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Market Access of Biosimilars

European and US perspectives

White Paper

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Introduction

Over the past two decades, biologics have established themselves as a highly innovative group of drugs with a significant impact on healthcare. At the same time, healthcare policymakers have been faced with challenges related to the funding of these innovations. With the expiry of patents of original biologics, a new market segment has emerged – the biosimilars.

Biosimilars are poised to improve access to biological medicines and their scientific advancement. As of the beginning of 2017, 23 biosimilars in the EU and 4 biosimilars in the US have obtained marketing authorisation. Although the market uptake of biosimilars has been relatively slow to date, the future role of biosimilars in the biotech market is promising. The number of biological products reaching patent expiry in the coming years, combined with the increased attention on managing the cost of care, are set to create a sound basis for a near-term increase in the biosimilar market.

Definitions

Conventional pharmaceutical products are inorganic, small-molecule compounds. The molecular structure of the final versions of these chemical drug products can be fully characterised with analytical techniques. Consequently, companies other than the originator can chemically replicate the original active ingredient, thus producing a generic version. The approval of a generic small-molecule drug by regulatory authorities is primarily based on the demonstration of bioequivalence and does not require large and expensive clinical trials.

In contrast to small-molecule compounds, biological products consist of large, complex and heterogeneous molecules that are difficult to characterise completely. The molecular weight of biologics ranges from 6,000 to approximately 150,000 Daltons for monoclonal antibodies (Amgen, 2015) compared to a few hundred Daltons for a small molecule compound, e.g. 180 Daltons for Aspirin. Biologics, also called biotech drugs, are typically comprised of proteins and antibodies derived from genetically modified living organisms. Biologics are used to treat serious and life-threatening diseases such as cancer, diabetes and rheumatoid arthritis.

The manufacturing of a biologic product involves technology-intensive biologic systems occurring in bioreactors. In a testimony prior to the United States House of Representatives on February 4th, 2016, J. Woodcock stated that "unlike generic drugs, biosimilars must be highly similar to, not the same as, the reference product to which they are compared." A biosimilar can have certain allowable differences, but it must demonstrate no clinically meaningful differences compared to its reference product.

The process resulting in the market authorisation of a generic is estimated to cost between USD 2 million and USD 3 million, and lasts 2 to 3 years. However, the effort leading to the market authorisation of a biosimilar represents an investment in the range of USD 100 million to USD 250 million over 7 to 8 years, involving a Phase III clinical trial.

The EMA (2017) defines biosimilars as:

"A similar biological or 'biosimilar' medicine is a biological medicine that is similar to another biological medicine that has already been authorised for use. Biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies.

Biosimilars can only be authorised for use once the period of data exclusivity on the original 'reference' biological medicine has expired. In general, this means that the biological reference medicine must have been authorised for at least 10 years before a similar biological medicine can be made available by another company."

The FDA's (2017) definition is:

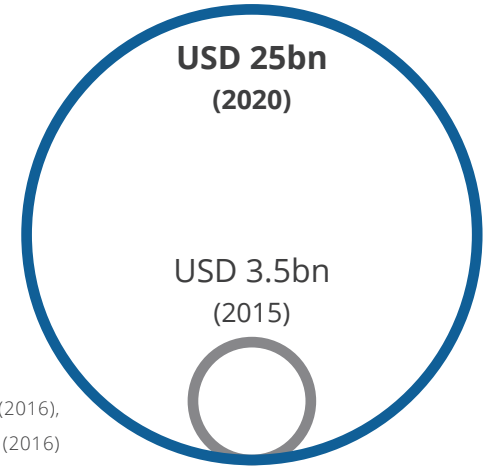
"Biosimilars are a type of biological product that is licensed (approved) by the FDA because they are highly similar to an already FDA-approved biological product, known as the biological reference product (reference product) and have been shown to have no clinically meaningful differences from the reference product. Minor differences in clinically inactive components are allowed. But there must be no clinically meaningful differences between the biosimilar and the reference product it was compared to in terms of the safety, purity, and potency of the product."

Global Market Value of Biosimilars

The global pharmaceutical market reached USD 1,069 billion in 2015 (IMS Health, 2016) with the North American market accounting for 48.7% of the total market (Statistica, n.d.).

