COMPETITION CONCERNS IN THE EX-PATENT BIOLOGICAL MEDICINES MARKET
A EUROPEAN PERSPECTIVE

Alejandra Scherk
151474

Project Tutor:
Paz Soler Masota
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Alejandra Scherk Fontanals
Barcelona, 03/06/2016
ABSTRACT

Biological medicines are the future of pharmacology and medicine. They derive from a biological source (a typical example being insulin) and those which are ex-patent, together with their copies—which are called “biosimilar medicines”-, conform the ex-patent biological medicines market.

The study of such a market reveals two issues: First, that although market shares of the main players of the industry do not show a problematic level of concentration (when looking at the aggregate of all medicines), high concentration levels do appear when subdividing the market for each drug. Second, that although the entry of biosimilars reduces market shares for branded biological medicines (also decreasing their prices), a different impact will be observed depending on the country.

The study suggests, thus, that there are competition concerns in the market, and to address them it is proposed to use legislation, creating common principles for the development and testing of biosimilars at a global level (facilitating international competition), setting an abbreviated pathway for biosimilars’ commercial approval (when they are already marketed outside Europe), giving biosimilars and their reference products the same International Non-Proprietary Name (so as to eliminate the perception of differences) and allowing interchangeability and substitution by law.
INDEX

INTRODUCTION .................................................................................................................... 1

SECTION ONE: PRELIMINARY CONCEPTS........................................................................ 3
  1.1 BIOLOGICAL MEDICINES VERSUS SMALL MOLECULE MEDICINES ........... 3
  1.2 BIOSIMILARS VERSUS GENERICS................................................................. 5
  1.3 BIOSIMILAR’S APPROVAL BY THE EUROPEAN MEDICINES AGENCY ...... 8

SECTION TWO: MARKET ANALYSIS .............................................................................. 10
  2.1 PRODUCT AND GEOGRAPHIC MARKET ...................................................... 10
  2.2 MAIN PLAYERS, MARKET PENETRATION AND PRICE EROSION ............ 12
  2.3 COMPETITION CONCERNS ........................................................................... 17

SECTION THREE: BIOSIMILAR MEDICINES REGULATION AND PROPOSED
AMENDMENTS .............................................................................................................. 20
  3.1 COMMERCIAL APPROVAL........................................................ ................. 20
  3.2 EXTRAPOLATION ........................................................................................... 23
  3.3 NAMING ........................................................................................................... 24
  3.4 INTERCHANGEABILITY ................................................................................... 25
  3.5 SUBSTITUTABILITY ......................................................................................... 26

CONCLUSIONS ................................................................................................................ 29

BIBLIOGRAPHY ............................................................................................................... 31
INTRODUCTION

This Paper analyses the competition degree of the ex-patent biological medicines market, a specific area of the pharmaceutical sector where branded biological medicines compete with biosimilar ones. It represents the first essay of its type, and it aims to make a critical review of the factors that influence the degree of competition of the aforementioned market, suggesting potential improvements at a regulatory level.

The ex-patent biological medicines market has been chosen as the subject-matter of study because of the great importance biological medicines will have for the entire economy and for healthcare systems\(^1\), which makes it vital to ascertain whether their regulation is adequate and whether they conform a competitive market (as competition has an influence on prices, innovation and product quality).

The study is centred in the European market, because it has the most developed and mature regulation (the European Medicines Agency was the first entity to regulate biosimilars, in 2006) and has set high safety standards, which are a candidate to be exported as a model for other countries.

competition. To conclude, it will summarize the main results arising from the study, pointing to future problems that will have to be addressed by the regulator.

The economic and juridical analysis carried out by this Paper is based on the study of public records issued by the main regulatory bodies in the pharmaceutical sector at a European level (including laws, guidelines and directives) and sector reports on biosimilar and biological medicines, published by the main consultancy firms of the sector (McKinsey & Company, Blackstone Group, IMS Institute for Healthcare etc.). Information has also been gathered on biosimilar conferences and interviews held with selected industry experts, which have contributed significantly to the investigation. In this regard, I would like to thank the College of Pharmacists of Barcelona and all the professionals that have been kind enough to answer my questions.
SECTION ONE: PRELIMINARY CONCEPTS

When analysing the biological ex-patent medicines market, there are highly technical terms, processes and products that come into play. In order to better understand the economic and legal analysis that will be conducted in further sections, it is important to introduce some of these technical concepts at this stage, which will also contribute to a first delimitation of the object of our study.

1.1 BIOLOGICAL MEDICINES VERSUS SMALL MOLECULE MEDICINES

Biological medicines derive from a biological source such as a bacterium or yeast and are usually based on proteins\(^2\). Clear-cut examples thereof would be human insulin or monoclonal antibodies\(^3\). Since they derive from life organisms, they are characterised by structural variability, micro-heterogeneity and instability. However, these traits do not prejudice the safety and efficacy of the resulting product. Instead, they contribute to provide the market with a higher level of differentiation.

Opposed to this concept we find small molecule medicines, which are produced by chemical synthesis (i.e. “combining certain chemicals in a defined series of chemical reactions”\(^4\)) and are much simpler than biological medicines (see comparison on Figure 1). Small molecule medicines are present in our everyday life, and one example of them would be the active ingredient of Aspirin (acetylsalicylic acid).


\(^3\) Monoclonal antibodies are molecules that mimic natural antibodies. They are typically used to treat cancer.

