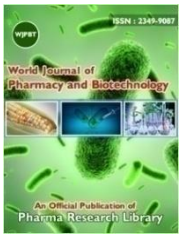

World Journal of Pharmacy and Biotechnology
Journal Home Page: www.pharmaresearchlibrary.com/wjpbt
e-ISSN: 2349-9087 | Publisher: Pharma Research Library
W. J. Pharm. Biotech., 2023, 10(2): 51-56
DOI: https://doi.org/10.30904/j.wjpbt.2023.4601

Possible Guidelines and Regulatory Issues on Biosimilars in INDIA, USA, EU.

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A b s t r a c t
The study delves into the principles guiding the development of similar biologics, data requirements for preclinical studies, and the application process for clinical trials in each jurisdiction. Additionally, the article examines the pharmacovigilance requirements for biosimilars in India and the EU, outlining roles and responsibilities of regulatory authorities, the structure of the pharmacovigilance division at CDSCO, pharmacovigilance plans, and adverse drug reaction reporting. The FDA's action plan for improving pharmacovigilance in biologics is discussed, with a focus on naming and pharmacovigilance in the US. In India, the regulatory framework for biosimilars is overseen by the Central Drugs Standard Control Organization (CDSCO). The guidelines emphasize a step-wise approach to demonstrate similarity with the reference product, involving comprehensive comparative analytical studies, preclinical and clinical trials. Indian regulations highlight the importance of a robust pharmacovigilance system for continuous monitoring post-approval. In the US, the Food and Drug Administration (FDA) plays a pivotal role in biosimilar approval. The Biologics Price Competition and Innovation Act (BPCIA) outlines the regulatory pathway. The FDA employs a totality-of-the-evidence approach, incorporating analytical, preclinical, and clinical data to establish biosimilarity. The interchangeability designation is also a focus, allowing substitution with the reference product without the involvement of the prescribing healthcare provider. The US regulatory landscape reflects a commitment to fostering competition while maintaining rigorous standards. In Europe, the European Medicines Agency (EMA) oversees biosimilar approval through a centralized procedure. The EMA emphasizes the need for a comprehensive comparability exercise, covering quality, preclinical, and clinical aspects. The agency also provides guidance on the extrapolation of data to multiple indications and the interchangeability of biosimilars. The research concludes by providing insights into the current scenario of the biosimilar market, examining market uptake variations by region, molecule, product, manufacturing, and indication. The status of biosimilars in India, the USA, and the EU is presented, offering a comprehensive understanding of the regulatory landscape and market dynamics in the field of biosimilars across these key regions.

Keywords: Biosimilars, CDSCO (Central Drugs Standard Control Organization), DCGI (Drug Control General of India), USFDA (United Stated Food and Drug Administration), EBRE (European Biopharmaceutical Enterprises), CBER (Center for Biologics Evalution and Research, Pharmacodynamics, Pharmacokinetics

A r t i c l e I n f o

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Article History
Received : 06 July 2023
Revised : 18 July 2023
Accepted : 29 Aug 2023
Published : 02 Oct 2023

Citation: Musti Kameswari, *et al.* Possible Guidelines and Regulatory Issues on Biosimilars in INDIA, USA, EU, 2023, 10(2): 51-56.

C o n t e n t s

1. Introduction

The pharmaceutical sector has witnessed remarkable growth in the field of biologics, a dynamic industry marked by the production of complex pharmaceuticals through biotechnological processes involving living systems and tissues. The advent of biologics approximately a decade ago brought about a transformative shift in the treatment of life-threatening and chronic conditions such as Psoriasis, Rheumatoid arthritis, Ulcerative colitis, Juvenile idiopathic arthritis, and Ankylosing arthritis. This category encompasses diverse substances and products, including recombinant vaccines, growth hormones, blood and blood products, monoclonal antibody products, and growth factors. The development of biological products involves a rigorous process, comprising highly controlled manufacturing, analytical similarity assessment, biological evaluations, and comprehensive clinical studies focusing on efficacy and safety, including immunogenicity analyses. According to the FDA, a biosimilar is defined as a biological product that is highly similar to an existing FDA-approved reference product, with no clinically meaningful differences. Similarly, the European Medicines Agency (EMA) describes a biosimilar as a medicine highly similar to another biological medicine already marketed in the EU, while the Central Drugs Standard Control Organization (CDSCO) defines a biosimilar as a product similar in terms of quality, safety, and efficacy to an approved Reference Biological product.