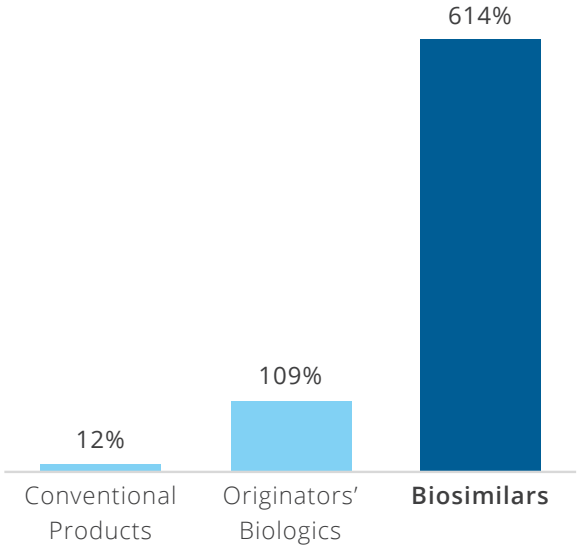
Worldwide sales of biologic medicines represented USD 178 billion in 2015 (Dureuil, 2016) whereas global sales of biosimilars were estimated at USD 3.5 billion in 2015 (Wyseguyreports, 2016).

Global sales of biosimilars



Source: Singh (2015), Report Buyer (2016), Wyseguyreports (2016)

2015-2020 Growth Expectations



The Institute for Healthcare Informatics (IMS) predicts that the global biologic medicines market will exceed USD 390 billion by 2020. Thus, biologics are expected to make up 28% of total sales of the global pharmaceutical market, which by 2020 is expected to be worth USD 1,390 billion (Aitken, 2016).

According to several analyses conducted by different institutions (Singh, 2015; Report Buyer, 2016), the biosimilars market is expected to cross the USD 25 billion mark by 2020 with Europe remaining the major revenue source (Singh, 2015).

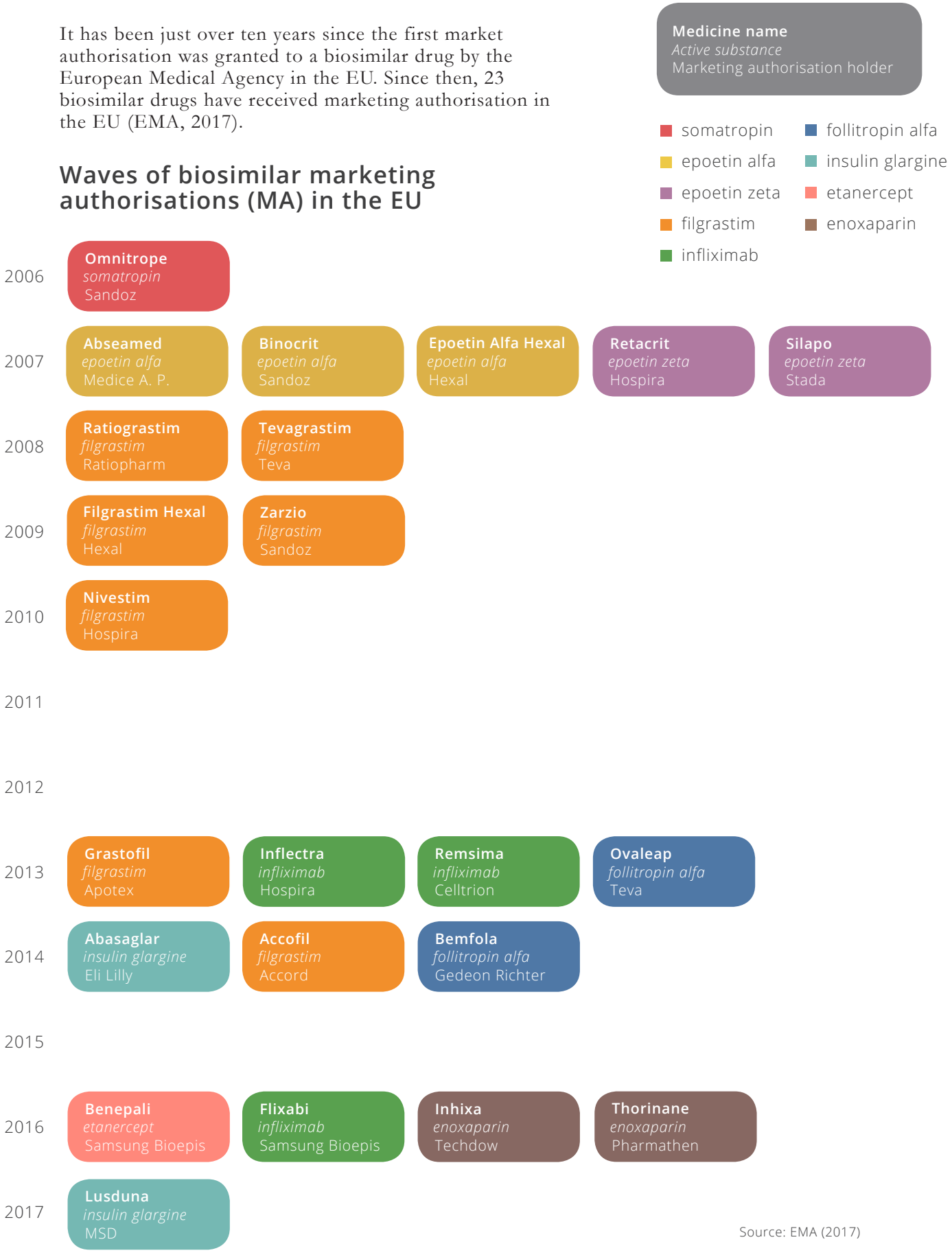
Source: Singh (2015), Aitken (2016), IMS Health (2016), Dureuil (2016), Report Buyer (2016), Wyseguyreports (2016)