During the 20th century most pharmaceutical newly developed products were small molecule medicines. On the 21st century, though, the tendency changed: today it is difficult to come up with new small molecule medicines, and biological medicines are gaining presence in the market. In this sense, it is worth noting that one of McKinsey’s reports highlights that “biopharma’s annual growth rate for 2014 was more than 8% (double of conventional pharma), and growth is expected to continue at that rate for the foreseeable future”.

Pharmaceutical sales are still dominated by small molecule medicines, but on 2015 biological medicines accounted for 1/3 of total sales of the market, which represents quite a high proportion, considering that it is to keep growing steadily.

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1.2 BIOSIMILARS VERSUS GENERICS

If creating a generic drug is like designing a tricycle, then a biosimilar is like building a spaceship, in terms of complexity and size.

Asthika Goonewardene

A biosimilar is a biological medicine that is designed to be similar to a previously approved biological medicine (hereinafter, the “reference product”). It must be remarked that the biosimilar is similar but not equal to this reference product; it is a quasi-copy because a perfect replica cannot be achieved with the current state of technology, given the complex nature of biological medicines.

Furthermore, it must be stated that biosimilars are not the same as generics: generics do have simpler chemical structures (as they replicate small molecule medicines) and are identical (or bioequivalent) to their reference product in terms of safety, strength, quality, dosage form, route of administration etc. Indeed, and compared to biosimilars, they have a very different process and cost of manufacture.

Concerning the manufacturing procedure, creating a biosimilar medicine requires a quite complex and expensive process of investigation and manufacture that generics do not need. The investigation process precedes manufacturing, and it requires the reference product to be analysed by scientists, who isolate its basic features and quality attributes. These attributes, in turn, will be taken into account to establish comparability with the reference product.

Once comparability parameters are set, the manufacturing process starts. Its first step involves isolating the genes that will ultimately produce the biosimilar, which are chosen to match the reference product’s features.

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8 Quotation by GOONEWARDENE A., Senior analyst with Bloomberg Intelligence, extracted from an article by LORENZETTI L. (2015), “Biosimilars may one day save your life. But what are they?”, Fortune Digital version (available at http://fortune.com/2015/02/06/biosimilars-what-are-they/).


The selected genes are inserted into host cells, using DNA technology, and the resultant genetically modified cells are selected and grown in large bioreactors, creating a cell line that produces the protein for the biosimilar.

Once this is accomplished, the proteins are extracted from the cells and purified through sophisticated and lengthy manufacturing processes. At the end of them, the biosimilar is finally ready for packaging and storage.

Figure 2. Summary for biosimilar’s manufacturing

The process to create generics follows a similar path, but contains relevant differences, as the investigation process is simpler (for it solely requires the use of reverse engineering to determine the chemical composition of the drug) and the manufacturing process cheaper and

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more efficient, as it is based on chemical synthesis and not on cell culturing with DNA technology (which is obviously more complicated to handle).

Furthermore, the process to create a generic is fairly constant and easy to control, but this does not happen for biosimilars, which are highly sensitive to manufacturing conditions and can be completely changed by any minor variation (generating a different medicine). Thus, the process is of utmost importance for this kind of drugs, to the point that the industry claims that “the process is the product”\textsuperscript{12}. This is also revealing of the difficulty in creating biosimilars, which is accentuated by the fact that the cell lines and production processes used by each biological medicines manufacturer are unique and different.

An example that may help to illustrate the relevance of the processes involved (and the difficulty of copying them) is Novo Nordisk’s commercial success. Novo Nordisk’s main product is insulin and, although there is a lot of competition in its market, Novo Nordisk has a particular production process that enables it to offer a differentiated insulin, making the company highly profitable (its return on equity is of 80\%\textsuperscript{13}, and the market average is around 12\%\textsuperscript{14}).

The differences between the production processes of biosimilars and generics are what explain the disparities on their production cost: as biosimilar are copies of biological medicines (which consist of intricate molecules) and are subject to a complex manufacturing and approval process, their production cost is much higher than that of generics, being closer to the cost of production of a new medicine.

The magnitude of the difference in cost is shown in Figure 3, and it is important to bear it in mind for further analysis, because it will have an impact on both i) the number of competitors which we will observe in the market and ii) the price reduction that will be achieved for consumers, as an aftermath of the introduction of biosimilars.

\textsuperscript{12} Note: Excerpted from the notes of the author taken from the contributions on occasion of the meeting “about biosimilars and insulin glargine”, held at the College of Pharmacists of Barcelona (31/03/2016), conducted by Dr. Fernando DE MORA, Professor of the Pharmacology, Therapeutic and Toxicology Department, at the Universidad Autónoma de Barcelona.


\textsuperscript{14} See SP500 data (available at http://csimarket.com/Industry/industry_ManagementEffectiveness.php?&hist=1).
Figure 3. Summary of the resources (in millions of US$) and time spent in developing a medicine\textsuperscript{15}

<table>
<thead>
<tr>
<th></th>
<th>New Product</th>
<th>Generic</th>
<th>Biosimilar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>400-1500 M$</td>
<td>1-3 M$</td>
<td>60-250 M$</td>
</tr>
<tr>
<td>Time</td>
<td>8-15 years</td>
<td>1-2 years</td>
<td>6-12 years</td>
</tr>
</tbody>
</table>

\textbf{1.3 BIOSIMILAR’S APPROVAL BY THE EUROPEAN MEDICINES AGENCY}

One of the factors that will be preeminent in determining the production cost and the number of competitors in the off-patent biological medicines market is the process that biosimilars producers have to follow to get commercial approval in Europe, which is defined by the European Medical Agency (hereinafter, “EMA”) in its Guidelines.

