The State of Biosimilars

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A FirstWord Perspectives Report
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The State of Biosimilars

Within the next decade, patents on some of the most widely used biological medicines are scheduled to expire in the EU and US. This will pave the way for new biosimilars from both big pharma and smaller upstarts to enter – and potentially transform – this lucrative market.

Biosimilars: from past to present

When biological medicines first entered the market some 25 years ago, they represented the cutting-edge of biomedical research. Since then, biologics have transformed the treatment of a number of conditions that previously had limited – and, in some cases, no – treatment options. These therapies, which are defined as any pharmaceutical drug product manufactured in, extracted from or semi-synthesised from biological sources, had a total global market value of $161 billion in 2014, and this is expected to increase to a staggering $390 billion by 2020.1

With the expiration of key patents on a number of biological medicines looming, interest in developing biosimilars is at an all-time high. The US Food and Drug Administration (FDA) defines biosimilars as biological products that are approved based on evidence that they are highly similar to FDA-approved biological medicines, known as a reference products, and have no clinically meaningful differences in terms of safety and effectiveness from the reference product. Figure 1 below depicts the pending patent expirations for major biological products in the EU and US between 2013 and 2020. Of these therapies, Humira leads the pack in terms of revenues, with $14 billion in global sales in 2015;2 Humira is scheduled to lose patent protection in 2016 in the US and 2018 in the EU, although in the US, non-composition of matter patents expire no earlier than 2022.

Regulatory environment

In 2006, the European Medicines Agency (EMA) approved its first biosimilar, Sandoz’s (Novartis) Omnitrope (somatropin). In the years since, the regulator has approved a total of 23 biosimilars within the product classes of human growth hormone (hGH), granulocyte colony-stimulating factor (GCSF, which stimulates the bone marrow to produce and release granulocytes and stem cells), erythropoiesis-stimulating agents.

Figure 1: Major biological drug patent expirations in the US and EU from 2013

Source: Generics and Biosimilars Initiative
(erythropoietin analogues used to treat anaemia), insulin, follicle-stimulating hormone (FSH) for reproductive procedures, and tumour necrosis factor (TNF) inhibitor (which suppresses the immune system in inflammatory and autoimmune diseases).

The EMA first developed a framework for approving biosimilars in 2003, and by 2006 had crafted guidelines for the approval of biosimilars via an abbreviated registration process. Currently, it takes an average of 15 months for an application to market a new biosimilar to be reviewed in the EU; a further two or so months is then taken for the European Commission (EC) to formally approve the new therapy. Increased familiarity with biosimilars and improved guidelines for manufacturers regarding the application process have helped to reduce review times over the last decade. Expert at INC Research notes that in the years since the framework was first introduced, “the EU has changed dramatically, with the adoption of product specific guidelines as well as the development of guidance specific to monoclonal antibodies (mAbs).”

Most recently, in May 2016, the EC approved Samsung Bioepis’ application to market a biosimilar version of Merck & Co. and Janssen Biotech’s (Johnson & Johnson) Remicade (infliximab) under the brand name Flixabi. This was the second biosimilar from Samsung Bioepis, a joint venture between Samsung BioLogics and Biogen, to garner approval in the EU, after the EMA in January granted approval to Benepali, a biosimilar version of Pfizer/Amgen’s Enbrel (etanercept) in each of the originator therapy’s indications.4

The FDA, meanwhile, has lagged significantly behind the EU in terms of approving biosimilars. It granted its first marketing authorisation – for Sandoz’s Zarxio (filgrastim-sndz)5 in March 2015 – and has approved only one other biosimilar application, for Celltrion’s CT-P13 (infliximab), which will be marketed by Pfizer in the US as Inflectra,6 in the months since. It should be noted, however, that the regulator’s timeline for the approval of Zarxio was a comparatively brief 10 months. Commenting on the progress to date, INC Research expert notes that “In the US, the regulatory environment has developed more gradually, however since the FDA introduced guidance to the industry in 2012, there is now a much clearer path for global biosimilar development programmes.”

“The regulatory environment is continually evolving and the most recent guidelines are still largely open to interpretation, as shown by the varying development pathways chosen by companies developing the current wave of mAb biosimilars. However, what is clear is that as regulators gain more experience, the requirements are holistically becoming more consistent and transparent,” according to expert from INC Research.

Reflecting on some of the clinical trial changes, INC Research notes that “regulators are being seen to be more pragmatic on the need of pre-clinical studies and encouraging the use of biomarkers to demonstrate biosimilarity. In some cases, the sensitivity of validated biomarkers are superior to clinical efficacy studies and might make large clinical studies obsolete. An example of this new concept has been implemented in EMA’s updated guideline from October 2014 and the specific guidelines for insulins and the concept paper from June 2015 on the development of G-CSF biosimilars.”