The inception of genetically engineered biologic medicinal products dates to 1982 with the approval of recombinant human insulin in the United States. Since the EMA's approval of its first biosimilar, omnitrope, in 2006, numerous biologic medications have entered the market, addressing various challenging-to-treat diseases. The increasing popularity of biologics over the years stems from their effectiveness in treating serious and chronic conditions such as cancers, inflammatory disorders, and diabetes. However, the development and manufacturing of biologics are more complex and expensive compared to small-molecule drugs. In response to market forces and evolving regulations, biosimilars have emerged as a new category of biologic drugs, gaining traction due to their reliance on data from previously approved reference products.

Pharmacovigilance, essential for monitoring the safety profiles of medicines in clinical use, becomes particularly crucial in the era of multisource biologics. This monitoring ensures timely risk communication and minimization measures when new safety signals emerge, especially considering that rare events, such as immune-mediated reactions, may only surface after products are in the market. While approved biosimilars are expected to demonstrate equivalent safety and efficacy, there remains the potential for differences in safety signals during the post-marketing phase. The challenge in pharmacovigilance for biologics lies in ensuring accurate data collection, specifying the brand and batch of the product used, to draw meaningful conclusions from reported adverse drug reactions for all biologics, including biosimilars.

2. Methodology

Navigating the Regulatory Landscape for Biosimilars in India: An In-Depth Overview

The following paragraph outlines the regulatory framework for biosimilars in India, offering a comprehensive overview of the key principles, authorities involved, and data requirements for the development and approval of Similar Biologics. In the context of India, the regulatory landscape is governed by entities such as the Central Drugs Standard Control Organization (CDSCO), the Department of Biotechnology (DBT), and various committees responsible for ensuring safety, efficacy, and quality in the development of biosimilars.

The regulatory pathway for Similar Biologics is clearly defined, emphasizing the need for extensive characterization studies to establish molecular and quality attributes compared to the Reference Biologic. The Reference Biologic serves as the benchmark, and its selection is crucial, requiring approval in India or International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) countries. The Similar Biologic's manufacturing process is expected to mirror that of the Reference Biologic, ensuring consistency and robustness. The excerpt details the data requirements for preclinical and clinical studies, emphasizing the importance of demonstrating similarity in critical and key quality attributes.

The regulatory process involves several competent authorities, including Institutional Biosafety Committees (IBSC), Review Committee on Genetic Manipulation (RCGM), Genetic Engineering Appraisal Committee (GEAC), and CDSCO. Each entity plays a distinct role, ranging from overseeing biosafety at the institutional level to approving clinical trials and granting marketing authorization. The principles for developing Similar Biologics are outlined systematically, emphasizing the need for stepwise processes to establish similarity through extensive characterization studies. The data requirements for preclinical studies include demonstrating the consistency of the process, product characterization, and specifications. Preclinical studies, including pharmacodynamics and toxicology studies, are designed to detect differences between the Similar Biologic and Reference Biologic.

For clinical trial applications, the applicant must submit data indicating the absence of differences in critical quality attributes and well-controlled key quality attributes. Pharmacokinetic studies, safety, and efficacy assessments are pivotal, and the excerpt discusses the conditions under which confirmatory safety and efficacy studies can be waived. Safety and immunogenicity data are crucial both pre- approval and post-approval, with an emphasis on conducting comprehensive post-marketing risk management.

Unlocking Biosimilars: A Glimpse into the Regulatory Landscape in the USA

The regulatory framework for biosimilars in the United States underwent a transformative shift with the enactment of the Biologics Price Competition and Innovation Act of 2009 (BPCIA) on 23 March 2010. This landmark legislation provided the foundation for the regulation of biosimilars, offering a pathway for the licensing of biological products that are related to already licensed reference products. The responsibility for overseeing this regulatory framework falls under the purview of the Food and Drug Administration (FDA), with specific committees dedicated to ensuring consistency and effectiveness.

CBER Biosimilar Review Committee (BRC), and the Biosimilar Implementation Committee (BIC). These committees collaborate to address policy issues, implement the BPCIA, and ensure a streamlined approach to the regulation of follow-on biologics. The biosimilar development process in the U.S. is characterized by a stepwise approach, commencing with detailed analytical characterization and comparison of the proposed biosimilar to the FDA-approved reference product. The manufacturer generates an array of comparative data, progressing from analytical studies to potential animal studies and, ultimately, to comparative clinical studies.