With a growing number of patent expiries and clearer regulatory pathways, biosimilars have emerged as one of the fastest-growing categories in the biopharmaceutical sector. Biosimilars, which may contribute to considerable savings within health care systems over the next 10 years, might also widen access to treatments for life-threatening diseases such as cancer, multiple sclerosis and diabetes.

Market Uptake in Europe

It has been just over ten years since the first market authorisation was granted to a biosimilar drug by the European Medical Agency in the EU. Since then, 23 biosimilar drugs have received marketing authorisation in the EU (EMA, 2017).

Waves of biosimilar marketing authorisations (MA) in the EU



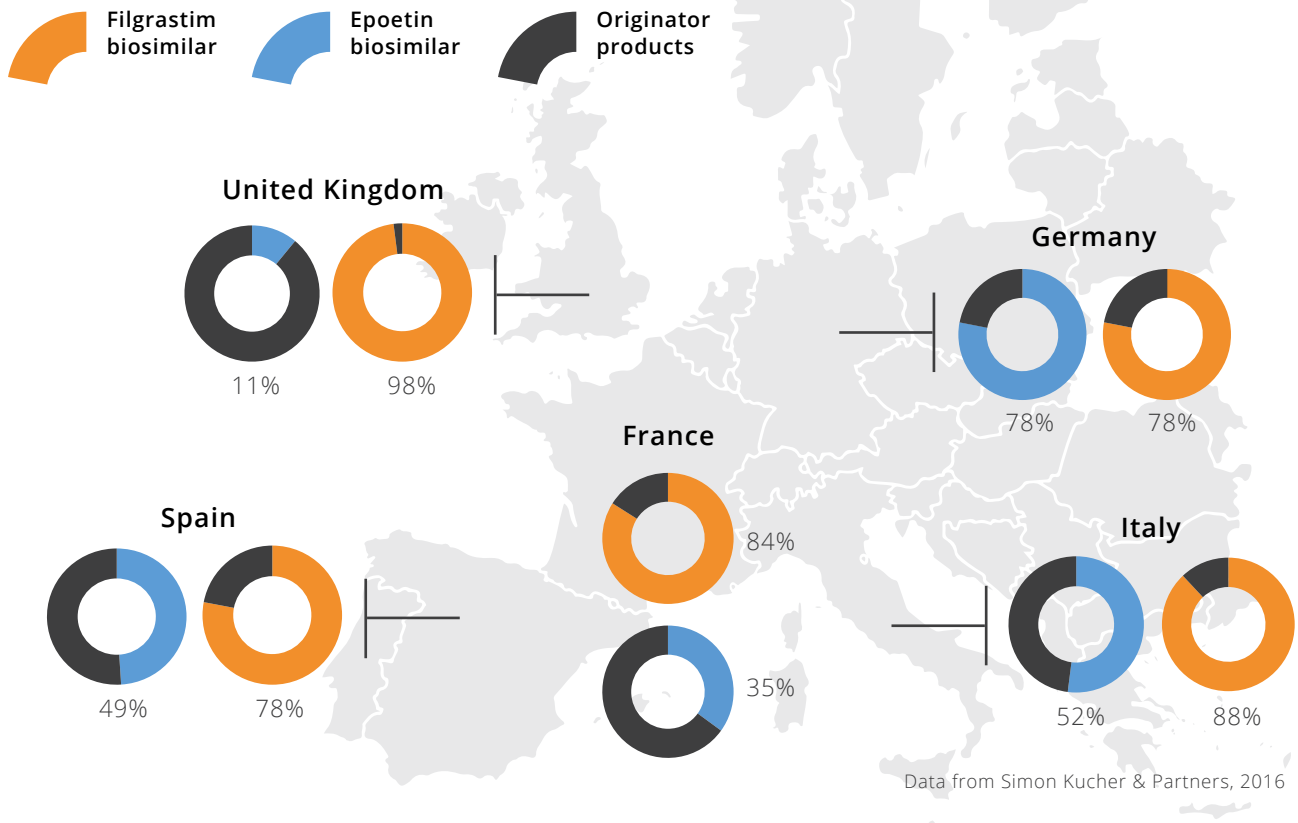
Source: EMA (2017)

