IJBPAS, November, 2024, 13(11): 5598-5608

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

A COMPARATIVE STUDY OF THE BIOSIMILAR DRUG APPROVAL PROCESS IN THE US, EU AND INDIA

KANZARIYA V[1], THAKKAR J[1*] AND PARMAR K[2]

1: Department of Pharmaceutical Regulatory Affairs, Parul Institute of Pharmacy and Research, Faculty of Pharmacy, Parul University, Vadodara, Gujarat, India-391760

2: Department of Pharmaceutical Quality Assurance, Parul Institute of Pharmacy and Research, Faculty of Pharmacy, Parul University, Vadodara, Gujarat, India-391760

***Corresponding Author: Ms. Janki Thakkar: E Mail: janki.thakkar2807@gmail.com**

Received 24th July 2023; Revised 25th Sept. 2023; Accepted 22nd Dec. 2023; Available online 1st Nov. 2024

https://doi.org/10.31032/IJBPAS/2024/13.11.8452

ABSTRACT

Biosimilar drugs increase patient access while growing the biotherapeutic market. This Regulatory authorization, market accessibility, and clinical evaluations conducted before regulatory approval were examined about the landscape of biosimilar goods in Europe and the US. In the US, the approval procedure for biosimilars. Analytical and clinical data are heavily weighted in this procedure to ensure that biosimilars exhibit substantial resemblance to their reference products. The FDA adopts a strict methodology and demands comprehensive pre-clinical and clinical testing. The European Medicines Agency manages the unified process for approving biosimilars in the EU. The EMA emphasizes the use of all available evidence, including analytical, non-clinical, and clinical data. Due to the EU's experience with biosimilars, there is a healthy market with several medicines that have been approved. India, in contrast, has its own set of biosimilar regulations that are overseen by the CDSCO. India's method is distinguished by a significant emphasis on comparability and a step-by-step methodology that involves in-depth analytical investigations and constrained clinical trials. The regulatory framework in India seeks to strike a balance between affordability and effectiveness. On a case-by-case basis, careful consideration is required for highly complex comparable biologics of monoclonal antibodies.

Keywords: Authorization, Approval, Biosimilar, FDA, EMA, CDSCO

1. INTRODUCTION:

Biosimilars are biological products created after the original biologic's patent has expired. Other names for them include similar biologics, follow-on biologics, and follow-on protein products. These biologics are believed to have the same therapeutic mechanism as the original biologic drug product for disorders that are similar to those treated by the original biologic medication product. The phrase "bio-generic" is deceptive because no two biological products can be similar due to the complexities of their manufacturing processes and approaches. As a result, the terms "follow-on biologics" and "biosimilars" are commonly used to characterize such products **[1, 2, 3]**.

Biosimilars (also known as bio-generics) differ from traditional "generic drugs" in that they are small molecule chemical drug products having active components that are identical to the revolutionary therapeutic product. In another sense, biosimilars drive competition in the market for biological products in the same way that chemo-generics drive competition in the market for new chemical substances **[4]**.

The term 'biosimilars' is discretely but without departing from the fundamental idea that a biosimilar drug product is a formally regulated and approved copy of an originator (innovative) biological drug product that has demonstrated similarity throughout the various stages of a rigorous similarity assessment procedure **[5]**.