Data Requirements for Approval:

The FDA evaluates each biosimilar product on a case-specific basis, tailoring data requirements based on factors such as the strength of comparative analytical studies, similarity in PK and PD profiles, and pre-existing information about the safety profile of the reference product. In essence, the U.S. regulatory framework for biosimilars reflects a balance between ensuring rigorous evaluation and providing a pathway that encourages efficiency and cost-effectiveness. As biosimilars continue to play a vital role in expanding therapeutic options and reducing healthcare costs, this regulatory landscape remains a critical aspect of pharmaceutical innovation in the United States.

Navigating the Regulatory Landscape for Biosimilars in the European Union (EU): An In-Depth Exploration

The journey of biosimilars through the regulatory landscape in the European Union (EU) is guided by meticulous scientific guidelines established by the European Medicines Agency (EMA). These guidelines have evolved to keep pace with the dynamic advancements in biotechnology and analytical sciences, emphasizing the need for developers to adhere to stringent regulatory requirements. At the core of the EU's regulatory framework lies the legal foundation articulated in Article 10(4) of Directive 2001/83/EC and Section 4, Part II, Annex I to the same Directive. This framework sets the stage for Marketing Authorization Applications (MAAs) based on demonstrating the similar nature of biological medicinal products concerning quality, safety, and efficacy.

Legal Basis and Relevant Guidelines:

The legal underpinning for similar biological applications is outlined in Article 6 of Regulation (EC) No 726/2004 and Article 10(4) of Directive 2001/83/EC. Specific dossier requirements are detailed in Part II, Section 4 of Annex I of Directive 2001/83/EC. Developers must align with guidelines such as those addressing quality issues and non-clinical and clinical aspects of biotechnology-derived proteins.

Biosimilar Approach and Principles:

The biosimilar approach distinguishes itself from the standard generic model, recognizing the complexity of biological/biotechnology-derived products. A robust comparability exercise, based on scientific principles related to evaluating manufacturing process changes, becomes imperative. Success in applying the biosimilar approach hinges on factors like the purity and characterizability of the product.

3. Results and Discussion

In total, 104/155 (67%) rheumatologists completed the survey. Seven surveys were excluded from the analysis as they were incomplete.

Current awareness of biosimilars and prescribing practices: Most respondents indicated that biosimilars were available in the country where they practiced (Figure 8A). However, some rheumatologists from Argentina, Chile, Peru, and Venezuela incorrectly reported that biosimilars were not approved for clinical use in these countries. Similarly, some rheumatologists from Bolivia and Peru were not aware of biosimilars or non- comparable bio therapeutics, even though they are approved in both countries (Remsima) (Figure 8B). Remsima and Inflectra are the product names for the infliximab biosimilar, CT-P13, developed by Celltrion (Incheon, Republic of Korea) and marketed worldwide.70 Only Remsima is marketed in Latin America.70 None of the rheumatologists reported the use of Inflectra.

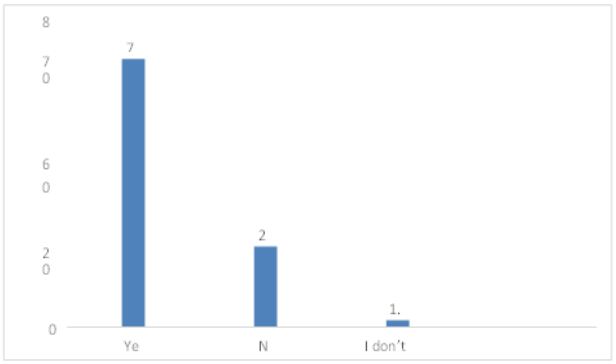

Fig.1 Awareness of biosimilars approved for use in rheumatology practice

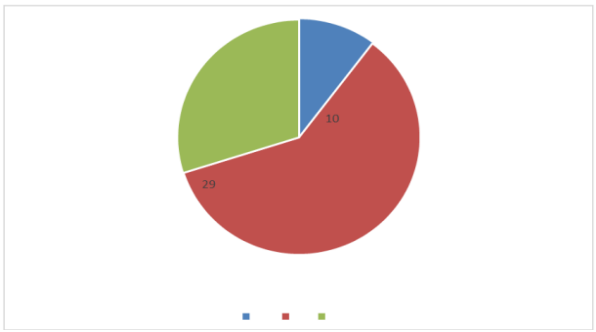

Fig.2 Prescription of biosimilars and non-comparable bio therapeutics by rheumatologists

