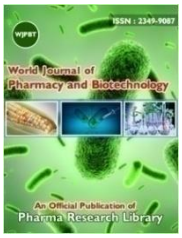

World Journal of Pharmacy and Biotechnology
Journal Home Page: www.pharmaresearchlibrary.com/wjpbt
e-ISSN: 2349-9087 | Publisher: Pharma Research Library
W. J. Pharm. Biotech., 2023, 10(2): 79-84
DOI: https://doi.org/10.30904/j.wjpbt.2023.4611

A Comparative Study of Regulatory Compliance for Biosmilars in US, EU and INDIA

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A b s t r a c t
A biosimilar is a medicinal product with a similar safety, efficacy, and quality as an already authorized biologic product. It is made by or derived from a biological source such as yeast or a bacterium. Thus, the lack of significant differences has to be clinically proven by appropriate development of each biosimilar. Biosimilars contain different inactive ingredients and may have different brand names, appearance, and packaging from the reference medicinal product. Several expressions have been used in the U.S., the European Union (EU), Canada, There is currently no global consensus regarding the source of reference products, although WHO guidelines have outlined fundamental principles and key considerations in the selection of reference products for the development of biosimilars. Further, WHO guidelines stipulate that only a reference product that was licensed on the basis of a complete registration dossier can serve as a reference product (i.e., an approved biosimilar cannot serve as the reference product in the development of another biosimilar). The study aims to evaluate the regulatory compliance for biosmilars in US, EU and India. Currently there are seven biosimilars approved in the United States. The most recent, biosimilar bevacizumab, was approved in September, 2017. In the case of infliximab and its biosimilar, it is likely that greater price differences will have to be seen before physicians will be convinced to switch away from the reference product. The reluctance of both patients and physicians to switch to a biosimilar may imply that increases in market shares for biosimilars will be a matter of time as more biologic-naïve patients are placed on biosimilars to begin their treatment regimen Biosimilar are not generic; biologics are larger and more complicated than chemical drugs, due to the complexity of biological/biotechnology derived products the generic approach is scientifically not appropriate for biosimilar products. There is need to use well-designed clinical trials to establish biosimilarity.
Keywords: Biosimilars, U.S., the European Union (EU), Canada, biologic product, WHO guidelines, generic.

A r t i c l e I n f o

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Article History
Received : 28 July 2023
Revised : 27 July 2023
Accepted : 05 Sept 2023
Published : 09 Oct 2023

Citation: Ubendran.J, *et al.* A Comparative Study of Regulatory Compliance for Biosmilars in US, EU and INDIA, 2023, 10(2): 79-84.

C o n t e n t s

1. Introduction

Biological or biopharmaceuticals are drugs produced from living cells through the biological process, and mimic natural biological substances such as hormones. Biosimilars are copy drugs similar to biological drugs that has already been authorized (the biological reference medicine), hence similar but not identical. Indian guidelines define a "similar biologics" as a biological product/drug produced by genetic engineering techniques and claimed to be "similar" in terms of safety, efficacy and quality to a reference biologics, which has been authorized by Drug Controller General of India (DCGI) for safe use in Indi. The active substance of biosimilar medicine is similar to one of the biological reference medicine and used in general at the same dosage

to treat the same disease. Biosimilars also known as similar biological products, follow-up biologics, subsequent entry biological, second entry biological, biogenerics, multisource products, and off-patent biotech products as synonyms. General public and insurance companies prefer economic alternatives, the long-term economic consequence of using biosimilars have not been studied. The total cost of therapy with biosimilars may rise.

Biosimilars are a new class of drugs intended to offer comparable safety and efficacy to the reference, off-patent biological. The active protein structure of biologicals makes them more prone to induce an acute and chronic immune response. The overall risk is modest with biosimilars, but regulatory pathways are required because of structural complexity, manufacturing process and risk for immunogenicity. The problems/limitations with biosimilar are that, the two biosimilar have a different origin, the two biosimilars may have same therapeutic effect, may have different side-effects and hence require thorough testing. Biopharmaceuticals are different from the conventional small molecule drugs because of the size and complexity of the active substance and nature of the manufacturing process. Even minor change in the process can lead to the fatal outcome (process is product), safety, and efficacy issues.

