IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Biosimilars: Current Trends And Future Prospects

[1]Harshali Nayak, [2]Gauri Bhamare, [3]Sunayana Ghodgaonkar, [4]Bhagyashree Chaudhary, [5]Gauri Patil

[1,5]Students, Shivajirao S. Jondhle College Of Pharmacy, Asangaon, India

[2]Assistant Professor, Department of Pharmaceutics, Shivajirao S. Jondhle College Of Pharmacy, Asangaon, India

[3]Assistant Professor, Department of Pharmaceutical Chemistry, Shivajirao S. Jondhle College Of Pharmacy, Asangaon, India

[4]Assistant Professor, Department of Quality Assurance, Shivajirao S. Jondhle College Of Pharmacy, Asangaon, India

Abstract : Biosimilars are officially approved versions of original biopharmaceutical products whose patents have expired. The first generation of biopharmaceutical products, developed using recombinant technologies, was introduced in the 1980s and are now approaching patent expiration. Biologics are produced by cultured cells or whole organisms, which naturally results in more variability compared to chemical synthesis methods As a result, unlike generic pharmaceuticals, it is not possible to create an identical copy of an innovator product. Biosimilars are approved based on the same rigorous standards of pharmaceutical quality, safety, and efficacy that apply to all biological medicines. In the coming decades, biosimilar drugs are expected to surpass small molecule pharmaceuticals. The uptake of biosimilars is expected to keep growing as new blockbuster biological drugs continue to enter the pharmaceutical market. This review discusses the current trends and future prospects of biosimilars.

Keywords : **Biosimilar, Biologics, Reference product, follow on biologics, Biopharmaceutical, Innovator biopharmaceutical product**

I. INTRODUCTION

Biologics

Biological medicines, or 'biologicals,' contain active substances derived from biological sources like living cells or organisms. These medicines are well-established in clinical practice and are often essential for treating serious and chronic conditions, including diabetes, autoimmune diseases, and cancers. Most biological medicines currently used in clinical practice contain active substances made up of proteins. These proteins vary in size and structural complexity, ranging from simple proteins like insulin or growth hormone to more complex ones such as coagulation factors or monoclonal antibodies.

Biosimilar

A biosimilar is a biologic product that closely resembles, but is not identical to, a reference product. As such, it requires separate marketing approval once the reference product's patent expires. Biosimilars are not considered generic versions of biologics[1].

According to US FDA, "A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product."[2]

According to EMA, "A biosimilar is a biological medicine highly similar to another already approved biological medicine."[3]

According to WHO, "Similar biotherapeutic product (SBP). A biotherapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product."[4]

Biologics, including both reference and biosimilar products, are created using living cells and biotechnology techniques like recombinant DNA technology, controlled gene expression, or antibody-based methods[5,6]. Because biologics are produced using cells in culture or whole organisms like plants, animals, and microorganisms, they tend to be more variable than small-molecule drugs, such as aspirin, which are created through chemical synthesis[5,7]. Recombinant DNA technology involves using enzymes to cut and assemble specific DNA sequences. These recombined DNA fragments can be inserted into vectors, which transport the DNA into host cells, allowing the modified DNA to be replicated or translated. First-generation biologics were produced directly from human and animal by-products, like human blood and porcine insulin. In contrast, second-generation biologics are created through genetic engineering of DNA within living organisms[9].

II. CLASSIFICATION[6]

- Protein therapeutics with enzymatic or regulatory activity (e.g., insulin growth hormone, factor 1x replacement therapies, and beta-gluco-cerebrosidase replacement therapy for Gaucher's diseases).
- Protein therapeutics with special targeting activity (e.g., monoclonal antibodies that bind specific therapeutic targets, such as the antitumor necrosis factor-α biologics).
- Vaccines (e.g., human papillomavirus (HPV) vaccine made using HPV major virus-like particles containing HPV major capsid protein L1); and,
- Diagnostics (e.g., biomarkers such as glucagon, and imaging agents such as technetium-labeled antibodies).

III. CHARACTERISTICS OF BIOSIMILARS[5]

- Biotechnologically produced by host cell lines
- High molecular weight
- Complex physiochemical properties
- Sensitive to heat and shear (aggregation)
- Heterogeneous mixture, broad specification which may change during development, difficult to standardize
- Usually administered parenterally
- Larger molecule primarily reach circulation via lymphatic system, subject to proteolysis during interstitial and lymphatic transit
- Distribution usually limited to plasma and/or extracellular fluid • Mostly receptor mediated toxicity
- Usually antigenic
- Difficult to characterize
- Lengthy and complex purification process
- High possibility of contamination, detection is harder and removal is often impossible
- Highly susceptible to slight changes in production process and environment.

IV. THERAPEUTIC USES[10]

Biosimilars are used in the treatment of various diseases such as:

- Chronic bowel diseases (such as colon, Crohn's disease, Ulcerative colitis and irritable bowel disorder)
- Chronic skin diseases (such as psoriasis)
- Diabetes
- Macular degeneration
- Kidney conditions
- Arthritis
- Multiple sclerosis
- Cancer
- Osteoporosis

V. ADVANTAGES

- There is huge market needs and growing affordability for biosimilars in universal and domestic market.
- Development and manufacturing of biosimilars are improved by existing manufacturing technology[11,12].
- Due to no investment in phase I-II of clinical trials, biosimilars are existing at cheaper prices than the reference products, so treatment price with biosimilars is minor than innovators biological drug[13].

VI. DISADVANTAGES

- Biosimilars are not as much of stable as chemical based pharmaceuticals and thus essential cold chain distribution and have a shorter shelf life. This increases the price and complexity of distribution.
- The cost of development will be importantly higher than for chemical based generics.
- The required capital venture in property plant and equipment and the cost of manufacturing will be much greater for biosimilars than for generic drugs[12].