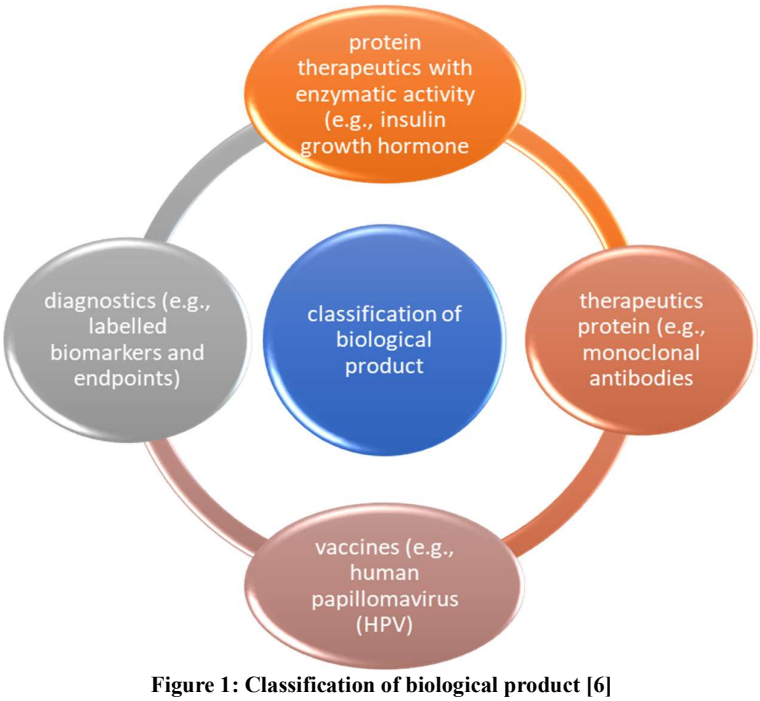


Figure 1: Classification of biological product [6]

2. A Comparison of Biosimilar Regulatory Approval Pathways In The European Union (EU), The United States (US), And India [7, 8]

Domain	EU-EMA	US-FDA	INDIA-CDSCO
Term	Biosimilars	Follow-on Biologics	Similar biologics
Legal framework	• The previously modified Directive 2001/83/EC • Recommendations for comparable biological pharmaceuticals. October 2005 (CHMP/437/04 Rev 1) was released. • Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1) (EMA/CHMP/BWP/247713/ 2012) • Guideline on similarbiological medicinal productscontaining biotechnology-derived proteins as active substances: non-clinical andclinical issues (EMEA/CHMP/BMWP/4283 2/2005 Rev1) • Committee for Medicinal Products for Human Use (CH MP) of the EMA	• The Patient Protection and Affordable Care Act of 2010[Public Law 111–148] • The Biologics PriceCompetition and Innovation Act of 2009 - a component of PPACA- [Pub. L. 111-148, Sect. 7001-7003, 124 Stat. 119.Mar. 23, 2010] • Guidance for Industry: scientific considerations indemonstrating similarity to areference product (April 2015) • Guidance for industry: quality considerations in demonstrating biosimilarity to a reference protein product. • Guidance on Considerations in Demonstrating Interchangeability with a Reference Product (2019)	• The Drugs & Cosmetics Act, 1940 • The Drugs & Cosmetics Rules, 1945 • New Drugs and Clinical Trials Rules 2019 • The Rules for the manufacture, use, import, export, and storage of hazardous microorganisms/ genetically engineered organisms or cells, 1989 (Rules, 1989) notified under the Environment Act, 1986. • Recombinant DNA Safety Guidelines 2017 • CDSCO Guidance for Industry, 2008
Definition of Biosimilar	A biological medicine that is very similar to another biological medicine that has already received approval is known as a biosimilar.	A biological product that bears little therapeutic significance and is extremely identical to an FDA-approved reference product currently on the market is called a biosimilar.	A biologic medication that is extremely similar to one that has already received approval is known as a biosimilar biologic medication or biosimilar.
Reference product	Original product approved in the EU after a thorough dossier.	For comparison with a non-US-approved product, the standards of Section 351(k)(2)(A) of the PHS Act must be met.	Novel items approved in India or ICH countries based on comprehensive safety, efficacy, and quality evidence
Pre-clinical studies	Clinical studies should not be started until non-clinical studies have been completed in a stepwise manner. In vitro testing should be completed before in vivo testing if necessary. To identify differences between the same biological product and the reference product, these studies ought to have a comparative design.	It is imperative to illustrate analogies with pre-clinical trial data, including toxicity assessment.	Before clinical trials, comparative toxicological and PD studies ought to be carried out to determine whether comparable biologics and the reference product differ significantly from one another.
Clinical studies	Clinical efficacy and safety investigations must come after PK/PD tests, and confirmatory studies are needed to show that clinical biosimilars are comparable. To identify potential	Human PK, PD, clinical immunogenicity, safety, and efficacy must all be compared. To evaluate any potential clinically significant variations	Clinical trials (PK, PD, and confirmatory safety and efficacy studies) are required. Phase 3 ought to comprise a cohesive, sensitive patient group