According to them, biosimilars have to undergo an approval process consisting of a series of tests, which include:

i. In vitro studies, to assess any potential difference in biological activity between the biosimilar and the reference product.

ii. In vivo animal studies (if needed), when in vitro studies cannot provide all necessary information.

iii. Clinical studies, to finally determine whether the medicine can be considered a biosimilar and become commercialised.

iv. Pharmaco-vigilance, providing data after commercialisation to identify any rare adverse effects.

Clinical studies are the longest and most hazardous test biosimilars have to pass through (although some are already discarded after in vitro or in vivo studies). In this stage, biosimilars have to undergo efficacy trials and pharmacokinetic and pharmacodynamic studies, to show that the efficacy, absorption, distribution, metabolism, and excretion of the biosimilar and the reference medicinal product are analogous.

Within the clinical studies, the trials are made on humans in different phases:

\textsuperscript{15} See note 12.
i. On phase I the drug is tested in a small group of healthy volunteers (20-80 people) to evaluate safety, dose range and side effects.

ii. On phase II the test is conducted in a bigger group of ill volunteers having the disease to be treated (100-300 people), to define the dose and prove effectiveness.

iii. On phase III, the drug is tested in an even larger group of ill patients (500-20,000 people), so as to confirm effectiveness, disclose side effects, and establish the right dosage for the future patient treatment.

After all these phases are successfully overcome (and in the hypothetical case that the biosimilar merits approval), the resulting product will be launched into a competitive market, as we shall describe in the following section.
SECTION TWO: MARKET ANALYSIS

2.1 PRODUCT AND GEOGRAPHIC MARKET

The product market to be analysed is the ex-patent biological medicines market, which includes ex-patent branded biological medicines and their substitutes (i.e. the biosimilars that copy them). Patent-protected biological medicines should conceptually be excluded from this market (given that they have exclusivity –rectius, ius prohibendi vis-à-vis third parties-, they are to be discarded from the market dynamics), but the study will take them into account when making estimates for the long term, for they shall eventually lose patent protection and become ex-patent biological medicines.

This market currently generates 65 billion dollars worldwide in terms of revenue. Biosimilars account for 1.5 billions thereof (approximately a 2%) and the rest comes from branded biological sales. By 2025, though, these numbers are expected to change: it is estimated that the global market will be worth 45 billion dollars, and that 18 billions of it will be biosimilar sales. This fact has two main implications: first, that biosimilars will increase their importance in the market (representing a 40% of its revenue by 2025); second, that they will significantly erode market revenues for branded biologics. In this regard: where it not for the biosimilars entry, the global market would be estimated to be worth 90 billion dollars by 2025; due to the abovementioned, the estimate is 45 billion, leading to a 50% savings through price erosion (see Figure 4).
Having set a broad idea of the worldwide market, it must be noted that the study will focus on the European Union (hereinafter, “EU”). This approach has been chosen given the strict European safety standards applicable to the development of biosimilars and the degree of sophistication of the regulation on biosimilars, accounting as a leading reference for other markets to follow. Evidence of this is the fact that 50% of worldwide biosimilars sales are in the EU\textsuperscript{17} -which has specific regulation for them since 2006, having approved 20 biosimilars- whereas the USA (the typical reference market) accounts for only 10% of the global biosimilar sales\textsuperscript{18} -having issued its first regulations on 2015 (with a high resemblance to the EU) and having approved only one biosimilar (Zarxio).

As a final observation, it must be said that the EU biological medicines market is very broad and covers heterogeneous types of medicines and countries. In this regard: official reports published by EMA distinguish different biosimilars (Epoetin, Insulines, Human growth hormone, Granulocyte colony-stimulating factor, Anti-tumor necrosis factor and Follitropin

\textsuperscript{17} TOSCANO D. (2013) “Are Biosimilars the Road to a Certain Success or a High Risk Venture?”, Frost and Sullivan’s presentations (complimentary webinar, available at http://es.slideshare.net/FrostandSullivan/are-biosimilars-the-road-to-certain-success-or-a-highrisk-venture).
\textsuperscript{18} TOSCANO D. (2013) “Are Biosimilars the Road to a Certain Success or a High Risk Venture?”, loc. ult. cit.
Alfa), and they all have different production processes and different impacts on the mechanics of competition (which, in turn, vary depending on the individual country).

An example of product heterogeneity is the comparison between insulin and monoclonal antibodies: the insulin submarket is quite a mature one, where there are many substitutes and competitors. Competition in it is, thus, not centred on creating new insulines, but on improving the existing ones (i.e. making them edible or migrating them from daily to weekly doses). The contrary happens, though, with monoclonal antibodies: these medicines are used to treat cancer and constitute a new field of study, in which competition is based on creating new substitutes.

An example of heterogeneity in the competition dynamics depending on the country can be seen in subsection 2.2 (see Figure 7 and preceding comments).

That these differences exist does not preclude the possibility of conducting a general market study, evaluating all biosimilars jointly. This can be done because all biosimilars share a common trend: they increase competition and erode price and market share for firms which are already in the market (incumbent firms).

2.2 MAIN PLAYERS, MARKET PENETRATION AND PRICE EROSION

As mentioned before, the biological medicines market is measured adding up biosimilar sales (which account for a 40% of total sales) and branded biological medicines (which account for the remaining 60%).