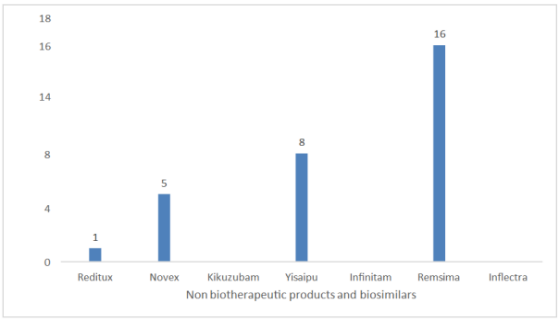

Fig.3 Awareness of the use of a nomenclature system for biologics including biosimilars

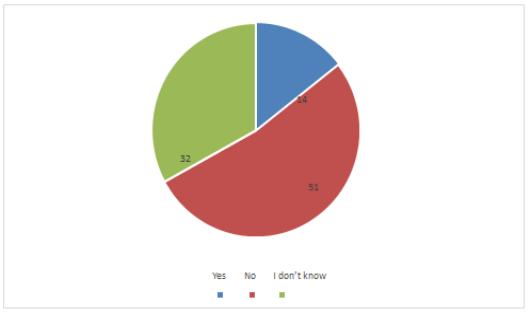

Fig.4 Adverse Drug Reactions (ADRs) among rheumatic patients because of automatic substitution of biologics and biosimilars.

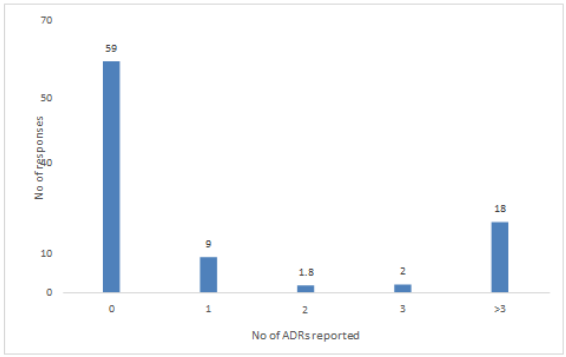

Fig.5 Frequency of ADR reports due to treatment with biologics, including biosimilars, by rheumatologists during the past 3 years

Discussion

Despite leading the field in the biosimilars market, Europe has faced challenges relating to uptake. Uptake varies significantly between countries in Europe, with some, such as Italy and Spain, having relatively low use of biosimilars compared with countries where there is high acceptance of biosimilars, such as Austria, Germany, The Netherlands and Sweden. This difference may be due to the use of different biosimilar policies; surveys carried out by European Biopharmaceutical Enterprises (EBE) have revealed significant variation in biosimilar policies in Europe. The EBE investigates pricing, tendering, substitution and international non-proprietary name prescribing policies for biosimilars in 42 countries (the EU-28 plus countries within the European region as defined by WHO, Canada and South Africa). Findings from EBE surveys suggest that one of the most important challenges for policymakers will be establishing effective measures to enhance biosimilar uptake, which will generate savings to fund innovation and ensure the sustainability of healthcare systems. Positive data from clinical trials of biosimilars as well as stakeholder education are likely to increase confidence in biosimilars and boost their uptake. Several clinical trials comparing originator and biosimilar infliximab have demonstrated that patients can safely and effectively be switched from the originator product to the biosimilar. Real-world data and findings from discussions with patient groups, clinicians, healthcare professional organizations, government bodies and industry have shown that a long-term, multi- stakeholder policy framework for off-patent biologicals and biosimilars is required to increase uptake. Price reduction strategies, including mandatory discounts, reimbursement procedures, tendering co-payments, incentivization of stakeholders and prescribing incentives are expected to increase the adoption of biosimilars among physicians and patients. Aggressive price discounts have been observed in markets with multiple biosimilar entrants. This was seen in the launch of Zarxio in the US in 2015, and in 2018 epoetin alfa and pegfilgrastim biosimilars were launched in the US at a significant discount compared with their originator products. Udenyca (pegfilgrastim-cbqv) was launched at a 33% discount compared with the originator pegfilgrastim Neulasta, and Retacrit (epoetin alfa-epbx) was launched at a 57% discount compared with the originator epoetin alfa, Procrit. Four new biosimilars were launched in the first half of 2020, bringing the total to 17 biosimilars on the U.S. market. The new biosimilars included Ruxience (rituximab-pvvr, biosimilar to Rituxan), Trazimera (trastuzumab-qyyp, biosimilar to Herceptin), Herzuma (trastuzumab-pkrb, biosimilar to Herceptin), and Ontruzant (trastuzumab-dttb, biosimilar to Herceptin). These and other biosimilars launched in the U.S. with discounts of 10 to 37 percent off the reference product list price, but not all have gained significant U.S. market share.