Representing 80% of global biosimilar spending, Europe is the most developed biosimilar market (Jacoby et al., 2015).

After a decade, the market uptake of biosimilars has been disappointing and is perceived as an underperformance in Europe (Aitken, 2016). Moreover, the competitive performance of the biosimilars in Europe is heterogeneous, both across countries and drug classes, with epoetin having a much lower market share of biosimilars across the European countries than filgrastim (Grabowski et al., 2014). Reasons for the slower than expected uptake in Europe include the lack of automatic substitution of biosimilars and the physicians' as well as patients' insufficient familiarity with biosimilars. Widely different reimbursement systems also appeared to be market uptake hurdles in certain countries.

In the five major EU countries, the market share (in Treatment Days = TDs) of epoetin biosimilars ranged from 11% in the UK to 78% in Germany in 2015. In contrast to epoetin's heterogenic situation, the market share (TDs) of filgrastim biosimilars ranged from 78% in Germany and Spain to 98% in the UK in 2015. Two years after the first marketing authorisations, the market share (TDs) of infliximab biosimilars in the 5 major EU countries spanned from 4% in France to 13% in Spain (Simon Kucher & Partners, 2016).

Market Share in Treatment Days 2015: Biosimilars vs. Originators



Data from Simon Kucher & Partners, 2016

With regards to price erosion, there are broad variations across the 5 major European countries and the different drug classes. The price reduction of epoetin biosimilars versus the originator's price, prior to the loss of exclusivity (LoE), ranged from 1% in the UK to 57% in Germany in 2015.

Prices of originators are eroding significantly and aligning with the biosimilars' price, especially in Germany and Spain. Filgrastim biosimilars also show considerable price decreases, up to 48% vs the originator's price prior to the loss of exclusivity (LoE). It is likely that price reductions are even higher, as the data is based on official price lists and does not reflect confidential agreements on rebates (Simon Kucher & Partners, 2016).

Market Situation in the US

According to the FDA's list of approved biologic products, also known as the "Purple Book", there were 4 biosimilar products approved as of the beginning of 2017 (FDA, 2016). Zarxio was the first biosimilar product to be approved in the US in March 2015. For over a year it remained the only biosimilar product licensed by the FDA. There was no further approval until April 2016, when Inflectra received the FDA's market authorisation. Since then, Erelzi and Amjevita were approved in August and September, respectively (FDA, 2016; Wikipedia, 2017).

With 4 approvals, the US lags far behind the approved 23 biosimilar products in Europe. In the US, biosimilar companies are afflicted by the late creation of a regulatory approval pathway for biosimilars and a number of remaining unknown factors in terms of future FDA regulations. Uncertainties surrounding patient, physician, and payer response are also an issue. Additionally, ongoing litigations between the originator and the biosimilar's market authorisation holder are slowing down the market uptake in the US. These factors, combined with the perceived moderate discount against the original biologic product, lead to frustration among stakeholders.

Pfizer only launched Inflectra in late November 2016, 9 months after the company obtained marketing authorisation for the product. Pfizer announced that Inflectra would be introduced at a 15% discount to the current wholesale price (Pfizer, 2016).

Similarly, it had taken more than 6 months for Sandoz to launch Zarxio. The American biotech group Amgen had tried to prevent the launch of Zarxio, but the Washington-based appeals court rejected the attempt. Zarxio was launched with a price discount of 15% to the original product (Hirscher and Shields, 2015).

The US Court of Appeals for the Federal Circuit has ruled that a biosimilar applicant is always required to provide a 180-day notice following the FDA license of the biosimilar product (Ramage, 2016). The rule was triggered as a result of the analysis of the patent dance and notice requirements in the case of Amgen versus Sandoz. Consequently, Sandoz and Amgen, with approval dates in August 2016 for Erelzi and September 2016 for Amjevita, will be able to launch their biosimilars in March 2017 at the earliest. Both the intensive patent litigations comprised in the biosimilar firms and the 180-day notice rule are substantially delaying commercial activities of the involved companies.

