

# Challenges in Global Biosimilar Development: A Regulatory Perspective

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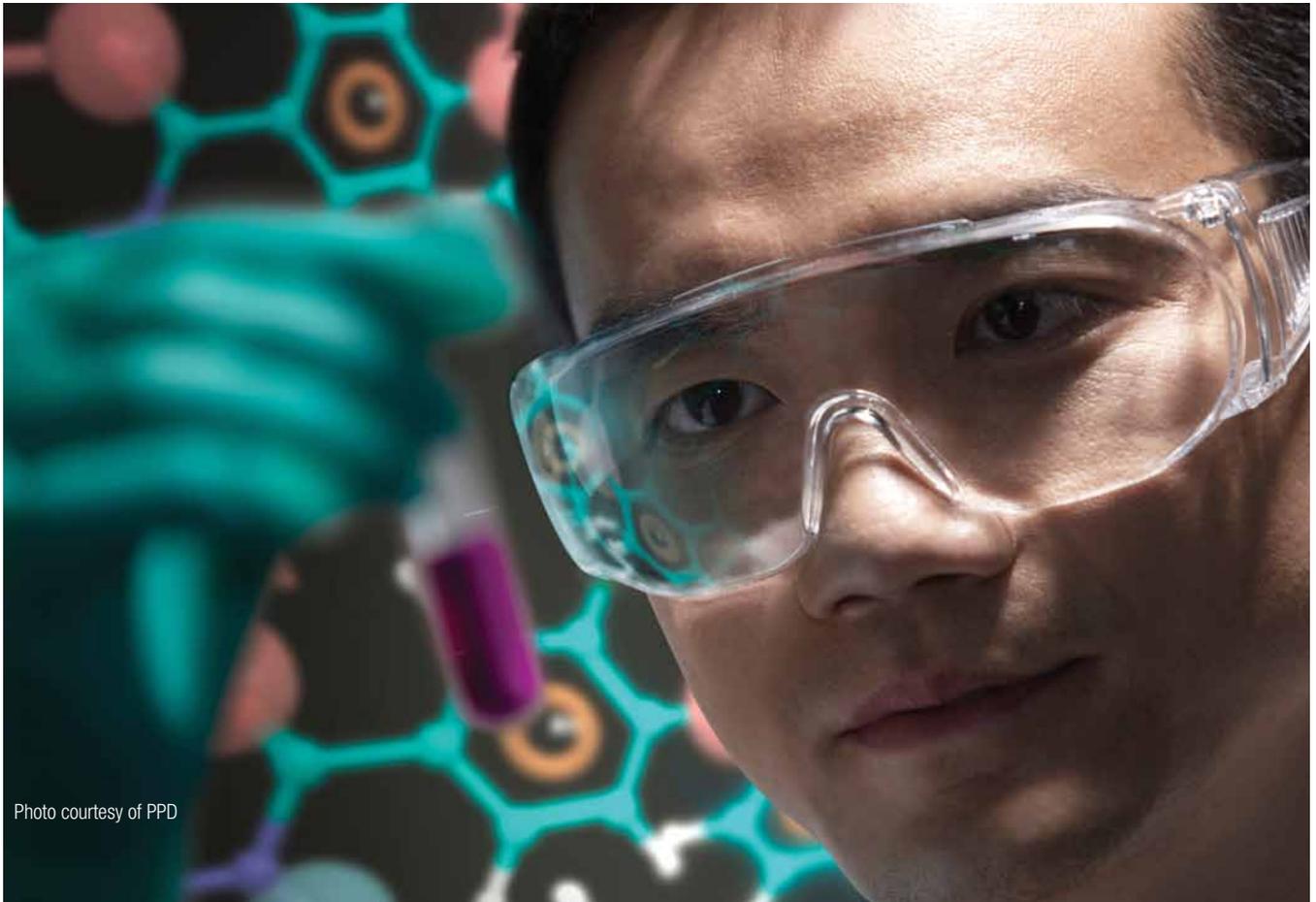


Photo courtesy of PPD

With an estimated \$67 billion worth of patents on biological products expiring before 2020 and governments pressured to reduce rapidly rising health care costs,<sup>1</sup> biosimilars represent a major opportunity for the pharmaceutical industry. The growing interest in biosimilars is evident by the approximately eightfold increase in the number of biosimilar clinical trials between 2007 and 2014 (Figure 1). Market growth of biosimilars is expected to increase significantly, worth approximately \$2 billion by 2018.<sup>2</sup>

A biosimilar is a biological product highly similar to an approved biological product, known as a reference product, with no clinically meaningful differences in terms of safety and effectiveness. In the U.S., if a biological compound demonstrates comparable data to a U.S. Food and Drug Administration (FDA)-licensed product from analytical, preclinical and clinical studies, it will be accepted as a

biosimilar after expiration of innovator patents through an abbreviated route. Interchangeable biological products are also biosimilars, but must meet additional criteria to match the reference product. Interchangeables can be substituted for the reference product without a prescription from a health care provider.