For Epoietin (Erythropoietin), minor change in the packaging process caused pure red cell aplasia. This prompted drug regulatory authorities to establish strict guidelines. European Medicines Agency (EMEA) and Committee for the Medicinal Product for Human use (CHMP) raised the objection that marvel insulin and reference human insulin were not comparable. Marvel Life Sciences Ltd., withdrew its application as they were unable to meet the standards set by CHMP, but biosimilar insulin continues to flood Indian market. Hence, legal and regulatory principals applicable to generic drugs cannot be applied to biosimilars.

CHMP Guidelines Concerning Biosimilar Drugs

EMEA-CHMP has published product specific guidelines to establish the similarity in terms of safety, efficacy and quality of biosimilar product. According to these guidelines the concept of similar biological products is applicable to any biological medicinal product. Moreover, in order to support pharmacovigilance monitoring, the specific product given to the patient should be clearly identified. The active substance of the biosimilar product must be similar in molecular and biological terms to the active substance of the reference medicinal product, and the same reference product throughout the comparability program. The pharmaceutical form, doses and route of administration of the biosimilar and the reference product should be the same. If the reference product has more than one indication, the safety and efficacy for all indications have to be justified or demonstrated for each indication separately. The clinical safety must be monitored on an ongoing basis after marketing approval. The issue of immunogenicity should always be addressed, and its long-term monitoring is necessary.

FDA Approach Regarding the Use of Biosimilar Drugs

FDA was given the authority to approve biosimilars, including interchangeable, to maintain safety, efficacy, and quality of biosimilar product. Biologics Price Competition and Innovation Act of 2009 authorizes the FDA to oversee an "abbreviated pathway" for approval of biologics that are "biosimilar" to already approved products. The abbreviated pathway will eliminate unnecessary and unethical testing of biosimilars in animal and human. This will save the time, money and manpower. The Patient Protection and Affordable Care Act of 2010 (USA) also supports this. Introduction of biosimilars also requires a specifically designed pharmacovigilance plan[1-10].

Indian Guidelines

The New India Guidelines "Draft Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India," were announced in June 2012, by Department of Biotechnology (DBT). The Indian guidelines on similar biologics address the pre-marketing and post-marketing regulatory requirement (i.e., "comparability exercise"), and also address the requirements related to manufacturing process and quality control. As such these Indian guidelines on similar biologics are comparable in many respects to biosimilar guidelines of USA and EU. India has adopted a "sequential approach" (like "stepwise approach" - US and EU) to market biosimilar products. The review committee on genetic manipulation of the Genetic Engineering Approval Committee (GEAC) with the permission of DCGI, approve clinical trials to be conducted in India related to biosimilar therapeutic products. The biosimilar has to demonstrate comparable data of non-clinical studies viz., pharmacokinetics and toxicology (safety pharmacology, reproduction toxicology, mutagenecity and carcinogenicity) and clinical studies (efficacy and tolerability for each indication) before it gets approval for all indication of the reference medicine.

Biosimilars in India consist primarily of vaccine, monoclonal antibodies, recombinant proteins and diagnostics, insulin (wosulin, insugen, recosulin), erythropoietin (hemax, epofer, wepox, ceriton, epofit), hepatitis B vaccine (Shanvac B, Revac B, Enivac B, Biovac B, Genevac B, Bevac), granulocyte colony stimulating factor (G-CSF–Grastim, Neukine), streptokinase (indikinase, shankinase, STPase), interferon alpha-2B (shanferon), Rituxinab (MAb), epidermal growth factor receptor (anti-EGFR) (MAb)–(reditux, bioMAB-EGFR). Therapeutic proteins, also known as biologics, are pharmaceutical agents created in a laboratory setting to mimic the structure of naturally produced proteins in the body. They may either mimic the natural protein's function or antagonize the function of the natural protein. These drugs are produced in living cellular systems, and they have proven to be effective treatment for many diseases including rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel diseases. Unfortunately, the high costs of therapeutic protein place a heavy financial burden on the healthcare system and limit the number of patients that are able to be covered. For example, monoclonal antibody therapy - one type of therapeutic protein - is projected to

reach $125 billion in global sales by 2020. As patents on biologic drugs expired, biosimilar drugs were developed and are helping to address this growing issue. The United States Food and Drug Administration (FDA) defines a biosimilar as "a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product." These drugs are still created using living cells, but the synthesis pathway of the reference biologic is proprietary. Biosimilar developers instead analyze the final biologic and attempt to reverse engineer a feasible synthesis pathway.