In the biosimilars field, the main players are Sandoz, Amgen and Hospira\(^\text{19}\). These three firms are expected to each have a 9% of the total relevant market, and other biosimilar companies with smaller market shares (as Mylan, Biogen, Momenta etc. –see Figure 6 for a more comprehensive list-) will accumulate together a 13%.

In the field of branded biologics (which will compete with biosimilars when going ex-patent), the main players are Roche, Abbvie, Sanofi and Johnson&Johnson\(^\text{20}\). These firms will account each for a 12% of the total market, and the remaining 12% of branded biological sales will be distributed amongst smaller players.

\(^{19}\) Hospira is now part of Pfizer.

\(^{20}\) CAMPBELL J.J. (2008), Understanding Pharma: the professional’s guide to how pharmaceutical and biotech companies really work, 2nd ed., Pharmaceutical institute, United States of America.
Given the number of players and their market shares, it can be asserted that concentration is rather low for the market as a whole. This is confirmed arithmetically by the Herfindahl-Hirschman Index (often used by the European commission to evaluate market concentration), which is less than 1,000 -a level not considered problematic by the authorities-. However, a further analysis should be made taking a closer look at individual medicines (as each one conforms a submarket of its own).

If we look at Figure 6 (containing estimates for 2025), we can derive that for each biological off-patent medicine different biosimilars will arise in the market (between two and nine). A priori, this suggests that the degree of competition is going to be rather high. However, this statement must be qualified: with estimated market shares in each drug of 60% for the incumbent and, probably, 20% for the leading biosimilar producer (sharing other firms the remaining 20%), the applicable Herfindahl-Hirschman Index ratio will raise up to 4,000, which is rated as oligopolistic by European Commission’s standards. It must be noted,

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however, that competition might not significantly be damaged by this fact, as if the number of producers for each medicine remains high enough, these will act as a constraining influence for bigger players.

Figure 6. Main biosimilar products and companies that will produce them (estimates for 2025)\(^{23}\)

![Table showing biosimilar sponsors and companies producing them]

The main effect of multiple players entering the market and producing biosimilars is typically a drop in prices of between 20%-30%, but since the launch of Zarxio in the US, previsions have been reviewed and some market analysts bet now for higher savings, up to 50% in 2025\(^{24}\).

It is interesting to see that the decline in prices is not comparable to the one achieved by generics, which are 60%-80% cheaper than the original product they replicate. Still, as the reductions apply to more expensive medicines (an annual treatment with a biological medicine can cost up to 50,000$), they will bring an important amount of savings to the healthcare system.

It must be said, however, that both in market shares and price erosion there will be important dissimilarities amongst medicines and countries. To show these differences, it is interesting to

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observe the price and market share evolution in the European countries as of Epoetin and Anti-tumor necrosis factor in 2014 (see Table 7 below).

i. Epoetin is a biosimilar that promotes the development of red blood cells and haemoglobin. In its submarket at a EU level it has an average market share of 15% (having led to a price drop of 27% for the incumbent firms). In Germany, though, its market share is 70% (with an associated price drop of 47%) and in Belgium a 0% (with an associated price drop of 12%).

ii. Anti-tumour necrosis factor, on the other hand, is a biosimilar that treats inflammatory conditions as arthritis or Crohn’s disease. In its submarket at a EU level it has acquired a market share of 1% (having led to a price drop of 1%), with similar results across all countries.

**Figure 7. Summary table**

<table>
<thead>
<tr>
<th></th>
<th>Average market share</th>
<th>Individual countries market share</th>
<th>Average price drop</th>
<th>Individual countries price drop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoetin</td>
<td>15%</td>
<td>70% (GR), 0% (BL)</td>
<td>27%</td>
<td>47% (GR), 12% (BL)</td>
</tr>
<tr>
<td>Anti-Tumor Necrosis Factor</td>
<td>1%</td>
<td>2% (CR), 1% (IR)</td>
<td>1%</td>
<td>4% (CR), 1% (IR)</td>
</tr>
</tbody>
</table>

From these examples three concepts are to be retained: first, that severe price reductions might appear even when the biosimilar does not acquire a significant market share (as in the case of Epoetin in Belgium); second, that the difference among countries can be very notorious (as in the Epoetin example); and third, that some biosimilars have modest effects on the market (as is the case of the Anti-tumor necrosis factor), although this is partly due to the recent introduction of the biosimilar.

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Regarding price decreases brought by biosimilars (even when they have low market shares): they derive from defensive actions taken by companies that are already present in the market. On this respect, data has shown that the correlation between market share and price decrease is small, suggesting that the simple threat of biosimilars entering the market already acts effectively on market prices, generating a competitive environment (see Figure 8).

**Figure 8.** Correlation between Epoetins market share and the increase in price per treatment days, for the whole submarket\(^{26}\).

![Figure 8](image)

Interpretation of the graph: as the dots lie roughly in a flat horizontal line, not showing a clear slope against the horizontal axis, we interpret that the discount is relatively independent of the market share, meaning that the mere entry of the biosimilar leads to a substantial price discount even without the incumbent losing market share.

On the other hand, the different impact of biosimilars in each country is explained by various factors that cannot be easily determined (i.e. and among others: whether patients are able to afford biologics, or whether payers, prescribers and patients advocate in favour of biosimilars), but in any case it implies that there will be different price levels depending on the country. Elaborating on this topic, it must be said that differential pricing by country is not always undesirable. There are two main reasons for price discrimination: i) increasing patient access (charging lower prices to poorer countries) and ii) mere profit improvement\(^ {27}\). In the former case, price discrimination is a justified and desirable action, but in the latter it amounts to an abuse of position -made by companies with great bargaining power-.