Table 1 (above) depicts the number and type of applications currently under review in the EU and US markets, respectively.

<table>
<thead>
<tr>
<th>Common name</th>
<th>Originator product</th>
<th>Originator company</th>
<th>Number of applications (EU)</th>
<th>Number of applications (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Humira</td>
<td>AbbVie</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Lovenox</td>
<td>Sanofi</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Enbrel</td>
<td>Amgen</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Lantus</td>
<td>Sanofi</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>Neulasta</td>
<td>Amgen</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Neupogen</td>
<td>Amgen</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade</td>
<td>Merck/J&amp;J</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rituximab</td>
<td>MabThera/Rituxan</td>
<td>Roche/Biogen</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>10</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>

*Source: Biosimilar Index*
From a pipeline perspective, a number of biosimilars are currently in late-stage clinical development in the EU and US. Table 2 (right) lists the manufacturers and names of the biosimilars of six major biopharmaceutical products in late-stage development in the EU and US.

The largest manufacturers of biopharmaceuticals in the US and EU are AbbVie, Amgen, Merck & Co., Roche and Sanofi. The most prominent player in the global biosimilars market is Novartis’ Sandoz unit, which received the first biosimilar approval in the EU and US in 2006 and 2015, respectively. Sandoz currently markets biosimilar versions of hGH, GCSF and erythropoietin alpha and boasts a biosimilar pipeline of 10 drugs, of which four are currently in late-stage development.\(^7\) This pipeline, coupled with the company’s focus on research and development (R&D) activities, positions Sandoz as a global leader in the biosimilar market in the coming years. The other key players in the biological medicine and biosimilar market are depicted in Figure 2 (left).

For manufacturers, entry into the biosimilars market is often based on a company’s willingness and ability to enter into agreements, partnerships, strategic alliances and collaborations with other key players. To date, deals have focused on collaborative agreements and strategic alliances that seek to off-set the financial risks associated with investing in the rapidly evolving biosimilars market, with 16 key deals announced between May 2014 and May 2015 alone.\(^8\) Mergers and acquisitions

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**Table 2: Biosimilars in late-stage development as of April 2016**

<table>
<thead>
<tr>
<th>Originator</th>
<th>Products in Phase III development in EU/US</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adalimumab (Humira)</strong></td>
<td>B1695501 (Boehringer) CHS 1420 (Coherus) SB5 (Samsung Bioepis) GP2017 (Sandoz) FKB327 (Fujifilm Kyowa Kirin)</td>
</tr>
<tr>
<td><strong>Bevacizumab (Avastin)</strong></td>
<td>ABP215 (Amgen) B1695502 (Boehringer) PB-06410293 (Pfizer) M923 (Momenta/Baxalta) MSB-11022 (Merck Group) MYL-1401A (Mylan)</td>
</tr>
<tr>
<td><strong>Etanercept (Enbrel)</strong></td>
<td>CHS-0214 (Coherus)</td>
</tr>
<tr>
<td><strong>Infliximab (Remicade)</strong></td>
<td>BOW015 (Epirus) PB-06438179 (Pfizer)</td>
</tr>
<tr>
<td><strong>Rituximab (Rituxan/MabThera)</strong></td>
<td>ABP798 (Amgen) PF-0528056 (Pfizer) RG03 (Gideon Richter) RTXM83 (mAbxience)</td>
</tr>
<tr>
<td><strong>Trastuzumab (Herceptin)</strong></td>
<td>ABP980 (Amgen) CT-P6 (Celltrion) MYL1401O (Mylan/Biocon) SB3 (Samsung Bioepis) PF-05280014 (Pfizer)</td>
</tr>
</tbody>
</table>

Source: Biosimilar Index

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**Figure 2: Key players in the biological medicine and biosimilar markets**
have also been fairly prominent, although biosimilars have generally been part of the deal, as opposed to the key driver of the purchase. One such example of a significant acquisition was that of Pfizer’s $17 billion takeover of Hospira, which was completed in September 2015 and “significantly advanced [Pfizer’s] biosimilars business with a broadened portfolio of marketed products and pipeline assets.”

Factors impacting biosimilar adoption

Regulatory environment

In some markets, the regulatory pathway for biosimilars is still being developed, resulting in both regulators and developers adopting a ‘learn as you go’ approach to filing for biosimilar approval. This means that the process is often confusing, drawn out and slower than hoped for. While uncertainties about the regulatory pathway for biosimilars still remain in both the EU and US, significant headway has been made in the past 18 months in terms of helping stakeholders understand not only how biosimilars will be reviewed, but also how they will be marketed and prescribed.