2. Methodology

There is currently no global consensus regarding the source of reference products, although WHO guidelines have outlined fundamental principles and key considerations in the selection of reference products for the development of biosimilars. WHO guidance documents state that a reference product is "the comparator used for head-to-head comparability studies with the similar biotherapeutic product in order to demonstrate similarity in terms of quality, safety, and efficacy". Further, WHO guidelines stipulate that only a reference product that was licensed on the basis of a complete registration dossier can serve as a reference product (i.e., an approved biosimilar cannot serve as the reference product in the development of another biosimilar). The EMA guidance document states that a single reference product, defined on the basis of its marketing authorization in the European Economic Area (EEA), should be used as the reference product throughout the similarity exercise for quality, safety, and efficacy studies during the development of a proposed biosimilar to facilitate a coherent approach throughout the process. With the overarching goal of encouraging the global development of biosimilars and to circumvent repetition of clinical studies, there is a certain degree of flexibility in selecting a reference product[11-18]. In light of this, the EMA has recently indicated a degree of acceptance of reference products authorized outside the EEA, provided that it is representative of the reference product authorized within the EEA.

The FDA accepts the use of a reference product that is not authorized in the United States, provided that comparability between the US- and non-US-licensed reference products has been adequately demonstrated. Indeed, bridging the selection of reference products licensed in the United States to the EU-approved reference product will likely facilitate the ongoing harmonization of biosimilars development. Guidelines in Canada and Republic of Korea state that the reference product should be authorized within a well-established regulatory framework. Indeed, the use of a globally accepted reference product would allow manufacturers to reduce the number of human subjects and possibly clinical trials required for global approval of potential biosimilars.

3. Results and Discussion

Currently there are seven biosimilars approved in the United States. The most recent, biosimilar bevacizumab, was approved in September, 2017. In the case of infliximab and its biosimilar, it is likely that greater price differences will have to be seen before physicians will be convinced to switch away from the reference product. The average cost per year for infliximab treatment as of 2012 was $24000. As of 2016, there was only a 15% price difference between infliximab and its biosimilar. The reluctance of both patients and physicians to switch to a biosimilar may imply that increases in market shares for biosimilars will be a matter of time as more biologic-naïve patients are placed on biosimilars to begin their treatment regimen. The reluctance of physicians also may affect clinical trials and even patient outcomes through the nocebo effect, which has been documented as causing generalized side effects despite a lack of plausible pharmacological mechanism based on the drug itself or side effects more severe than observed when medication use is blinded. The way in which a physician discusses the effects of a drug with a patient influence the possibility of a nocebo effect. As such, patients receiving biosimilars from physicians who are reluctant to prescribe them may experience more adverse events or decreased treatment efficacy.

Additional studies will also be needed to further examine interchangeability of biologics and biosimilars. The case of switching from a biosimilar to a biologic if the biosimilar does not produce significant clinical improvement should also be explored, especially considering the number of biologic-naïve patients who may be started on a biosimilar rather than biologic therapy. However, as illustrated above, numerous studies have shown to carry similar efficacy when switching from an original biologic agent to a biosimilar. Biosimilars have great potential to improve access to disease modifying therapies over a wide range of chronic illnesses, extending even to some cancers. The more cost-efficient manufacturing process of biosimilars may also open the way to greater experimentation with pharmacological therapies. Patents for many branded biologics will expire during the next few years, allowing biosimilars manufacturers to seek FDA approval for generic versions of these agents.[1] The Biologics Price Competition and Innovation Act (BPCIA) of 2009, which was passed as part of the health care reform legislation enacted into law in 2010, authorizes the FDA to establish a long-awaited regulatory pathway for biosimilars. In 2012, the FDA issued draft guidance summarizing the proposed criteria for this pathway; this guidance is yet to be finalized.

These criteria have inspired debate and the emergence of several critical issues, such as to what extent the biosimilars pathway should be abbreviated, how much clinical data should be required for approval, or when an agent should be designated as comparable or interchangeable with an originator biologic.[2] These parameters will determine the ease and cost for a manufacturer to develop and market a biosimilar and will also ultimately influence the price of these medications. The availability of biosimilars is eagerly anticipated, because these agents are expected to improve affordability and promote wider and earlier access to critical, often lifesaving therapeutic interventions.[3,4] Ideally,

the FDA's finalized guidelines will establish a regulatory path for biosimilars that will ensure patient safety, control development costs, and encourage innovation by manufacturers.