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The problem in the EU is that the preeminent reason for price discrimination is profit making, and this can be seen after comparing medicines cost with the Gross Domestic Product (hereinafter “GDP”) per capita of every EU country: as a lower GDP per capita does not necessarily translate into lower prices\(^\text{28}\), it can be said that the differential is designed to increase profit (if its objective were to increase patient access, the price would show an almost perfect correlation with the GDP per capita, being lower for poorer countries and higher for richer ones, which is not the case).

### 2.3 COMPETITION CONCERNS

Forward to the previous considerations, it might be reasonably deducted that there are some competition concerns at an industry level, independently of the various price elasticities should we drive a comparison between countries.

However, these concerns are not severe at this stage for two reasons: first, because if we aggregate all drugs as if they were a single market, the main players do not show a relevant level of concentration –see Figure 5 and the following paragraph-. Second, because even though from an individual medicine standpoint the resulting Herfindahl-Hirschman Index might be high (thus indicating oligopoly risk), it is believed that other firms will enter the market, ensuring a reasonable level of workable competition. In brief: the entry of biosimilars would erode market power for insiders, which would experiment a decrease in their market shares, rivalry would be the key note and prices would, ultimately, be competitive (see Figure 6 and comments below).

Still, relevant problems might appear in a medium and long-term perspective. These are related to the fact that incumbent firms might fiercely defend their current position by rising artificial barriers of entry to the market. As an example of defensive moves taken by the incumbents, it must be noted that only large companies are being successful in biosimilars.

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\(^{28}\) The list of countries that pay the most for medicines does not coincide with the list of richer countries of the UE. To see the different prices paid in each EU country, see KANAVOS P. et. al. (2010), “Differences in Costs of and Access to Pharmaceutical Products in the EU”, Directorate General for Internal Policies – Policy Department A, figure 2, p. 12 (available at http://www.europarl.europa.eu/RegData/etudes/etudes/join/2011/451481/IPOL-ENVI_ET(2011)451481_EN.pdf). To see the GDP per capita of these countries, see the World Bank database for GDP per capita (available at http://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD).
Small companies either do not enter the industry or, if they do, have low profitability. For instance: Momenta Pharmaceuticals Inc. (a small company wholly dedicated to biosimilars creation) has always had losses and is expected to have them at least until 2019; moreover, its market value in the stock exchange is equal to the capital paid out by its shareholders, indicating zero value creation. Coherus Biosciences Inc. (a similar company) has also experienced and will have persistent losses at least until 2019, although in this case there is a modest value creation, as its market value is about 1.6 times the capital disbursed by the shareholders. These figures contrast with the ones of bigger companies (such as Roche, Amgen, Sandoz, etc.) which have been and will be profitable every year, and whose market value is, approximately, 5 times the value of the capital disbursed by the shareholders\textsuperscript{29}.

The fact that only big and well established companies enter the market of biosimilars can also be troublesome because of the high amount of mergers and acquisitions that characterize the pharmaceutical sector\textsuperscript{30}, which could lead to a higher level of concentration and give rise to anti-competitive dynamics. Nonetheless, if the European Commission takes proper action when mergers occur -setting the adequate requirements so as to ensure competition-, inefficient concentration and market sharing agreements (such as a market share-out for products, or a geographical distribution) could be prevented.

Regarding this issue, it can currently be affirmed that the European Commission is following a reasonable path to protect competition insofar as biosimilars are concerned. This assertion can be illustrated through the analysis of the most recent case involving companies that create biosimilars\textsuperscript{31}, where the Commission evaluates Pfizer’s proposal to acquire Hospira.

In the case, the Commission focuses its investigation on three biosimilar drugs where the merging firms compete (Infliximab, Rituximab and Trastuzumab). After analysing each medicine’s market, the Commission concludes that there are competition concerns for infliximab, but not for Trastuzumab and Rituximab\textsuperscript{32} (for which there will be more than six sellers in a short period of time, competition being guaranteed). Accordingly, the Commission approves the merger with one condition: the full divestment by Pfizer of the

\textsuperscript{29} Data extracted from the financial statements of Momenta Pharmaceuticals, Coherus Biosciences, Roche, Sandoz (part of the Novartis group), Amgen, Hospira (now part of Pfizer) and Abbvie.


development, manufacturing and marketing rights of its infliximab biosimilar, that must be sold to a company that i) is independent from the merging firms, ii) has sufficient financial resources, expertise and incentive to continue the development of infliximab, iii) is an active competitive force in the market and iv) does not generate competition concerns by purchasing the biosimilar business\textsuperscript{33}.

Such a solution can be deemed optimal for competition (and thus, it is recommended that the Commission continues to follow this approach), because i) it is based on a deep and accurate study of the markets involved (whose characterizations highly resembles the one we would obtain with the data of Figure 6), ii) it conditions the approval of the transaction on the sale of the whole production unit devoted to the production of the Infliximab and iii) it defines the characteristics the purchaser should have so that, after the sale, no competition concerns are generated and a new competitor is born.