Name of biosimilar
Active substance - four letter identifier
Marketing authorisation holder

Original product
Originator company

Date of Biosimilar FDA Approval

March 6, 2015

Zarxio
filgrastim-sndz
Sandoz

Neupogen
Amgen

April 5, 2016

Inflectra
infliximab-dyyb
Celltrion/Pfizer

Remicade
Janssen Biotech

August 30, 2016

Erelzi
etanercept-szzs
Sandoz

Enbrel
Amgen

September 23, 2016

Amjevita
adalimumab-atto
Amgen

Humira
Abbvie

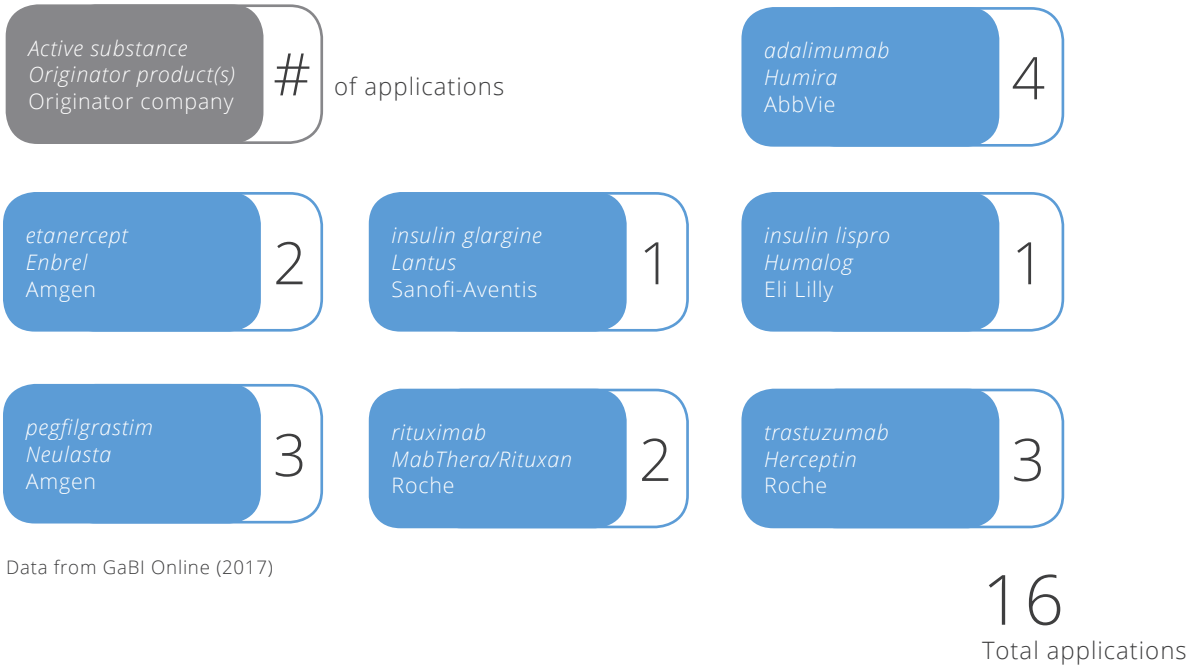
Source: FDA (2016), Wikipedia (2017)

Upcoming Biosimilars

Numerous applications for biosimilar versions of major drugs have been submitted to the EMA and to the FDA in 2016. With 16 biosimilars presently being reviewed by the EMA, several waves of new approvals can be expected, including approvals for rituximab and adalimumab.

The applications that are currently under review by the FDA represent a real transition for the US biosimilar market. These applications include the biosimilars of three active substances for which no biosimilar is approved so far. Thus, 2017 offers a real potential for market enlargement and it may become a watershed year for FDA approval and launches of biosimilars in the US.