In particular, TNF inhibitors have struggled. Although the FDA has approved 12 TNF inhibitors, only two are on the market: Inflectra and Renflexis, both Remicade (infliximab) biosimilars. These infliximab biosimilars launched in 2016 and 2017, respectively, but recent reports indicate that these biosimilars "lack market penetration." Ongoing antitrust litigation in the Eastern District of Pennsylvania is addressing allegations that Janssen's alleged exclusionary contracts, anticompetitive bundling, and coercive rebates are the root cause of these market trends for infliximab biosimilars. Other TNF inhibitors have not yet launched. Both Sandoz and Samsung Bioepis have FDA-approved Enbrel (etanercept) biosimilars but are embroiled in ongoing patent disputes with the reference product sponsor. Nine companies developing Humira (adalimumab) biosimilars, including several with FDA approval for their biosimilars, have settled with AbbVie under terms that delay launch until at least 2023. Recently, a district court dismissed antitrust claims against AbbVie related to both these settlements and AbbVie's patenting strategies. That case is currently on appeal.

Biosimilars may also play a role in ongoing efforts to develop a vaccine or treatment for COVID-19. In June 2020, Celltrion's infliximab biosimilar (Remsima, CT-P13) was chosen for testing in the CATALYST study, collaboration between the University of Birmingham and the University of Oxford to assess the effectiveness of potential therapeutics for the treatment of patients hospitalized with COVID-19. The biosimilar market and regulatory and legal landscape have remained dynamic in the first half of 2020. Ongoing activity indicates that the remainder of 2020 should bring more interesting developments.

4. Conclusion

In conclusion, the pharmaceutical landscape is undergoing a transformative shift with the rise of biosimilars, presenting a cost-effective alternative to expiring biologic drug patents. Regulatory bodies like the FDA emphasize the need for comprehensive evidence, requiring biosimilars to demonstrate similarity in quality, safety, and efficacy within a specified range. The growing interest among biopharmaceutical companies in biosimilar development aligns with global efforts to mitigate escalating healthcare costs. Regulatory guidelines, exemplified by the FDA and EMA, advocate for a holistic approach, encompassing analytical comparability studies, preclinical testing, and stringent adherence to GMP and GCP principles.

India, a key player in the biosimilar market, faces both opportunities and challenges, necessitating technological upgrades and workforce improvements to maintain its global leadership. Overcoming obstacles related to interchangeability and addressing concerns about immunological responses to frequent switching between biosimilars and reference biologics are critical. The concept of extrapolation gains regulatory consideration, allowing for broader application if a comprehensive comparability analysis establishes biosimilarity in key aspects. With an increasing influx of biologics and biosimilars, robust post-marketing monitoring becomes indispensable, necessitating strategies for traceability, risk-benefit evaluations of multiple switches, and dedicated pharmacovigilance programs. As the biosimilars market experiences exponential growth, projected to reach $23.63 billion by 2023, Europe takes the lead, driven by the imperative to curtail healthcare costs and the introduction of innovative biosimilars. The Asian market, with the highest projected Compound Annual Growth Rate, underlines the global impact of biosimilars. In this dynamic landscape, a concerted effort towards refining regulatory frameworks, bolstering post-marketing surveillance, and fostering global collaboration remains imperative. Ultimately, biosimilars stand poised to play a pivotal role in ensuring patient safety, improving treatment accessibility, and effectively addressing the challenges posed by healthcare costs on a global scale.

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