\textsuperscript{33} Note that the biosimilar has been finally sold to Sandoz (part of Novartis group). The information regarding the transaction can be consulted on Novartis’ webpage (see https://www.novartis.com/news/media-releases/sandoz-strengthens-its-biosimilars-portfolio-acquisition-pfizers-biosimilar).
SECTION THREE: BIOSIMILAR MEDICINES REGULATION AND PROPOSED AMENDMENTS

When the market was analysed (see Section two above), both ex-patent branded biological medicines (sold by the incumbent firms) and biosimilars (sold by “competitor firms”) were included as market players. However, in order to propose amendments to current laws and improve competition, this Section will mainly analyse the regulation on biosimilars, as it is their number and market share that will increase competition in the sector. The analysis will be centred on the most problematic fields of biosimilar regulation, which, according to multiple authors\(^\text{34}\), are: commercial approval, extrapolation, naming, interchangeability and substitutability.

3.1 COMMERCIAL APPROVAL

In the EU, it is the Committee for Medicinal products for Human Use (which is integrated in the EMA) who evaluates marketing applications for biological medicines and issues a recommendation on whether to accept them or not. According to it, the European Commission grants or denies commercial authorisation, being its decision valid for all EU Member States.

The necessary procedures and requirements of this process are set on three legal sources: i) Regulation (EC) No 726/2004 - which lays down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use-; ii) Directive 2001/83/EC - relating to medicinal products for human use-; and iii) EMA’s scientific guidelines. Let us briefly describe herein their main contents, respectively:

Regulation (EC) Nº 726/2004 is a generalist law stating the documents and data that should be provided to the European Commission in order to get a marketing authorisation. Three are its main goals: first, the data to be included in the application dossier are those executed by Directive 2001/83/EC; second, the form of the application is that specified by EMA’s

guidelines (available at EMA’s webpage); and third, applicants who carry clinical trials outside the EU should also include a statement that these meet the ethical requirements of the aforesaid Directive.

Directive 2001/83/EC is a more specific regulation, which clearly states the requirements a company should comply with for a successful application. The relevant parts most directly affecting biosimilars are article 8, article 10.4 and Section 4 from Part II of Annex I:

i. Article 8 sets forth a general framework that applies to all medicines, stating that commercial approval will only be granted to applicants established in the European Community and that, moreover, applicants should provide various types of data, including the name of the applicant, the name of the medical product, the qualitative and quantitative particulars of all the components of the medicinal product, etc.

ii. Article 10.4 refers specifically to biosimilars, requiring applicants to provide information about bio-equivalence, bio-availability and other pharmaceutical, chemical and biological characteristics, establishing furtherly the obligation to carry out pre-clinical tests or clinical trials (and providing their results) when the biosimilar does not comply with the definition of a generic medicinal product.

Note that a generic is identical to the original product it replicates and a biosimilar complying with this definition is extremely unlikely: given the actual state of technology, biosimilars differ from the reference product regarding both raw materials and manufacturing processes, and identity with the reference product is non achievable.

iii. Section 4 from Part II of Annex I is also specific to biosimilars, and complements the regulation from article 10.4, indicating the additional information that should be provided when similarity cannot be proven under the mechanisms indicated in the aforementioned article. The information required will vary depending on the case, addressing toxicology and other non-clinical and clinical issues, according to the principles of EMA’s guidelines.
EMA’s scientific guidelines are a non-legally binding regulation, but several legal documents regulating biosimilars request that applicants follow them when submitting marketing applications. They provide a harmonised basis for the interpretation and application of the requirements from the Community directives to prove quality, safety and efficacy, and cover a wide variety of issues including, among others and essentially, the quality, biological and non-clinical matters, clinical efficacy and safety.

Regarding the effect of the abovementioned regulations and guidelines: as they require specific tests and data that are not harmonised at an intercontinental level, they happen to limit competition standards within the European frontiers, disregarding international competition and so focusing in setting up a market aligned with local industries, which might be prone to succumb to oligopolistic behaviour. In order to outbalance this risk, all health (objective) security guarantees being equal, an aperture to other regions should not be initially disregarded. Mutatis mutandis, this opening move is not alien to the European doctrine held for other sectors\(^35\), resulting in a boost in terms of competitiveness.

That could be driven through, at least, the following main actions:

i. The promotion of a joint (international) working platform, with the goal to set forth a common estate of basic principles for biosimilars’ development and testing. This working platform should be claimed and promoted within the frame of the Agreement on Trade-Related Aspects of Intellectual Property Rights (hereinafter “TRIPS Agreement”), to assure a harmonized global improvement and the approval of general rules, to be enforced within all the signatory parties. This proposal might be qualified as naïve or idealistic, but it rescues the very original philosophy underneath the TRIPS Agreement\(^36\). Such a proposal would carry along a previous attempt to reinforce the competitive position of European pharmaceutical enterprises in a global negotiation and, at the end of the day, this might ameliorate the degree of transparency at

\(^{35}\) Such an opening has already been observed in various sectors on the UE (remarkably on textiles, steel, automobiles or chemicals) thanks to its membership to the World Trade Organisation.

European level (should European pattern of regulation be exhibited as the leading model to be implemented in other countries).

ii. Without prejudice of the above, and from a material perspective, all efforts should be devoted to set up an abbreviated pathway for biosimilars’ commercial approval, in particular when the biosimilar has been already and securely commercialised in countries from other regions. This abbreviated pathway should require reduced testing, being supplemented by a study made by European authorities, taking into account the experience of the country where the biosimilar is already sold.

3.2 EXTRAPOLATION

Closely related to commercial approval is the concept of extrapolation, consisting of the idea that, if a biosimilar works out in one indication, it could be reasonably assumed that it should further work in other indications where the medicine of reference is approved37.