BIOSIMILARS IN USA

Biological products, including therapeutics, vaccines, and blood products, have been regulated in various ways by the US federal government since the early twentieth century. The last quarter of that century saw the emergence of recombinant proteins and monoclonal antibodies (mAbs), and they were also generally regulated as biological products. The scheme for regulating biological products in the United States under the Public Health Service (PHS) Act differs from that for drugs, which are regulated under the Federal Food, Drug, and Cosmetic Act. For example, unlike a drug, a biological product is licensed under the PHS Act, and in addition the license is for the product and its manufacturing sites.

In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act (also known as the Hatch-Waxman Act) (**3**), which established a formal structure for generic drug regulation in the United States. However, Hatch-Waxman does not apply to biological products. This is because, for many decades, it was not deemed feasible to produce near copies of biological products. Vaccine performance was highly dependent on manufacturing conditions; recombinant proteins and mAbs were challenging to manufacture and control; and regulators were cautious about accepting manufacturing or site changes proposed by the companies. However, by the turn of the twenty-first century, experience with these products and advances in analytical methods signaled the possibility of creating an abbreviated pathway to market for products that were close to identical to a licensed biological product. The idea of an abbreviated pathway for biological products was of great interest to legislators and government officials because biotechnology products are among the most expensive pharmaceuticals, and governments worldwide have an interest in managing healthcare costs. In 2004, the European Union (EU) amended a directive establishing an abbreviated pathway to market for similar biological medicinal, or "biosimilar," products. The European Medicines Agency (EMA) was charged with setting up the regulatory plan and regulating these products. Since that time, many biosimilar products have come onto the European market[19-22].

In the United States, after several years of debate, on March 23, 2010, Congress passed the Biologics Price Competition and Innovation (BPCI) Act of 2009 as part of the Patient Protection and Affordable Care Act (**6**). The BPCI Act amended the PHS Act, establishing a pathway to market for biosimilar products in the United States. Congress charged the US Food and Drug Administration (FDA) with implementing a regulatory framework around the statutory provisions. Two years later, a user fee program was signed into law, permitting FDA to assess fees for the consultations and regulatory review required to conduct the program. To date, FDA has licensed three biosimilar products, and with a number of active development programs ongoing, clinicians should expect to see many biosimilar products appearing on the US market over the coming decade. This article describes the regulatory framework and technical requirements for these products in the United States, presents an overview of FDA's approach to assessing biosimilarity, and describes some current challenges and controversies surrounding biosimilar products.

BIOSIMILARS IN EU

Legal instruments that limit the marketing of biosimilar medicines European Union Biosimilar medicines are developed once the exclusive industrial exploitation rights of the original, innovative or reference medicine have expired, or, in other words, once the patent of the reference medicine expires. Therefore, biosimilar medicines could be marketed in the European Union (EU) 20 years after the inscription of the original medicine patent. To register a biosimilar medicine, protection of reference medicine by legal instruments of commercial nature (for example, patents) is not the only factor that is considered, but also exclusivity period of the data provided by the competent regulatory authorities. In the EU, through Directive 2004/27/EC of the European Parliament and of the Council, of 31 March 2004, amending Directive 2001/83/EC, a single period of exclusivity of the data, fixed in 10 years, was established for innovative medicines and harmonized throughout Europe. Furthermore, the said period will be extended up to a maximum of 11 years if, during the first eight of the ten-year period, the laboratory that holds the marketing authorization of the reference medicine obtains authorization for one or several new therapeutic indications, and if during prior scientific evaluation, it is established that those indications would provide a significant clinical benefit in comparison with the existing therapies. This data protection period is known as 'Bolar provision'.

Data required for the approval of biosimilars in the EU

According to the EU guidelines, biosimilarity can be demonstrated by analytical tests, biological assays, non-clinical and clinical data which is in conjunction with data required for the US. There is a huge emphasis on analytical studies [16]. However clinical and non-clinical studies are not required to be done if extensive analytical studies done can provide enough proof of comparability. Clinical trials are targeted to confirm biosimilarity and to clarify any key questions from previous analytical or functional research. An adequately powered clinical trial should be designed to get comparative data with respect to pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity. The evidence required for proving biosimilarity in India is also similar to the US and EU. However, animal studies should be conducted to study the immunogenicity of the biosimilar and how it compares with the reference biologic. Toxicological studies must be conducted in pharmacologically relevant species. At least one repeat dose toxicity assessment with the expected route of administration must be performed. Clinical studies must evaluate the adverse events due to the proposed biosimilar in comparison with the reference product. Also, Indian regulations allow for the waiver of clinical safety and

efficacy studies if physicochemical, in vitro techniques and preclinical studies provide strong evidence for biosimilarity between the biosimilar and the reference product. A post marketing risk management plan must also be in place in such cases[23-27]. However there seems to be a problem here. Experts have stated that the analytical and preclinical testing requirements in India are not at par with those of US FDA, EU or WHO. Also phase 3 studies are not conducted if there is considerable PK, PD evidence of biosimilarity.