	variations in efficacy and safety, It is necessary to conduct at least one study in a vulnerable population with adequate power and an equivalent design.	**between the reference product and the proposed biosimilar.**	**with pertinent primary objectives.**
Data requirement	• **Analytical, quality comparison/characterization step-wise approach** ○ **Analytical, quality comparison/characterization of Manufacturing processes** • **Non-clinical studies data** • **Clinical studies data** • **Extrapolation to other indication** • **Reference product req.**	• **Demonstrating Biosimilarity** • **Analytical Characterization** • **Comparative Studies** • **Immunogenicity Assessment** • **Extrapolation**	• **Analytical and quality characterization data** • **Non-clinical & clinical studies** • **Extrapolation to other indication**
Biosimilarity assessment Threshold	• **High resemblance to an already approved biological medication in the EU** • **Strict oversight of the production and MFG processes** • **Acceptable small clinically insignificant differences from the reference medication.**	• **High similarity to the benchmark product** • **The guiding principle is that there should not be any clinically significant discrepancies in the PB and RP's potency, purity.**	• **Comparable similarity to an already approved reference biological** • **A phased approach to biosimilar development.**
Interchangeability	**The EU Member States have the authority to make the decision.**	**A pharmacist can replace an interchangeable product with a reference product without consulting the clinician who prescribed the reference product.**	**Without reference determined at random by the pharmacist or prescriber using the product's price and the patient's presumptive affordability**
Pharmacovigilance	**The most recent EU regulations should be followed when creating the risk management and pharmacovigilance plan. One possible issue that needs to be properly addressed is immunogenicity.**	**For biosimilars, a post-marketing safety monitoring and mitigation approach is necessary. A clinical trial or post-marketing research may also be needed to assess particular safety hazards.**	**The producer should create a pharmacovigilance plan to further assess the clinical safety. Phase 4 post-marketing research could be necessary, ideally within two years of approval.**
Similarity data	**Stability, quality comparability studies, clinical studies, nonclinical studies, and analytical studies.**	**Stability, quality comparability studies, clinical studies, nonclinical studies, and analytical studies.**	**stability, quality comparability studies, clinical studies, and nonclinical studies.**
Actions to remove barriers/approach to offset challenges	**Designing a thorough teaching program on the EMA approval process, including post-marketing monitoring studies to verify safety and efficacy and comparability evaluations.**	**Creating strict MFG SPON instructional programs on the FDA approval and how PMS programs function to ensure the safety of biosimilars.**	**Programs for educating stakeholders (doctors, patients, and payers) on the safety and effectiveness of biosimilars.**

3. Key Segments of The Bio-Biosimilar Market: [9, 10]

By diseases	By categories
• **Cancerous conditions**	• **Erythropoietin**
• **Insufficient growth hormone levels**	• **Insulin**
• **Autoimmune and chronic illnesses**	• **Granulocyte-Colony Stimulating**
• **Disorders of the blood**	• **Monoclonal antibodies**

4. Exemptions In CTD Data: [11]

Pharmaceutical dossier requirements:

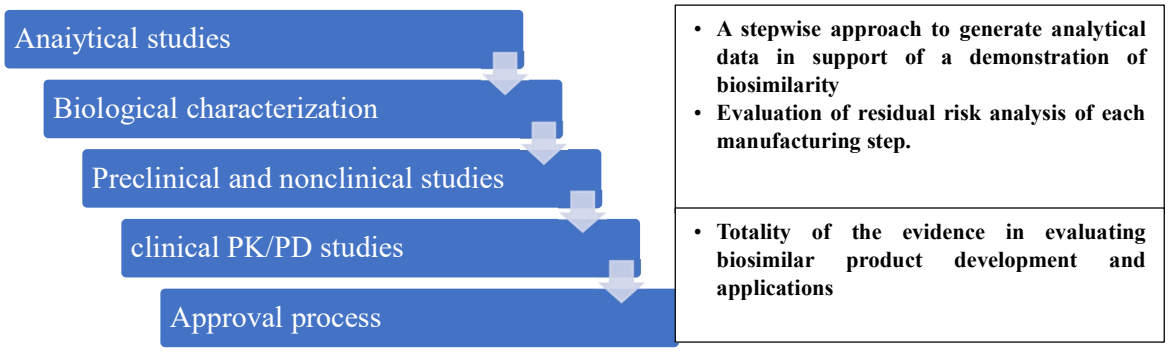
Several exemptions have been made available for biological drugs, including biosimilars approved for marketing by FDA, EMA, and CDSCO regulatory authorities, who have established strict biosimilarity assessment criteria for registration. This has made the regulatory process for biosimilars remarkably quick and easy. The following is a list of the CTD (Module 2-5) exemptions for new drug products, generics, and biosimilars.

5. BIOSIMILAR APPROVAL PROCESS

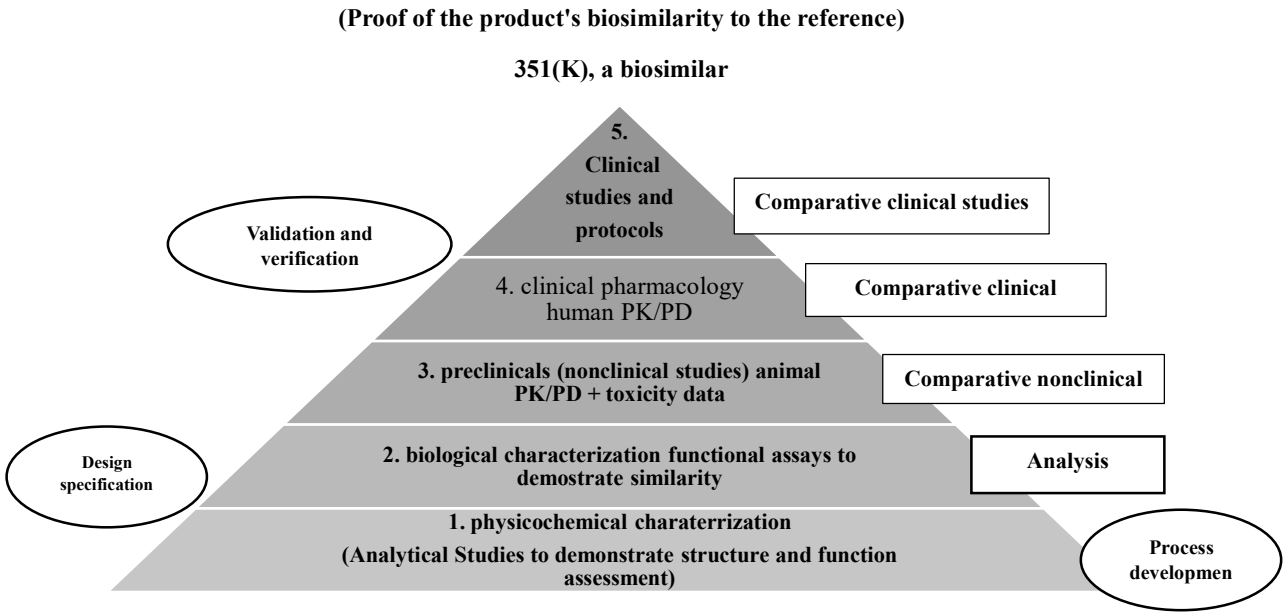
USA:

It is not believed that biosimilar pharmaceuticals are chemically equivalent to their original medications. The sponsors of 351(k) applications are required to submit analytical characterization, pharmacokinetic and pharmacodynamic profiles, and comparative clinical studies before the approval of biosimilars.