In November 2014, for example, the EMA made a series of changes to its overarching guidelines on similar biological medicinal products, which had last been revised in 2005. The most significant change to the guidelines – which describe the application of the biosimilar approach, the choice of the reference product and the principles for establishing biosimilarity – pertains to the decision to allow for biosimilar developers to use a comparator authorised outside the European Economic Area (EEA) when conducting clinical trials. It is hoped that allowing these comparators will facilitate the global development of biosimilars, as well as reduce the repetition of clinical trials between markets.

European regulators have also released product-specific biosimilar guidelines for nine separate classes of biologic medicines. The guidelines for all classes of biologics provide specific details on the various studies that need to be carried out for biosimilars, both preclinical and clinical. Within all class level guidelines, the issue of indication extrapolation is discussed. While each guideline uses slightly different wording as appropriate to the class of product being discussed, the guidelines suggest that extrapolation is possible on the basis of the totality of the evidence provided from a comparability exercise, but warns that extrapolation is more justifiable in some classes than in others. The expert from INC Research notes that “the product-specific guidelines by the EMA for various biologics have provided biosimilar developers a clear path for their programmes – even more so with the revised version that allow for the use of PD markers negating the necessity for lengthy clinical efficacy studies.”

In the US, meanwhile, the past 18 months has seen a flurry of activity. Perhaps most significantly, in May 2015, the FDA released three newly finalised guidelines on biosimilars, including a questions and answers document on the implementation of the Biologics Price Competition and Innovation Act (BPCIA) of 2009, as well as various quality and scientific considerations that need to be taken into account when trying to demonstrate biosimilarity to a reference product. In reviewing the guidelines, it was observed that all references to interchangeability had been removed and instead a statement was added that the topic of interchangeability will be addressed in a separate guidance document. In April 2016, Steven Kozlowski, Director of the FDA’s Center for Drug Evaluation and Research’s Office of Biotechnology Products, told delegates at a conference that a guideline on interchangeability, the process whereby a pharmacist can substitute a biosimilar for the original biologic without a physician’s approval, would be published in 2016, but did not comment on the content.

In addition, the FDA in March 2016 issued its draft guidance on the labelling of biosimilars. The guidance recommends that biosimilar product labels incorporate “relevant data and information from the reference product labeling, with appropriate product-specific modifications.” The draft guidelines also recommend that there is a biosimilarity statement which reads “[BIOSIMILAR PRODUCT’S PROPRIETARY NAME (biosimilar product’s proper name)] is biosimilar to [REFERENCE PRODUCT’S PROPRIETARY NAME (reference product’s proper name)] for the indications listed.”

Expert from INC Research suggests that “with a clearer regulatory pathway across the EU and US, and a more pragmatic approach by the regulators, companies will be able to develop biosimilars quicker, cheaper and more efficiently driving down the cost and ultimately increasing competition in the biosimilar market.”

Pricing and reimbursement

One of the most appealing aspects of biosimilars is their potential to lower healthcare costs by being priced at a significant discount to their originator therapies, making them more accessible to patients with limited resources. Specifically, analysts suggest that over the next five years, the combined savings in the EU5 (Germany, France, Italy, Spain and the UK) and US could range from $55 billion to as much as $110 billion.
How much of this cost saving will be realised depends on biosimilar uptake during this period, which in turn will be influenced by policy development, regulatory decisions and buy-in across stakeholders within the healthcare system. Expert at INC Research suggests that “the current trend has shown that initial pricing models [regarding biosimilar pricing] have been overly optimistic.”

In Europe, in particular, ongoing budgetary pressures are driving payers to explore new and innovative ways to limit growth in healthcare spending, with a particular interest in spending on pharmaceuticals. As a result, some countries have restricted or limited access to expensive therapies, such as biological medicines, in order to preserve scarce drug funding. In England and Wales, for example, the National Institute for Health and Care Excellence (NICE) restricts access to biologic treatments in certain indications.

Despite having a shared goal of wanting access to lower-priced biologics, individual member states in the EU are allowed to develop their own pricing and reimbursement policies on biosimilars. In Germany and the UK, for example, the price of a biosimilar is set by the manufacturer but cannot be higher than the branded price, while in Spain, mandatory biosimilar price discounts are applied. In Italy, the price discount applied is equivalent to that required for a generic product, while in France, the price is simply negotiated. Certain countries in Europe have used these varying strategies to obtain steep discounts on biosimilars – such as Norway’s 69 percent discount on a biosimilar infliximab offered by Orion Pharma – prompting payers to argue that deep discounts should become the ‘new norm.’