The European Medical Association (EMA) has mandated that all medicines produced using biotechnology must be approved through the EMA (centralized procedure). For certain biosimilars, such as low molecular weight heparins derived from porcine mucosa, exceptions are made. Data is reviewed by the EMA Scientific Committees on Human Medicines and Protection (CHMP and PRAC) as well as by EU Biological Medicines Experts (Biologics Working Group]) and Biosimilars Specialists (Biosimilar Working Party) when a company applies for a marketing licensure at the EMA. The assessment by the EMA leads to a scientific consensus, which is then referred to the European Commission, which eventually offers an EU-wide marketing authorisation. The agency, upon receipt of the application, commences validation at the next deadline for submissions indicated on its website. The validation procedure for biosimilars of centrally authorized medicinal products starts in the same month. For biosimilar applications, whose reference medicinal product was authorized through national procedure of a member country, the EMA shall request the concerned authorities in that member state to confirm that the reference medicinal product is authorized, along with details on the complete composition of the reference medicinal product within a span of one month. The assessment process will however only begin once all the necessary and appropriate information is obtained. If any member of the CHMP (Committee for Medicinal Products for Human Use) has not obtained the parts of the dossier which were requested from the applicant within a month from the start of the evaluation process, the clock will be stopped by the EMA till the resolution of the issue. The opinion of the CHMP will be given within 210 days (clock-stops within the procedure are not counted) which will be ensured by the EMA. The comprehensive day-wise review process can be found in the EMA's "Procedural advice for users of the centralized procedure for similar biological medicinal products applications".

BIOSIMILARS IN INDIA

Biologics are derived from the natural resources such as human, animal, or microorganism and manufactured by various biotechnology methods such as recombinant deoxyribonucleic acid technology, controlled gene expression, and antibody technology. Biologics have benefitted the patients with rheumatologic diseases, inflammatory bowel disease, malignant conditions, dermatological conditions, and other connective tissue disorders by halting the disease progression, alleviating the symptoms, and improving the quality of life. Biologics are one of the top selling drugs worldwide as well as in the United States but the major drawback of this drug has been its exorbitant cost, which makes it unaffordable and inaccessible to many patients, especially in developing countries where a large number of people are poor and the concept of health insurance is at its nascent stage.[5,6] But the silver lining is that once the innovator company loses their intellectual property right and patent protection after a stipulated period, it opens the window of opportunities for companies evince an interest in manufacturing similar products, which cost less, and at that time, it is known as biosimilar or similar biologic. Biosimilar is a biologic product, which is very similar to Food and Drug Administration (FDA)-approved biological product known as reference product and has no clinically meaningful differences in term of safety and effectiveness from the reference product. But similar biologics are not exactly identical to reference biologics because of the complex structure, which may be affected by minor alteration in sequences and posttranslational modifications.

Many believe that biosimilars will have a positive impact on the drug pricing. Health-care experts and physicians are optimistic that use of biosimilars may reduce the cost of biologics and eventually lead to better patients' access to these lifesaving drugs.[10] The biosimilars have huge potential to reduce the overall cost of treatment, which was evident from a study carried out in United States where it was estimated over 10 years biosimilar can save 54 billion US dollar in the United States.

4. Conclusion

Biosimilar are not generic; biologics are larger and more complicated than chemical drugs, due to the complexity of biological/biotechnology derived products the generic approach is scientifically not appropriate for biosimilar products. There is need to use well-designed clinical trials to establish biosimilarity[28-30]. The challenge with biosimilars is to know the differences which matter clinically. The specific product given to the patient should be clearly identified. Despite these questions and concerns, a robust US program is in place for the licensure of biosimilar biological products. With three biosimilar products already licensed and multiple development programs under way, it is clear that biosimilars will become a reality in the United States. Nevertheless, the growth rate of market availability is difficult to predict, as is the number of competitor products that will be available for any given biological product. Continuing advances in analytical science and increasing clarity of regulatory requirements will improve predictability for industry. Clinical experience with biosimilars should ease the concerns of prescribers and patients.

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