Stepwise Evidence Development



Totality of Evidence [12]

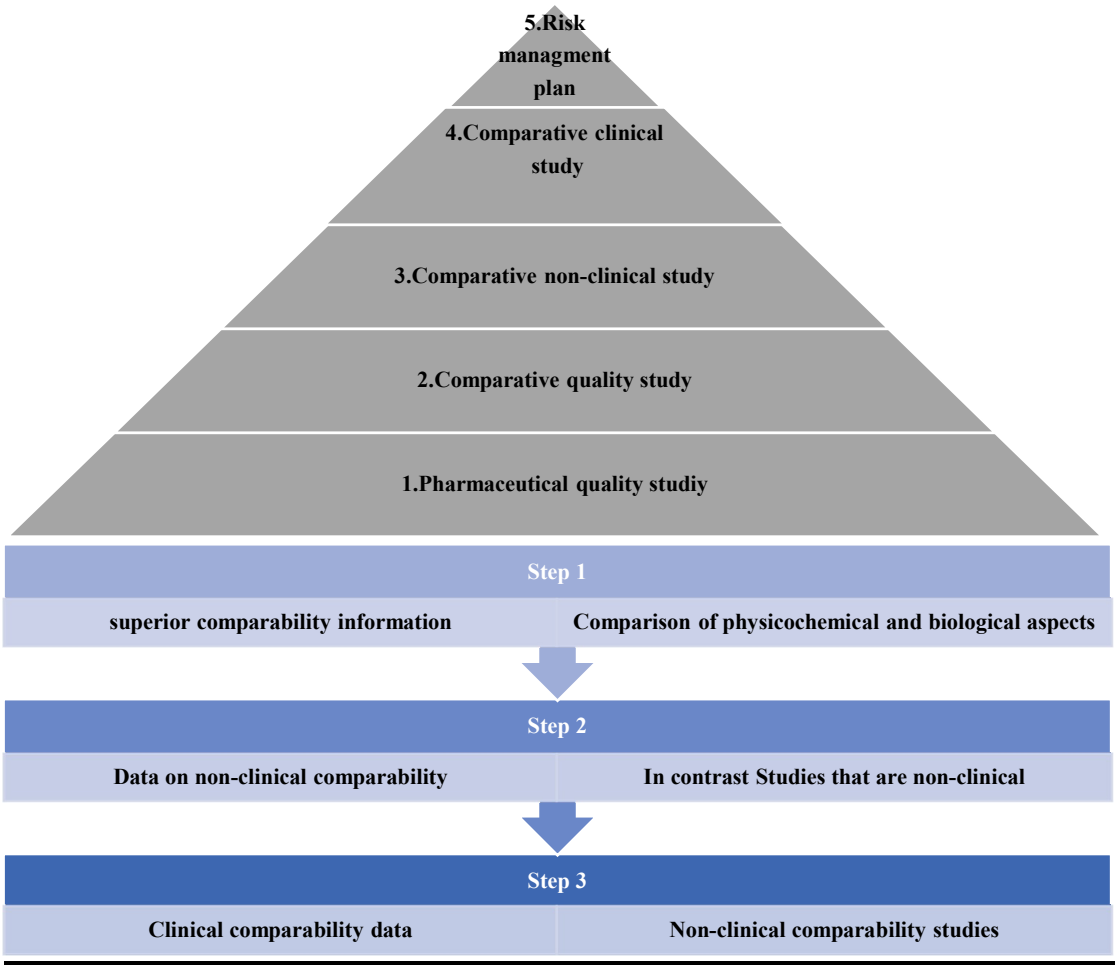


Biosimilar regulations for regions:

Before the passage of the BPCIA in 2009, the United States lacked any kind of regulatory structure. However, policymakers have begun to pay more attention to biosimilars as a result of educational efforts made by stakeholders and other manufacturers in recent years. The slow adoption of biosimilars in the United States reflects the branded approach taken by both patients and doctors. One of the reasons for the slow growth of the biosimilar industry in the United States is a lack of knowledge and inadequate training programs **[13]**.