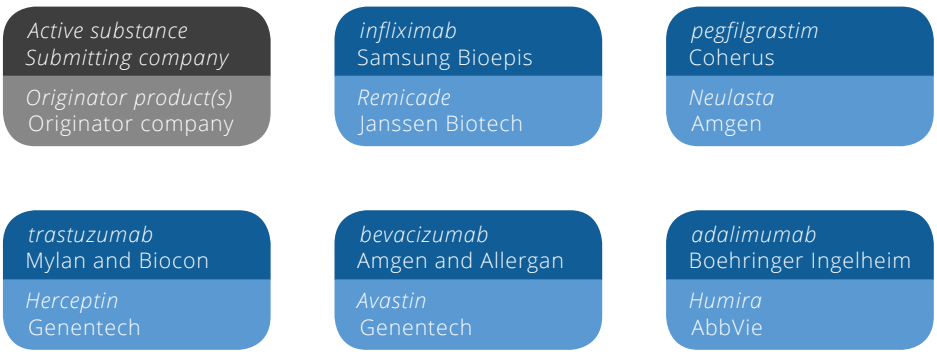
Biosimilars under review by the EMA as of January 2017



Data from GaBI Online (2017)

16
Total applications

Biosimilars under review by the FDA



Data from Sutter (2017)

Key Players

Key players in the biosimilars market include Amgen (US), Pfizer (US), Biocon (India), Celltrion (South Korea), Dong-A Socio Group (South Korea), Dr. Reddy's Laboratories (India), Genentech – a Roche company (Switzerland), Mylan (US), Sandoz – a Novartis company (Switzerland), Samsung Bioepis (South Korea), Stada Arzneimittel (Germany), Teva Pharmaceuticals Industries (Israel). These key players have established developmental strategies in order to gain a competitive edge in the market.

SANDOZ

Sandoz is already holding marketing authorisations for three biosimilars in Europe and two biosimilars in the US, including the first biosimilar approved in the US. The company aims to secure FDA approval for several mega-blockbusters (Farooq, 2016).

AMGEN

In 2014, Amgen had acknowledged biosimilars as a growth opportunity with the potential to deliver more than USD 3 billion in annual revenues. After the launch of Amgen's first biosimilar in 2017, four others are expected to be launched through 2019 (Amgen, 2014).

CELLTRION

Celltrion is currently conducting clinical trials with biosimilars of Avastin and Humira. This will represent the "second wave" for the company's biosimilar introduction (Kim, 2016).

PFIZER

After the acquisition of Hospira in 2015, biosimilars became a new focus for Pfizer. Currently, the company has three biosimilars approved in the EU and one that received FDA approval. Biosimilars may start showing meaningful impact in Pfizer's revenues by 2019 (Forbes, 2016).

Global Regulatory Background

The first specific regulatory pathway for the approval of biosimilars was defined in the EU in 2003. Since then, many countries have established specific legal frameworks and regulatory pathways for the registration of biosimilars. Australia, Japan and Korea issued guidelines in 2008-2009 (Nick, 2015).

In the US, on the 15th of June 2009, President Obama acknowledged: "We need to introduce generic biologics into the marketplace. This will save us billions of dollars. But today there is no pathway for approving biosimilars at the FDA". The legal framework for approval of biosimilars in the US was implemented in 2010, followed later by India and China.

International Regulatory Pathways for Biosimilars

EU	2003/2004	Legal Framework
Australia	2008	Adopted EU guidance
Japan	2009	Final guideline
Korea	2009	Guidelines
USA	2010	Legal framework
India	2012	Guidelines
China	2015	Guidelines

Data from Nick, 2015

Regulatory Background in Europe

Since 2003, an approval pathway for biosimilar medicines has been in place in the EU. The main regulatory texts for biosimilars in the EU are Directive 2003/63/EC, Directive 2004/27/EC, as well as a series of guidelines (Osmane, 2014).

The company developing the biosimilar needs to provide the authorities with data demonstrating that there are no significant differences between the biosimilar medicine and the original biologic in terms of quality, safety, and effectiveness. Information on the reference medicine is already available. Therefore, the amount of information that is required (on safety and efficacy) in order to recommend a biosimilar for authorisation, is usually less than the amount needed to authorise an original biological medicine (EMA 2012). Decision-making on the interchangeability between a biosimilar product and the reference medicine remains the responsibility of healthcare professionals – the EMA does not make recommendations.

The EMA launched a "tailored scientific advice pilot project" in February 2017, whereby companies developing biosimilars may seek advice from the EMA. The EMA advice will focus on the studies companies should conduct, based on a review of the available quality, analytical and functional data (EMA, 2017).

Regulatory Background in the US

Following the Patient Protection and Affordable Care Act (Affordable Care Act) signed by President Obama on the 23rd of March 2010, an abbreviated approval pathway was created for biological products that are demonstrated as "biosimilar" to or "interchangeable" with a biological product. These statutory provisions are also known as the *Biologics Price Competition and Innovation Act of 2009* (FDA, 2017). According to these provisions, the sponsor seeking the approval of a biosimilar product should provide the FDA with data from analytical studies demonstrating that the biological product is "highly similar" to the reference product. Additionally, the data should include animal studies and at least one clinical study in one or more appropriate conditions of use for which the reference product is licensed (FDA, 2017).