Over the past ten years, regulatory authorities worldwide have been focusing on developing guidelines for biosimilars. However, until a global development strategy is adopted, regulatory, therapeutic and legal challenges remain. While the prospect of cost savings and efficiency make the biosimilar market attractive, companies and their outsourcing partners planning to enter this market must be aware of current regulations and issues in the global marketplace and be prepared to respond quickly to changes. As the regulatory landscape evolves, it is vital for clients to approach regulators early to validate their intended development plan.

This article addresses current regulations and challenges impacting the development of biosimilars. Early awareness of changes and challenges will allow biosimilar developers to move more quickly into key markets.

**GLOBAL REGULATIONS: WHERE DO WE STAND?**

The FDA approval of the first U.S. biosimilar product—Zarxio (filgrastim) from Sandoz—in March 2015 marked a major milestone in the biopharmaceutical industry. Still, the U.S. lags behind other countries in biosimilar development, with the approval coming nearly a decade after the first biosimilar drug was approved in Europe, and five years after the Biologics Price Competition and Innovation Act (BPCI) of 2009 was passed and went into effect in 2010, providing a legal framework for the 2012 FDA draft guidelines. The guidelines propose steps for comparability and encourage early engagement with the agency. Data demonstrating biosimilarity to the reference product must be based on analytical, preclinical and clinical studies, including pharmacokinetic (PK), pharmacodynamic (PD) and immunogenicity assessments.<sup>3</sup> The FDA released final guidance documents on biosimilar products on April 28, 2015, that address comments from the industry and are intended to provide predictability and clarify the scientific and regulatory considerations for sponsors initiating biosimilar development programs.<sup>4,5,6</sup>

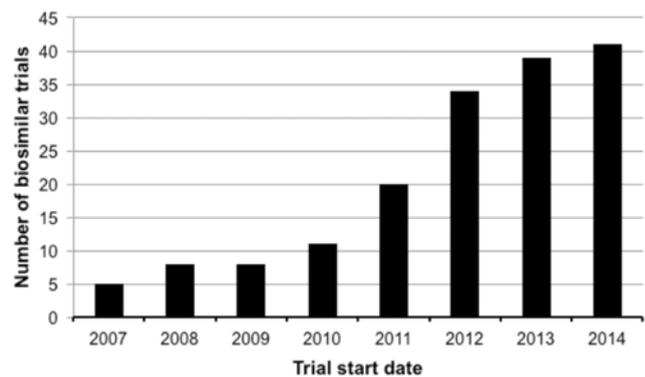
The European Medicines Agency (EMA) was the first authority to issue guidelines for biosimilars, which came into effect in 2005.<sup>7</sup> The guidelines included requirements for quality, safety and efficacy, and clearly defined the distinction between the development of biosimilars and generics. These were followed by guidelines on nonclinical, clinical and quality issues as well as product-specific guidance, which were updated in 2013.<sup>8</sup> The World Health Organization (WHO) published its own guidelines in 2009 and these, together with European and U.S. guidelines, are being used as a reference in many countries, from Latin America to Asia Pacific and the Middle East.

As outlined in Table 1, several countries have issued guidelines for biosimilars in line with EMA and WHO principles, requiring full quality information on the biosimilar and side-by-side comparative characterization with the reference product. Australia and Malaysia adopted the EMA guidance. The biosimilar guideline released in February 2015 by the Chinese Regulatory Authority (CFDA) shares similar principles with EMA, FDA and WHO.<sup>9</sup> However, key differences exist among countries with regard to the choice of reference product and extrapolation of indications from the innovator.

The draft guideline of the Colombian agency proposes an abbreviated pathway for biosimilar evaluation as well as a comparability pathway. However, there is criticism that developers choosing the abbreviated pathway will not be in line with WHO guidelines and may put patients at risk. To date, Russia has not developed specific biosimilar guidelines, but is gradually adopting global standards.