6. Biosimilar Approval Process EU:

In the EU, biosimilar medications are authorized and marketed. The majority of applications for marketing authorization are assessed by the scientific committees of the European Medicines Agency (EMA).



European Medicines Agency Approval Processes for Biosimilar Development [14]

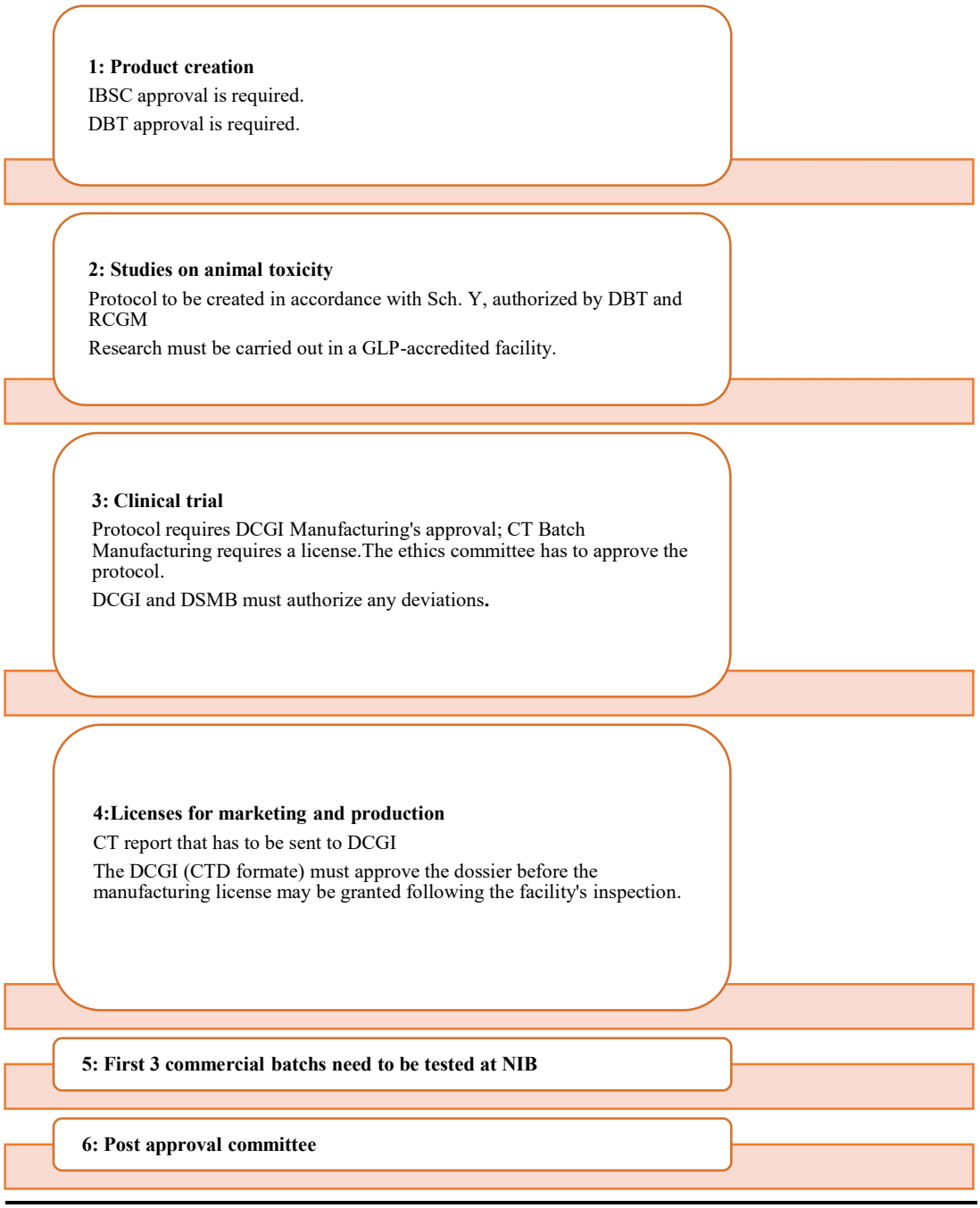
Biosimilar Regulations Regions:

The European Medicines Agency's (EMA) CHMP has been in charge of regulating biosimilar laws since 2005. Europe established a regulatory approval process for biosimilars before any other developed country. Early on, EMA acknowledged the financial impact that biosimilars would have on the healthcare system. In Europe, "Omnitrope," the first Sandoz somatotropin biosimilar drug, was approved in 2006 **[15]**.