Now that the FDA has approved its first biosimilar, the US government is developing strategies for how biosimilars should be reimbursed by payers. In March 2015, the US Centers for Medicare and Medicaid Services (CMS) published two documents outlining how biosimilars will be reimbursed under Medicare. Specifically, as part of its 2016 Physician Fee Schedule Final Rule, the agency stated that “the payment amount for a biosimilar biological drug product is based on the average sales price of all National Drug Codes (NDCs) assigned to the biosimilar biological products included within the same billing and payment code. In general, this means that CMS will group biosimilar products that rely on a common reference product’s biologics license application into the same payment calculation, and these products will share a common payment limit.”

Perhaps most controversial, however, is a proposal by the agency related to its Part D drug plan, which would give plan sponsors the flexibility to replace a more expensive reference biologic on their formulary with a biosimilar. The move has been viewed by some as ‘a path to ‘de facto’ interchangeability for biosimilars.” To call biosimilars and brands “the same” means that all biosimilars, regardless of designation, will be viewed as interchangeable with the brand, despite no switching studies having been completed for the biosimilar.

It should be noted, however, that in many markets, originator therapy manufacturers are offering higher rebates on their therapies or service agreements to disincentivise physicians and patients to make the shift to biosimilars. These discounts – which include both discounts to ensure brand loyalty, as well as incentives for new patients – could potentially limit the market potential for biosimilars.

**Payer perception**

FirstWord research has revealed that payers view price as the primary driver of biosimilar use. Specifically, they believe that biosimilars offer a solution to increasing demands and limited resources, as well as a significant opportunity to provide enhancements in care by making biopharmaceuticals, which could be out of the reach of some patients due to their price point, available to the masses.

Concerns remain regarding the dearth of long-term data regarding biosimilar safety and efficacy, however. While payers believe that the switching of patients from original branded biologics to biosimilars is justified in order to save money for health services, they anticipate that getting physicians and patients to make the switch will be a challenge and instead believe that the battle for biosimilar market share will be focused on treatment-naïve patients. Significant differences of opinion also emerge in areas such as automatic substitution, biosimilar naming, pricing and indication extrapolation.

In short, payers are confident that increased biosimilar adoption will drive cost savings, but acknowledge that these savings could be limited and take time to be realised. Further, FirstWord research has revealed that some payers would prefer to make savings on original branded biologics rather than drive the biosimilar agenda, as this is likely to remove the need for difficult conversations with physicians and patients.
Physician perception
Data suggest that physicians are generally supportive of the use of biosimilars, although the level of understanding and enthusiasm for the products varies significantly depending on experience with using the therapies. According to a recent survey by market intelligence group InCrowd, nearly half of US physicians surveyed anticipate expanding the number of their biosimilar prescriptions in the next three years as biosimilar availability increases, and nearly one in five suggested that biosimilars would become the norm or replace biologics in the next three years.16

The chief concerns among physicians are that manufacturers are able to demonstrate the safety and efficacy of their products, particularly in the post-marketing setting. Opinions on pharmacy-level substitution and interchangeability vary by provider type, with oncologists and endocrinologists being more likely to prescribe a biosimilar than dermatologists, gastroenterologists and rheumatologists.

To ensure greater buy-in from physicians – and thus drive higher biosimilar prescribing rates – physicians must be confident in prescribing these newer therapies; however, surveys reveal that physician knowledge of these products is significantly lacking. Therefore, manufacturers, as well as government agencies and regulatory bodies, must ensure that doctors are receiving comprehensive and unbiased education about biosimilars and their safe and effective use in order to ensure their success in the marketplace. Reflecting on the hesitation among physicians, INC Research notes that “clearly, awareness and education on the safety, efficacy and benefits of biosimilar are the key drivers to alleviate any hesitation physicians may have.”

Patient perception
The ageing population, coupled with an increased prevalence of chronic conditions within the general population, is driving the need for biological therapies, with biosimilars being an obvious choice for cash-strapped patients. Most patients have no idea what a biosimilar is, however, or under which circumstances one should be a treatment option.

Research has suggested that the lower price point of biosimilars has piqued the interest of consumers and helped them overcome some of the initial feelings of uncertainty about their use, but consumers would also benefit from unbiased education campaigns, as well as transparent data on biosimilars’ safety and efficacy.

Market competition
Market competition for biosimilars originates from at least two sources: “brand on brand” competition between biosimilars and reference products and competition from ‘biobetters,’ which are versions of the originator products that have been modified to provide greater efficacy or efficiency. These modifications are often minimal in nature, such as a simplified dosing regimen, but can make products more appealing to physicians or patients and thus possibly limit the biosimilars’ potential market shares.