In the U.S., the approval of the first biosimilar may trigger a deluge of many biosimilar drugs currently available in other parts of the world. Apotex, Hospira and Celltrion have submitted applications to the FDA for biosimilar products, and Novartis is

**FIGURE 1:** Number of biosimilars clinical trials started between 2007 and 2014



Source: Citeline.

working on five other biosimilars. In Europe, 21 biosimilars have been approved by the EMA since 2006, with 19 still marketed, and have shown a significant reduction in cost compared to their reference products. Biosimilar products have also been registered in Australia, Canada, India, Japan and South Korea.

**CLINICAL DEVELOPMENT**

Clinical trials for biosimilars must demonstrate comparable safety and efficacy to the reference product, including sequential PK/PD and efficacy/safety trials. Regulators anticipate PK/PD comparability data from a Phase I trial will support further efficacy/safety assessments in pivotal Phase III trials. Stand-alone Phase III studies or combined Phase I/III designs without supporting PK data are unlikely to be accepted. Clinical comparability requirements may vary on a case-by-case basis subject to a risk-based approach. Three-arm Phase I trials are increasingly being used to demonstrate comparability between the biosimilar and two licensed versions of the same reference product that may exist in different markets, allowing developers to proceed with pivotal trials using a single version of the reference product.

Due to potential differences between the biosimilar and reference product, immunogenicity profiling is the primary safety aspect that must be assessed from the outset of the investigation. In Europe, if immunogenicity has proven not to be a serious risk, the EMA may accept six-month data on the day of filing, with additional six-month data to be submitted during the review period.<sup>10</sup>

India is an appealing market for developing biosimilar products because of its large potential patient pool, but newly revised legislation has limited the number of clinical trials an Indian investigator can be involved with to three at any one time. In Brazil, the recently released clinical dossier of drug development (CDDD) will be similar to an IND filing process and help reduce approval timelines of clinical trials. Similarly, implementation of a new European clinical trials regulation in 2016 will affect the way applications for interventional trials are managed in Europe.

**REGULATORY CHALLENGES**

As global regulations and guidelines progress, questions such as the following are broadly being debated in the pharmaceutical industry:

**TABLE 1:** Countries with specific biosimilars guidelines, and year in which guideline was published in each country

Year of publication	Country with specific biosimilars guidelines
2005	European Union
2007	Australia
2008	Malaysia Turkey Taiwan
2009	Japan Korea Singapore (World Health Organization)
2010	Brazil Canada Saudi Arabia South Africa
2011	Argentina Cuba India Iran Mexico Peru
2012	Colombia (draft) Egypt (draft) Jordan (draft) Thailand (draft) United States (draft)
2014	European Union (revised guidelines)
2015	China

- Should interchangeability and automatic substitution be allowed?
- Should biosimilars have the same international non-proprietary name as the reference product?
- How much longer will patent litigation hinder the U.S. market?

In countries without biosimilar guidelines, interaction with regulators can be challenging. It is advisable to approach agencies proactively for scientific advice to avoid potential questions and delays in clinical trial approval. In most cases, reviewers need to be guided through the FDA, EMA and PMDA (Japan) guidelines. This is important in order to receive agency validation of the development program, discuss issues, identify gaps in the submission package, review the protein characterization steps conducted, agree on the source of the reference product and familiarize the assessors with the biosimilar product before submitting clinical trial applications.

Biosimilar developers and their outsourcing partners must be aware of the chosen country's regulatory landscape, and have extensive knowledge of any existing biosimilar approval pathway and the latest regulatory agency guidelines. Providing regulatory authorities with certificates of analysis (CoA) for a U.S.-marketed comparator could be challenging. Contrary to European practice, U.S. manufacturers tend not to make CoAs available to parties

involved in the supply chain or support the development of a competitor by releasing CoAs for batches purchased for clinical trials. Providing pedigree statements for the reference product usually is accepted as an alternative.

Companies should evaluate the feasibility of routes to market when considering key countries for clinical trials. Regulations and laws favoring local businesses exist in emerging markets, and approval for clinical trials may not be conducive to successful marketing. Conditions favorable to local development also play a major role in China. In these countries, developers may benefit from partnering with local companies.

The provisions made in the Brazilian Productive Development Partnership (PDP) legislation and by the Scientific and Technological Research Council of Turkey (TUBITAK) regulate the technology transfer from foreign to local companies and the joint development between public institutions and private entities. In return, participating developers benefit from an expedited regulatory process, access to restricted funding and exclusive access to public tenders. Companies outside these agencies are locked out of public tenders and confined to sell only to the retail market in Brazil and Turkey. In Russia, innovative conversion and development of the local pharmaceutical industry is supported by the Pharma 2020 strategy.