Assessment of the Application: [16]

Day	Take action
1	Procedure commencement
80	obtaining evaluation reports from EMA and CHMP participants. To be transparent about the outcome, EMA forwards this report to the applicant. The 80-day assessment period is what is known as this.
87	The Risk Management Plan (RMP) assessment report and list of questions are distributed by the Pharmacovigilance Risk Assessment Committee (PRAC).
90	Acceptance of the inspection report on good practices.
100	EMA receives comments.
115	EMA and its members received a draft of numerous questions and a discussion regarding the recommendations made by the CHMP. The Biotech Working Party (BWP) reviewed dossier module 3 (quality).
120	CHMP reviews the available scientific data and comes to an overall conclusion.
121	Submission of response.
150	Distribute the RMP report through the Pharmacovigilance Risk Assessment Committee.
157	The joint response assessment report, also known as the 150-day assessment report, was given by CHMP. The applicant received this report solely for informational purposes.
170	CHMP, EMA, and other members' comments. BWP assessed the response to the Module 3 Quality questions.
180	If there are critical issues requiring a CHMP decision or an oral application, the applicant is allowed to provide an oral explanation. During this oral presentation, the clock stops to allow the applicant sufficient time for preparation.
181	Restart the clock and distribute the completed report.
183	The RMP assessment report is distributed by the Pharmacovigilance Risk Assessment Committee.
197	Approval of the Pharmacovigilance Risk Assessment Committee's recommendations and RMP summary.
210	Approval of the assessment report and judgment from CHMP.
additional 5 days after the assessment report	The applicant sends EMA SmPC, categorization, and packaging pamphlets in many EU languages for evaluation.
Additional 22 days after R.	Within nineteen days of the evaluation report's adoption, several member nations sent their comments.

7. Indian Regulatory Pathway for Biosimilar Approval [17]



The Schedule that the Regulatory Authority Has Set for the Approval of Biosimilars [18]

Procedure	Timeline
RCGM clearance for preclinical research	45 days
DCGI's approval of the protocol for human clinical trials	45 days
Analyzing clinical trial data with DCGI	90 days
DCGI and GEAC rulings	45 days

Formats Necessary for the Acceptance Process:

Stages	Authority for licensing	Application Made	Acceptance
License to manufacture for inspection, testing, or analysis	State licensing authority	Form no.30	Form no.29
License for (Examination, test, or analysis)	zonal office (CDSCO)	Form no.12	Form no.11
Cellbank import/export	RCGM	Form no. B1/B3/ B5/B7	
Investigation and Creation	RCGM	Form no. C1	
Authorization for preclinical research	RCGM	Form no. C3A	
Submittal of a preclinical study	RCGM	Form no. C5A	
Conducting Clinical Trials	Central licensing body, also known as CDSCO	Form 44	Permission for Clinical trial
Bring in Supplies for Production	Central licensing body, also known as CDSCO	Form 44	Form 45A/ 46A for API and Form 45/46
Manufacturing License	State and Central Licensing Authority	Form 27D	Form 28D
Certificate of Import Registration	Central licensing body, also known as CDSCO	Form 40/Form 44	Form 41/ Form 45
License for imported products	Central licensing body, also known as CDSCO	Form no. 8 & 9	Form no. 10

CONCLUSION:

The regulatory agencies in several nations provide shortened approval processes for biosimilar pharmaceuticals in an attempt to streamline the approval process. For a biosimilar product to be authorized for sale, it needs to first show its similarity to the reference product through the production of equivalent analytical, non-clinical, preclinical, and clinical data. The conventional generic method of proving similarity using various comparability exercises, such as bioavailability/ bioequivalence tests with a reference biologic product, which applies to most biopharmaceutical drugs, is not suitable for biosimilars because of their complexity. More scientific evidence is needed to approve a biosimilar medication than a generic small molecule medication, while less evidence is needed to approve a reference biological product.