A third source of competition, meanwhile, is other biosimilars of the same reference product. As the regulatory pathway for biosimilars becomes further defined and the number of biosimilar approvals in select markets increases, both big pharma and smaller upstarts will become interested in entering the biosimilar market space and further drive competition.

Complexity of development
One of the major barriers to widespread investment in biosimilars is the complex manufacturing processes, with biologics and biosimilars sensitive to and altered by even minor changes during manufacturing. Companies with experience in manufacturing biologics, such as Amgen and Biogen, may have a considerable advantage over new companies as they can build out a more efficient and potentially cost-effective biosimilar production programme. Further, they have the R&D, marketing and sales networks necessary to further dominate the market. Experienced companies thus have a significant advantage in the marketplace and are viewed as strong candidates for alliances with smaller, lesser known companies seeking to enter the biosimilars arena.

Brand recognition
Another potential area of resistance when it comes to the uptake of biosimilars is the heritage and track record of the company that manufactures the biosimilar product. While trust in the EMA and FDA’s ability to approve safe and effective products is explicit, it is at the physician level that company reputation and heritage could have significant influence, with physicians more likely to trust biosimilars that have been manufactured by large, well-known biotechnology
companies. These reservations are likely to be overcome as biosimilars become more widely available in the marketplace and physician familiarity with once unknown companies increases.

**Key success factors for biosimilars**

In order for biosimilars to gain a strong foothold in the EU and US pharmaceutical markets – and set themselves up for long-term success – manufacturers must focus on the following key areas:

**Figure 3: Key success factors**

![Key success factors for biosimilar manufacturers](image)

- **Compete on price**
  As discussed previously, cost is the number one factor that drives interest in biosimilars at the payer level. Payers are expecting biosimilar manufacturers to offer discounts of 30 to 50 percent compared with the originator therapy. Payers also recognise the investment that goes into developing a biosimilar, however, and caution manufacturers from discounting too deeply, lest their product be viewed as sub-standard.

  "Current precedent shows that a pure price driven strategy alone might not be successful. Instead, an approach which connects all stakeholder interests (payer, physicians, patients) will offer greater chances for success. Further, education, publications and payer engagement during development may assist in obtaining greater payer approval,” Expert from INC Research suggests.

- **Focus on quality and extensive clinical data**
  In order to compete in the biologics market, biosimilar manufacturers need to provide a high-quality, safe and effective product. To ensure market adoption of their product – and achieve buy-in from reluctant physicians and patients – biosimilar manufacturers need to provide clinical data in as many indications as possible. While providing such data will most certainly impose a financial burden on manufacturers, payers have stated that they would preferentially list biosimilars that have more clinical data than other products, as long as the cost of the drugs was comparable.

- **Commit to tracking long-term safety**
  As previously mentioned, there remains a certain degree of apprehension among physicians and patients over the long-term safety and efficacy of biosimilars. With this in mind, there is strong support for biosimilar manufacturers to participate in patient registries to track the efficacy and long-term safety of biologics across a wide range of indications in order to assuage these concerns. The PATRO registry, for example, is a multi-centre, open-label, longitudinal, non-interventional study being conducted in children's hospitals and specialised endocrinology clinics to assess the long-term safety of biosimilar somatropin (Omnitrope) in routine clinical practice. The British Society for Rheumatology Biologics Register (BSRBR), meanwhile, tracks patients treated with biologic agents for rheumatoid arthritis to monitor the therapies’ safety and effectiveness over time. Other registries that assess the long-term safety of biosimilars include the ORHEO and OncoBOS studies, both of which evaluate the efficacy and safety of erythropoietin biosimilars for the treatment of chemotherapy-induced anaemia in the clinical setting.

- **Provide an extensive portfolio**
  Turning again to the need to build trust and to create a commercially attractive proposition, stakeholders believe that biosimilar manufacturers need to offer a diversified portfolio that includes branded therapies, generics and biosimilars that are tailored to their area of expertise and to the needs of the market. In offering a greater range of products, a company can establish itself as an expert in a particular disease area and build brand recognition with other companies, as well as consumers.

- **Offer education and support**
  Much confusion still surrounds the field of biosimilars, particularly in terms of how and when biosimilars should be prescribed. To avoid losing out on market opportunities due to a lack of credible information, biosimilar manufacturers need to be more proactive and informative with their biosimilar educational activities, so that pricing, reimbursement and market access decisions can be grounded in facts rather than opinions or hearsay.
Endnotes