Since the abbreviated approval pathway in the US was enacted, the FDA and the industry have been working on practical issues related to its implementation.

US law has adopted a unique approach in creating a specific designation for interchangeable biosimilars. No other country has a separate "interchangeability" appellation in the regulatory approval process. The acquisition of a designation of interchangeability involves additional data provided by the sponsor. The data in question shows that the patient may receive either the biosimilar or the originator's product without impacting safety or efficacy. The denomination of interchangeability allows the pharmacist to substitute the originator's product by the biosimilar (Novartis, 2016). In January 2017, the FDA released a long-awaited document regarding the practical implementation of interchangeability. The document, which is still in its draft form for public consultation and comments only, is called "Considerations in Demonstrating Interchangeability with a Reference Product Guidance for Industry" (FDA, 2017).

A further challenge in the clarification of the US regulatory context is related to the naming of biosimilars. The FDA's issuance of a draft guidance on Naming Conventions in April 2016 triggered a controversy among stakeholders: a potential for confusion resulted from the four-letter suffix to the nonproprietary names shared with the originators' biologics. In January 2017, the FDA released the "Nonproprietary Naming of Biological Products - Guidance for Industry" by which a suffix without specific meaning and composed of four lowercase letters will be used for biosimilar products. The FDA stated that it "is continuing to consider the appropriate suffix format for interchangeable products" (FDA, 2017).

Pricing & Reimbursement in Europe

Although the EMA has implemented a centralised regulatory approval pathway, each European country has the right to develop and implement their own pricing and reimbursement policy for biosimilars.

Consequently, the market access situation across the EU is very heterogeneous with varying levels of incentivisation among stakeholders. Germany has had the highest uptake of biosimilars due to the implementation of measures stimulating the prescription of biosimilars. By contrast, Austria's approach with a pricing and reimbursement system, following the model of the generics, has had the opposite effect. This approach resulted in some biosimilars such as Infliximab being excluded from the market for several years (Racamier, 2016; Aitken, 2016).

FRANCE

In 2016, the CEPS (Comité Économique des Produits de Santé) clarified its policy for biosimilar pricing. In the retail setting, biosimilars are expected to be priced ~25-35% below the originator. Subsequently, the originator's price is expected to be cut by 15% to 20%. In the hospital framework, the CEPS is expected to apply a 10% price cut on the originator's product. The biosimilar will be priced at parity to this new price (Alff, 2016).

GERMANY

The following measures have been effective in promoting considerable biosimilar market share in Germany: fixed reference price (FRP) groups, tendered contracts, prescribing share quotas, and automatic pharmacy substitution (Alff, 2016).

ITALY

Facing great financial pressure, the regions have solicited the Ministry of Health to implement national measures aimed at supporting expenditure control and access to innovative drugs. Regions have specifically requested the implementation of market access rules for innovative drugs, with an emphasis on cost-benefit and therapeutic efficacy criteria (Alff, 2016).

SPAIN

Towards the end of 2014, the Spanish Ministry of Health announced its new reimbursement policy for biosimilars. The price expected after discounts, at both national and regional level, was 30% lower than the originator's price (The Pharma Letter, 2015).

UNITED KINGDOM

As published in January 2015, the National Institute for Health and Care Excellence (NICE) will evaluate biosimilar products in the context of an MTA (Multiple Technology Appraisal in parallel with their reference products (NICE, 2016).

Pricing & Reimbursement in the US

Back in 2014, Covance conducted a survey among payers representing 100 million covered lives. Payers agreed on including biosimilars into their formularies, with the cost being a driving factor. Key factors influencing their decision-making were the cost differential between the brand and the biosimilar, the interchangeability status and the coverage by the Centers for Medicare & Medicaid Services (CMS). Back in 2014, the majority of payers expected biosimilars to be priced at a 20% to 30% discount as compared to the branded product (Carlsen and Skoridja, 2014).

At this stage, two biosimilar products have been launched in the US, namely Zarxio by Sandoz and Inflectra by Pfizer. Both products have a 15% price discount to the originator's medicine (Hirscher and Shields, 2015; Pfizer, 2016).

As of the 1st of January 2016, the Centers for Medicare & Medicaid Services (CMS) issued a payment rule for biosimilars, placing each biosimilar into a single billing and payment code, or J-code, with its reference product. Biosimilars are thus treated as multiple source drugs (Burich, 2016). The payment scheme released by CMS raised a lot of concern among stakeholders. Unlike generics, biosimilars may have clinical indications that are different from the ones of the reference product. Additionally, only certain sponsors of a biosimilar class may have sought and obtained an interchangeability designation from the FDA (Woollett and Jackson, 2016).