For the EU, extrapolation is regulated succinctly on both (i) Directive 2001/83/EC (Annex 3.2) and (ii) EMA’s Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance:

On the one side, Directive 2001/83/EC, in its Annex 3.2, states that extrapolation will only be valid when justified or proven. More specifically, it indicates that if the reference product has more than one indication, the efficacy and safety of the biosimilar has to be “justified or, if necessary, demonstrated separately for each of the claimed indications”.

On the other side, EMA’s Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance complements the abovementioned regulation, stating that extrapolation can be accepted if enough clinical data is provided and whenever biosimilar comparability has been demonstrated in one therapeutic indication by thorough in vitro functional tests and physico-chemical and structural analyses. Additional data

37 TESCH H. et. al. (2013), "Clinical experience with Zarzio in Europe: what have we learned?", National Centre for Biotechnology Information (available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3765845/).
is required, though, when it is unclear that the safety and efficacy of one indication is relevant for the others and when a different impact is expected from the drug in other indications.

Both the Directive and the EMA’s Guidelines are based on a quite restrictive approach and do result in a hurdle for competition, exempted after the performing Jiminy Cricket role of a “necessary evil” to protect public health and EU’s population: a more tolerant position would lead to less safety for citizens and therefore, the status quo should be preserved as it is. In this regard: it would not be consistent to propose changes downgrading the requirements to extrapolate, because it would jeopardise and run counter to the key principles of the European configuration for the pharmaceutical industry, which are based on patient safety and would never admit such a modification.

3.3 NAMING

In general, medicines are named through their commercial brand name and their International Non-Proprietary Name (hereinafter “INN”), which is a unique name globally recognized and coordinated by the World Health Organization38. For instance: Infliximab is the INN for a biological medicine, and it is marketed by Merck under the commercial brand name of Remicade, by Hospira under the commercial brand name of Inflectra and by Celltrion under the commercial brand name of Remsina.

In the biosimilar world naming has been a big controversy, as the medical community is divided on whether or not biosimilars should have the same INN as their reference product. Because of such a polemic, so far it has not been possible to develop any formal rules for biosimilar naming in the UE. In practice, however, biosimilars are given the same INN as the reference product39.

In order to improve competition, the absence of a global compromised regulation on this issue should be overcome and the same INN should be given to biosimilars and their reference products: not doing so could impact quite severe and negatively the uptake of biosimilars,

differentiating them from the reference product and suggesting that they are not a real or feasible alternative.

Arguments against this solution might be that using the same INN could bring up trouble in the post-marketing monitoring\textsuperscript{40}. Aside that there is no substantial evidence yet on this issue (as biosimilar medicines prescriptions and adverse effects reports include their brand name, so monitoring should not be a major problem), it seems reasonable to conclude that measures could be taken to counterbalance any given potential risk (for example, setting up a regulation to reinforce the rigor of internal state reports, making sure they adequately identify every medicine through their INN, their batch number, their product name, their manufacturer and their assigned regional regulator code\textsuperscript{41}).

Other arguments are based on the fact that biosimilars are somewhat different to the reference product\textsuperscript{42}, but even assuming this, it cannot be denied that the reference product itself differs from its subsequent versions, as it evolves on time when there are post-approval manufacturing changes. Hence, if further versions of the reference product use the same INN, so should do the biosimilar medicines that imitate them.

### 3.4 INTERCHANGEABILITY

According to the European Commission, interchangeability is the medical practice of "changing a medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient with the agreement of the prescriber"\textsuperscript{43}.

Interchangeability is regulated at a country level, and regulations (as in the case of naming) are not complete and thorough. For example: Spain’s regulation states somehow laconically

\textsuperscript{40} Johnson&Johnson submitted a Citizen Petition to the US Food and Drug Administration on January 8th of 2014 based on this argument, asking that biosimilars were named after an INN that was similar but not equal to that of the originator product.


that “in the case of biosimilars, the current rules about substitution and interchangeability will be respected”\footnote{The European Association for Bioindustries (2014) “EuropaBio guide on biosimilars in Europe”, p. 15 (available at http://www.europabio.org/sites/default/files/position/europabio_guide_to_biosimilars_europe_2014.pdf).}, and it does neither prohibit nor allow interchanges. Indeed, this is the case of the majority of EU member states, where –at present- there is nothing that legally prevents doctors from interchanging the reference product for a biosimilar, but there is also nothing enabling them to do so. This places healthcare professionals in a context of legal uncertainty, leading them to be overcautious and to recommend the reference product so as to avoid potential liabilities.

At this stage, considering the scope and perspective of this essay, in order to revert this dynamic and to restore a reasonable legal certainty and workable competition, the optimal solution seems to be promoting a solid interchangeability at a European level, protecting healthcare professionals’ criteria so that they are more inclined to promote biosimilars.

To attain this, it is proposed making explicit that biosimilars are interchangeable with the originator medicines under the supervision of a healthcare professional, taking a similar approach as the Finnish Medicines Agency in Finland’s healthcare system\footnote{Finnish Medicines Agency (2015), “Position on Interchangeability of Biosimilars”, p.4 (available at https://www.fimea.fi/documents/542809/838272/29197_Biosimilaarien_vaihtokelpoisuus_EN.pdf).}. This would imply fixing in law one of the essential principles of physicians, which, in the context of biological medicines, would provide greater guidance and legal security for the entire sector, having a positive effect on biosimilars prescription and on competition.