ACKNOWLEDGEMENTS:

The author wishes to thank the **INTERNATIONAL JOURNAL OF BIOLOGY, PHARMACY, AND ALLIED SCIENCES (IJBPAS)** for providing the publishing opportunity for this research.

REFERENCES:

[1] K. Raju MM. Biosimilar current status in India. Asian J Pharm Clin Res. 2017;10(1)

[2] Ramanan S, Grampp G. Drift, evolution, and divergence in biologics and biosimilar manufacturing. Bio Drugs 2014; 28:363–72.

[3] Edward Li. Biologic, biosimilar, and interchangeable biologic drug products - Background paper

prepared for the APhA Policy Committee, 2015–2016; University of New England College of Pharmacy.

[4] Chow SC. Quantitative evaluation of bioequivalence/bio similarity. J Bioequiv Availab S1, 2011; doi:10.4172/jbb. S1-002.

[5] Vivek S. Biosimilars Market Overview [Internet]. Allied market research; 2015[Cited 2019 Feb 11]. Available from: https://www.alliedmarketresearch.com/global-biosimilarsmarket.

[6] Alliedmarketresearch.com. [cited 2023 Oct 16]. Available from: https://www.alliedmarketresearch.com/global-biosimilarsmarket.

[7] EMA. Multidisciplinary: biosimilar [Internet]. European Medicines Agency. 2018 [cited 2023 Oct 16]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-biosimilar

[8] Fda.gov. [cited 2023 Oct 16]. Available from: https://www.fda.gov/vaccines-blood-biologics/general-biologics-guidances/biosimilars-guidances.

[9] Biosimilardevelopment.com. [cited 2023 Oct 16]. Available from: https://www.biosimilardevelopment.com/doc/changes-inregulatory-requirements-for-biosimilar-development-inindia-0001

[10] Pooja P, Harvinder P, Ankit S, Anamika J. Current Scenario of Biosimilar. Current Scenario of Biosimilar The Pharmajournal.com. 2018;7(7):188–93.

[11] Researchgate.net. [cited 2023 Oct 16]. Available from: https://www.researchgate.net/publication/359822038_Biosimilars_A_Comparative_Study_of_Regulatory_Safety_and_Pharmacovigilance_Monograph_in_the_Developeds

[12] Marino D. Biosimilar Development - Drug Development & Delivery; 2020 [cited 2023 Oct 23]. Available from: https://drug-dev.com/biosimilar-development-biosimilar-biological-products-development-applications.

[13] Pharmavoice.com. [cited 2023 Oct 24]. Available from: https://www.pharmavoice.com/article/2019-05-

[14] Researchgate.net. [cited 2023 Oct 24]. Available from: https://www.researchgate.net/figur

e/European-Medicines-Agency-EMA-approval-processes-for-originator-and-biosimilar_fig1_298318830

[15] Gabionline.net. [cited 2023 Oct 24]. Available from: http://www.gabionline.net/Biosimilars/General/Biosimilar.

[16] Europa. eu. [cited 2023 Oct 24]. Available from: https://www.ema.europa.eu/en/documents/scientificguideline/guideline-similar-biological-medicinalproducts-containing-biotechnology-derived-proteinsactive_en-0.pdf.

[17] Medicinestoreurope.com. [cited 2023 Oct 24]. Available from: http://www.medicinestoreurope.com/wpcontent/uploads/2016/04/Medicines

[18] Pooja P, Harvinder P, Ankit S, Anamika J. Current Scenario of Biosimilar. Current Scenario of Biosimilar. The Pharmajournal.com. 2018; 7(7): 188–93.