The number of clinical studies required to support marketing authorization in Europe varies greatly depending on the product. Minimally, Phase I and Phase III studies must be included in the marketing authorization application. When the reference product is approved for multiple indications, claims for the same indications must be justified based on safety and efficacy data. If claimed indications were not part of the biosimilar clinical program, extrapolation may be accepted. In Europe, extrapolation claims are possible as long as similar mechanisms of action and receptors are common across indications, and studies involve the most sensitive population.

## FUTURE REGULATORY LANDSCAPE

Defined regulatory pathways for biosimilars are slowly paving the way toward the goal of pharmaceutical industry stakeholders: automatic substitution at the pharmacy level. Legislators in the U.S. and Japan have made provisions for interchangeability, but the FDA has not clarified how this can be scientifically demonstrated, and Japan has discouraged automatic substitution. The FDA has indicated that interchangeability will be granted in the post-approval setting. The EMA guidelines have not addressed interchangeability or substitution, which are left to member states to determine. In Germany, automatic substitution is acceptable provided the production of original and biosimilar products occurred at the same manufacturer site following the same process.

In France, substitution is allowed, provided the prescribing physician has not marked the prescription as "non-substitutable," substitution takes place when initiating a course of treatment (or to allow the continuation of a treatment started with that biosimilar), and the biosimilar belongs to the same "similar biologic group" as the prescribed product as established by the French regulatory authority (ANSM). ANSM criteria for inclusion in this group, a detailed procedure for the registration by pharmacists in the biosimilar register, and more precise conditions for substi-

tution are expected to be further defined once legislation is approved by the French Supreme Court's decree. When this is rectified later in the year, France is well placed to be the first member state to open the door to biosimilar substitution despite the fierce attempt by the pharma industry to derail the change.<sup>11</sup>

**LOOKING AHEAD**

Currently there are more than 150 reference products for biosimilars to emulate, including about 40 with sales in the blockbuster (more than \$1billion per year) revenue range. Even 10 percent of this market could be enough for biosimilars to be profitable. With biosimilars as marketing opportunities, it makes sense for companies to outsource their development if it can be demonstrated cost effective.<sup>12</sup>

In terms of regulatory progress, the number of agencies that have adopted key principles from the U.S. and/or EU guidances on biosimilars is steadily increasing. The common principles underpinning these provisions are effectively contributing to the global alignment on the development of biosimilars, with Latin America becoming a key market for pharmaceutical and biotechnology companies. However, until specific guidelines are established in other major markets, such as Russia, it will continue to be difficult for manufacturers to define a truly global development strategy. How biosimilars will ultimately be regulated, defined and marketed and how current issues will be resolved remains to be seen. **CP**

*References*

1. GaBI online. June 29, 2012. <http://gabionline.net/Biosimilars/General/US-67-billion-worth-of-biosimilar-patents-expiring-before-2020>
2. Markets and Markets report. Nov. 18, 2013. <http://www.marketsandmarkets.com/PressReleases/global-biosimilars-product-market-worth-19.4-billion-by-2014.asp>
3. US FDA. *Guidance for Industry, Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, Draft Guidance, FDA Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2014.*
4. US FDA. *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.* <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291128.pdf>
5. US FDA. *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product.* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf>
6. US FDA. *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009.* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf>
7. EMA. *Guideline on Similar Biological Medicinal Products, CHMP/437/04, 2005.* [www.ema.europa.eu](http://www.ema.europa.eu)
8. EMA. *Guideline on Similar Biological Medicinal Products, CHMP/437/04 Rev 1, 2014.* [www.ema.europa.eu](http://www.ema.europa.eu)
9. CFDA. *Technical Guideline for Development and Evaluation of Biosimilars, CFDA, China, 28 February 2015.*
10. *Presentation by Andrea Laslop, Scientific Office, AGES, Austria, Biosimilar Global Congress 2014 Europe, London, UK, September 17-19, 2014.*
11. *Fierce Pharma.* ([www.fiercepharma.com/story/big-pharma-tries-short-circuit-frances-move-towards-biosimilar-substitution/2014-04-14](http://www.fiercepharma.com/story/big-pharma-tries-short-circuit-frances-move-towards-biosimilar-substitution/2014-04-14)).

12. *Langer ES and Rader RA. Biosimilars Improving Efficiency, Cost for All Biologics. BioPlan Associates. Accessible at: [http://www.contractpharma.com/issues/2015-04-01/view\\_columns/biosimilars-improving-efficiency-cost-for-all-biologics](http://www.contractpharma.com/issues/2015-04-01/view_columns/biosimilars-improving-efficiency-cost-for-all-biologics)*



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