### 3.5 SUBSTITUTABILITY

Substitution involves dispensing one medicine instead of another equivalent and interchangeable medicine at a pharmacy level, without consulting the prescriber\footnote{European Commission (2013), “What you need to know about Biosimilar Medicinal Products” (available at http://ec.europa.eu/DocsRoom/documents/8242/attachments/1/translations/en/renditions/pdf).}. In other words, it is the equivalent to interchangeability but with the change being made by the pharmacist (not the doctor).

Substitution is customarily regulated at a country level, but all European countries’ specific legislations have been issued after the same lines and either prohibit substitution or grant it...
under severe conditions. For instance, Spanish law forbids substitution\(^{47}\) whereas French regulation permits it on very restrictive terms, namely when: i) the treatment has not yet started, ii) the biosimilar belongs to the same group as the prescribed product -according to the French healthcare authority-, and iii) the prescribing physician has not explicitly prohibited substitution indicating “non-substitutable” on the prescription\(^{48}\).

It is obvious that this sort of regulations might represent an obstacle to competition, so it is worth considering alternative strategies that could be adopted by the EU authorities, such as following the section of USA’s law that refers to substitution.

USA’s law about substitution is still pending, but amongst its main principles (which have already been announced\(^{49}\)), it includes the distinction of two biosimilar categories: basic biosimilars (which are not granted substitutability) and “substitutable biological products”\(^{50}\) (which are biosimilars proven to have the same clinical result as the reference product in any given patient, being substitutable at a pharmacy level).

Enacting such a distinction in the EU would clearly weaken the competitive profile of the basic biosimilars, but it would also strengthen that of the substitutable biological products, leading to a situation that could increase competition whenever the regulation assured that i) the procedure to acquire the status of “substitutable biological products” was transparent and based on a competitiveness standard (taking into account a medium and long term perspective) and ii) that there was an active engagement of the acquirers of this status to exploit their privilege in an effective way. Indeed, if both conditions were met, USA’s proposed regulation will be valuable so as to promote competition.

Still, establishing such measure would require a great legislative effort in the EU, as it would require to develop a specific set of scientific guidelines and to regulate a matter that typically fell on hand of the member states. Thus: in order to accurately evaluate all costs and benefits and decide whether it is worth to implement such a regulation, it would be advisable to

\(^{47}\) See article 86.5 of Law 10/2013, of 24 July, by which the Law of Guarantees is modified.

\(^{48}\) See article 47 of the Law of 23 December 2013, concerning the budget of Social Security.


\(^{50}\) Note that the FDA uses “interchangeable biological product” instead of “substitutable biological product”. This is due to differences in terminology, but the definition given by the FDA coincides with the one the EU gives to substitutable products. Thus, this is the term used by this report.
observe first the final USA guidelines (whose publishing is expected in 2016) and check how they affect competition in the USA market.
CONCLUSIONS

One of the main conclusions arising from this paper is that the off-patent biological medicines market is not wholly competitive, given that it hosts price discrimination and a high concentration level in each medicine submarket. Nevertheless, it must be noted that the situation is not highly problematic, because i) if all drugs are packed together in a single market, the market shares of the main players of the industry do not show a problematic level of concentration, ii) from an individual medicine standpoint, even though the Herfindahl-Hirschman Index is high, it is believed that enough firms will enter the market so as to ensure competition, iii) the entry of biosimilars will erode market power for insiders, which will lose some of their market share, and iv) prices are estimated to decrease.

That prices are estimated to decrease is the most important factor to argue that competition deficiencies are not too relevant. This statement, however, does not mean that competition could not and should not be increased. In this regard, it is recommended to implement some changes to the laws governing the European market, including:

i) The creation of a joint set of basic principles for biosimilars’ development and testing at a global level (following the philosophy of the TRIPS Agreement), plus an abbreviated pathway for biosimilars’ commercial approval -especially when the biosimilar has been already commercialised outside the EU-;

ii) Implementing a regulation confirming that biosimilars and their reference products are to be given the same INN, ratifying to the physicist and patient community that biosimilars are fully comparable to their reference products;

iii) Allowing interchangeability by law, not only de facto, increasing legal certainty and, thus, biosimilar promotion by physicists (which will in turn increase competition); and

iv) Adding a new biosimilar category to foster substitution by pharmacists, based on USA’s regulation, once this country’s experience confirms that such a measure is profitable for companies and an effective tool to increase competition.

A last recommendation would be that the European Commission continues to follow a conservative approach when applying merger law in this sector, imposing strict conditions to ensure that competition is maintained.
Finally, it must be said that this paper has evaluated the current situation of the market, where biosimilars replicate somewhat simple biological medicines. However, many changes are expected to come, as we are now observing the dawn of the biological medicines era. In this regard, it must be pointed that extremely complex biological medicines will be developed in the near future, and the creation of their biosimilars will raise new challenges for the regulator, who will have to design specific guidelines and tests to establish similarity between highly complex molecules\(^{51}\).

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\(^{51}\) Actual measures will not be enough to characterise more complex molecules and assure they are similar to their reference product. See Ash RAMZAM (2015), “The Future of Biosimilars: monoclonal antibodies and beyond”, *The Organisation For Professionals In Regulatory Affairs*, conclusions of p. 9 (available at https://embed.topra.org/sites/default/files/regrapart/1/6182/2015-9-regulatory-rapporteur-future-biosimilars-2sept.pdf)
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