In its final version of the Physician Fee Schedule issued later in 2016, CMS amended the payment policy, requiring the addition of a modifier that identifies the manufacturer of the specific product. Modifiers will be used to identify biosimilar products that appear in the same J-code but are made by different manufacturers. Accordingly, the modifier for Zarxio is ZA-Novartis/Sandoz and the one corresponding to Inflectra is ZB-Pfizer/Hospira (CMS, 2016).

The two differentiators, namely the FDA's non-proprietary name suffix and the CMS' manufacturer-specific modifier, lead to a complicated coding environment, which is not encouraging the prescription of biosimilars. As a result, this double source might lead to confusion among healthcare professionals.

The Prescribers' View

Two large surveys were conducted among prescribers in Europe and in the US across physicians with different specialities with a high exposure to biologics. The timing and the design of the surveys was not fully identical. Nevertheless, the comparison related to key aspects of biosimilars is insightful.

DESIGN

EUROPEAN SURVEY

2013

470

In Europe in 2013, a 15-minutes long web-based survey was conducted among 470 prescribers. The survey was distributed equally across France, Germany, Italy, Spain and the United Kingdom. Among the prescribers were dermatologists, oncologists, nephrologists, endocrinologists, neurologists and rheumatologists (Reilly, 2013).

US SURVEY

2015/16

1201

In the US, a survey comprising 19 questions was conducted at the end of 2015/in the beginning of 2016. The survey counts 1,201 physicians, amongst which are dermatologists, gastroenterologists, haematologist-oncologists, medical oncologists, nephrologists, and rheumatologists (Cohen et al., 2016).

RESULTS

54%
basic understanding

22%
very familiar

54% of the European respondents stated that they only possessed a "basic understanding" of biosimilars and 22% considered themselves as "very familiar" with biosimilars.

>50%
aware that biosimilars must be comparable to originators

The US survey reviewed the criteria for the evaluation of biosimilars. More than half of the respondents were aware that biosimilars must be consistent with the originator's product in terms of safety and efficacy.

One fundamental premise of biosimilars holds that a product will be clinically evaluated in one or more indications of use. The authority may 'extrapolate' the data in order to approve the biosimilar for use.

In Europe 63% of the respondents knew that a biosimilar may be authorised for certain indications if not all, while only 12% of US respondents were comfortable with the concept of extrapolation.

EUROPEAN SURVEY

72%
supported sole prescribing authority

72% of the European respondents considered it important to have the sole prescribing authority on the most suitable biologic medicine.

US SURVEY

60%
understood concept of interchangeability

Among the US respondents, almost 60% correctly understood the concept of interchangeability. However, a staggering 80% of respondents were not aware that interchangeability would enable a pharmacist to switch from an originator biologic to a biosimilar, and vice versa.

Both in Europe and in the US, published literature was considered the most important source of information for learning about medicines. This applies to 97% of the cases in Europe and to 82% of the cases among US physicians.

In both surveys, a need for additional education and information on biosimilars among physicians was identified. Although the majority of physicians have heard about biosimilars, their knowledge of the fundamentals of biosimilars, such as extrapolation, was low. This was especially true for prescribers in the US, which is justified by the fact that so far, US prescribers have had less exposure to biosimilars than their European counterparts. The understanding of the technicalities of interchangeability and substitution also needs to be increased.

Discussion

The number of biological products reaching patent expiry in the coming years, and the growing cost pressure on healthcare institutions, announce a promising future development of the biosimilar market. There is a growing awareness that biosimilars play a role in the solving of the problems faced by payers and physicians in today's constrained budgetary environment. However, so far the necessary steps to create the optimal conditions for a substantial uptake of biosimilars, have yet to be taken. In Europe, a greater implementation of reimbursement policies is required in a number of countries to allow the optimal leverage of the potential of biosimilars. In the US, the FDA and CMS need to further fine-tune and coordinate their policies regarding biosimilars. The clarification and the simplification of several regulations, as well as guidances, would be beneficial to allow payers, physicians, and patients to gain a clearer understanding of biosimilars, and thus more confidence.

The biosimilars are still a young market. New waves of biosimilars are getting ready to make their entry into the market in Europe and in the US. The further implementation of a favorable framework, in terms of guidelines and reimbursement policies, will pave the way for the development of the biosimilar's market.

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