direction of causality regarding the relation between number of competitors and biosimilar prices, no radical conclusion can be drawn for biosimilars of other INNs. On the market of *filgrastim*, the entry effect predominates, while on the market of *epoetins*, the competition effect holds the upper hand. A 1% increase in *filgrastim* biosimilar prices leads to 38,5% increase in the number of competitors from one month to the next. Each next *epoetin* entrant would bring about 7% decrease in the price growth rate of biosimilars of that product from one month to the next.

In terms of the effect of the number of biosimilar competitors on the prices of incumbents, an important insight is that competition is not the single factor defining originators' price decrease. For *filgrastim*, the model predicts that a long-term 10% price erosion is reached when the competitors have tripled in number. Given that in reality such price erosion can be reached much earlier, it can be concluded that many of the drivers of price erosion remain in the hands of national authorities who exercise much leverage via regulations on biosimilar prices.

The nature of the topic studied here does not easily lend itself to a numerical estimation. Due to the fact that biosimilars are still in their infancy, the rigorousness of the results obtained with this approach will be rising proportionately with the products' longevity on the medicines market. Thus, whether the growth of molecular size of the next wave of biosimilars will be able to bring about more sizeable profits as well, remains to be seen.

APPENDIX

A. Glossary of terminology

Biologic medicine	Biologic medicines are based on proteins (hormones, enzymes, or monoclonal antibodies). Some of them are naturally encountered in the human body. Biologic medicines have a very complex molecular structure and high molecular mass. They are not easily replicable and variability of the structure of the medicines may occur even within the same batch produced by a given company.
Biologic originator	The producer of a biologic drug who also holds a patent on it.
Biosimilar manufacturer	The producer of a medicine which is based ('references') a biologic product which has lost patent protection.
Biosimilar medicine	Biosimilar medicines are based on originator biologic medicines but as it is not possible to replicate the 'reference product' completely, biosimilars are not considered exactly the same as the originator product. Thus, their market dynamics are much different from that of small-molecule drugs. The product cannot be considered completely equivalent to the originator.
Biotech company	A company which produces medicines explicitly based on biologic organisms, such as proteins.
Cost containment measures	Practices generally adopted by European national authorities in response to shrinking budgets and attempts to cut down costs on healthcare expenditure. There is a wide variety of CCMs and they can be applied to different members of the value chain (manufacturers, wholesalers, pharmacists).
European Biopharmaceutical Enterprises (EBE)	An organisation of some members of the biotech industry in Europe. Beside organising some workshops and initiatives, they also

	publish position papers and write reports on relevant biopharmaceutical topics.
European Medicines Agency (EMA)	The main European regulatory body which grants marketing authorisation for medicines on a pan-European level. It also issues guidelines for the use of certain medicines.
European Price Referencing (EPR)	The system of international price comparison of medicines which can be based on INN prices or the respective manufacturer's own prices abroad.
Generic medicine	A small-molecule medicine which has the same molecular structure as an originator product ('reference product') that is off patent. The product can be considered an equivalent to the originator.
Indication	The specific disease or condition for which the respective medicine is used. Some medicines receive marketing authorisation for more than one indication.
International non-proprietary name (INN)	The name which is given to the molecule of a certain innovative drug and this name is used for all medicines with the same molecule which are produced after the patent expiration of the originator.
mAbs	A specific type of biologic medicines which is said to lead the next big wave of products on the drugs market. The revenues brought about by these products are considerable (accounting to billions of euros), thus there is increasing interest on behalf of the entire industry in the pricing and market share development of these products.
National price referencing (NPR)	The system of price referencing on a national level, whereby the prices of products in the same therapeutic or INN class are compared and the lowest one is used to set the

	reimbursement level for that class of medicines.
Pharmaceutical originator	The manufacturer of a small-molecule medicine who still holds patent rights on it (usually for the duration of about 20 years).
Pharmacovigilance	The practice of monitoring the medical performance on patients of a certain drug in terms of side effects, adverse reactions or any life-threatening issues. Biosimilar products are normally subjected to such strict monitoring.
Small-molecule medicine / pharmaceutical	Chemical medicines which have relatively simple molecular structure. Being based on simple chemical synthesis, they are easily replicable in laboratory environment.
Substitution	The practice of fulfilling the prescription at the pharmacy and dispensing a drug based on the INN, regardless of the brand name. In most European countries it is possible to substitute generic medicines, but it is hardly anywhere the case for biosimilars.
Switching	The practice of changing the brand of the medicine, but not the active ingredient (or INN) with which a patient is treated. This is usually performed by physicians and is particularly important for biologics and biosimilars, since biosimilars are not considered to be exact copies of the originator (or 'reference') product. Safety and tolerability are among the ain concerns when switching patients from an originator biologic product to a biosimilar or vice versa.

B. Country effects from regression estimates

Table 11: Country fixed effects*

filgrastim	epoetin

	COUNTRY	EFFECT		COUNTRY	EFFECT
1	Bulgaria	0.245176	1	Bulgaria	-0.579337
2	France	0.456326	2	France	0.000294
3	Germany	-0.287050	3	Germany	0.186414
4	Greece	-0.317019	4	Greece	0.248465
5	Hungary	-0.010674	5	Hungary	0.244722
6	Italy	0.343748	6	Italy	-0.312923
7	Netherlands	-0.474200	7	Netherlands	0.192242
8	Norway	-0.336114	8	Norway	0.078872
9	Poland	0.096841	9	Poland	-0.226839
10	UK	0.282965	10	UK	0.168088

* *Filgrastim*, equation (2):
$$\Delta(N) = \beta_0 + \beta_1 \Delta LCP + \beta_2 N(-1) + \beta_3 LCP(-1) + \beta_4 \Delta LSTD + \beta_5 LSTD(-1)$$
Epoetin, equation (6):
$$\Delta(LCP) = \beta_0 + \beta_1 \Delta N + \beta_2 N(-1) + \beta_3 LCP(-1) + \beta_4 \Delta LSTD + \beta_5 LSTD(-1)$$

Table 12: Country fixed effects**

	filgrastim			epoetin	
	COUNTRY	EFFECT		COUNTRY	EFFECT
1	Bulgaria	-0.365478	1	Bulgaria	-0.939750
2	France	-0.080849	2	France	-0.007868
3	Germany	0.275615	3	Germany	0.300269
4	Greece	0.066545	4	Greece	0.259049
5	Hungary	0.104203	5	Hungary	0.126254
6	Italy	-0.247829	6	Italy	-0.268472
7	Netherlands	0.120619	7	Netherlands	0.201047
8	Norway	0.174328	8	Norway	0.308939
9	Poland	-0.251951	9	Poland	-0.158310
10	UK	0.129675	10	UK	0.178842

** *Filgrastim*, equation (4):
$$\Delta LOP = \beta_0 + \beta_1 \Delta LN + \beta_2 LOP(-1) + \beta_3 LN(-1) + \beta_4 \Delta LSTD + \beta_5 LSTD(-1)$$
Epoetin, equation (4):
$$\Delta LOP = \beta_0 + \beta_1 \Delta LN + \beta_2 LOP(-1) + \beta_3 LN(-1) + \beta_4 \Delta LSTD + \beta_5 LSTD(-1)$$

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