VII. MANUFACTURING BIOSIMILARS

The manufacturing processes for biologics are more complex than those for small molecule drugs, involving multiple steps that can be influenced by variations that impact the biological and clinical characteristics of the product[914].

In the development and manufacturing of a biosimilar, it is crucial to match the key characteristics of the originator molecule, known as Critical Quality Attributes (CQAs), as closely as possible to ensure biosimilarity. Biologics are complex molecules that inherently exhibit variability due to both the biological processes in the organisms used for their production and the manufacturing processes involved in their creation.

VIII. DEVELOPMENT OF BIOSIMILARS

The development of a biosimilar involves four key stages:

- Product development and comparative analysis
- Process development, scaling up, and validation
- Clinical trials
- Regulatory review and approval (by agencies such as EMA, WHO, and FDA).

Each stage has distinct requirements and timelines, which collectively influence the overall cost of biosimilar development.

Product development and comparative analysis: This phase includes the production of the target protein from cell culture and assessment of its stability. Additionally, the product must demonstrate biosimilarity to the reference product.

Process development, scale-up, and validation: In this phase, the manufacturing process is scaled up to enhance product yield. The process must be conducted in accordance with good manufacturing practices, and the reproducibility of the manufacturing process must be demonstrated.

Clinical trials: Clinical trials are necessary for nearly all biosimilar products to establish bioequivalence to the reference product[16].

IX. CURRENT TRENDS

The field of biosimilars is experiencing strong growth driven by increasing demand for cost effective alternatives to biologics. Phase I-II trials are generally not required for biosimilar approval, except in special cases. However, phase III trials involving at least 100 patients are mandatory to establish bioequivalence. As a result, the total development cost of biosimilars ranges from $10-20 million, enabling pharmaceutical companies to offer their products at 25-40% lower prices than innovator biologics[17,18]. Europe was the first region in the world to establish a policy framework for the approval of biological products[19]. The first biosimilar omnitrope (a recombinant human growth factor) was approved in Europe in 2006 and 86 biosimilars are approved in the EU since 2006[20,21,22]. The United States followed much later, approving filgrastim-sndz, a biosimilar to filgrastim (granulocyte CFS), in 2015 and total 62 biosimilars are approved in the US since 2015[23,24]. Today, numerous biosimilars developed by

biopharmaceutical companies are used worldwide in a wide range of areas, including diabetes, ophthalmology, respiratory conditions, cancer, and connective tissue diseases[25,26,27,28]. India has developed a robust ecosystem, positioning its pharmaceutical companies as global leaders in biosimilars. The country approved its first biosimilar well before the United States and Europe. In 2000, India approved and marketed its first biosimilar for hepatitis B, despite the absence of specific guidelines for the development and marketing of biosimilars at that time[29]. In 2024, total 18 biosimilars are approved by FDA[30].

X. FUTURE PROSPECTS

Within the three major geographic clusters, several factors will influence the value generation potential for biosimilars, such as short-term accessibility, speed of adoption, regulatory clarity, and especially the involvement of public and private stakeholders. As a result, the majority of immediate value is expected to come from emerging pharmaceutical markets, driven by the anticipated influx of new patients[31]. The biopharmaceutical sector in India is expected to focus on biosimilar development, driven by lower development costs and risks, reduced research and development expenses, faster time to market, and expertise in reverse engineering drug development[32].

- Biosimilar Market: According to a report by Towards Healthcare, the global biosimilar market is projected to expandfrom $25.1 billion in 2022 to approximately $1.3 trillion by 2032, with a compound annual growth rate of 17.6%, driven mainly by the increasing prevalence of cancer and the cost-effectiveness of biosimilars[33].

Table.10.1. Biologics that go off patent in the near future[34]

Sr.No.	Proprietary Name	Proper Name	Applicant	Patent expiration date
1	Rituxan	Rituximab	Genentech, Inc	March 8, 2025
2	Xolair	Omalizumab	Genentech, Inc	November 4, 2025
3	Humira	Adalimumab	AbbVie, Inc	April 11, 2025
4	Avastin	Bevacizumab	Genentech, Inc	March 8, 2025
5	Tysabri	Natalizumab	Biogen, Inc	April 4, 2026
6	Lucentis	Ranibizumab	Genentech, Inc	July 8, 2028
7	Herceptin	Trastuzumab	Genentech, Inc	July 8, 2028
8	Prolia and Xgeva	Denosumab	Amgen, Inc	January 19, 2030
9	Neulasta	Pegfilgrastim	Amgen, Inc	June 21, 2030
10	Actemra	Tocilizumab	Genentech, Inc	August 6, 2030
11	Stelara	Ustekinumab	Janssen Biotech,Inc	July 6, 2032
12	Eylea	Aflibercept	Regeneron Pharmaceuticals	October 26, 2036

XI. CONCLUSION

There is broad consensus that the future of medicine lies in biotechnology, particularly biological medicines. Biosimilars are already well-established in clinical practice and play a crucial role in improving access to treatments and medications. Because biosimilars are significantly cheaper than their reference biologics, they contribute to greater financial sustainability for healthcare systems. Offering the same safety, quality, and efficacy as the original biologics, they enable more patients to benefit from advanced therapies.

REFERENCES

[1] Schellekens H. Biosimilar therapeutics-what do we need to consider? NDT Plus 2009;2(Suppl 1):i27-36
[2] US Food and Drug Administration (2017) Biological product definitions [Internet]. Silver Spring (MD): US Department of Health and Human Services; 2017 Oct 12
[3]https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM581282.pdf
[4] Biosimilar medicines: Overview [Internet]. London (UK): European Medicines Agency; cl1995–2018. http://www.ema.europa.eu/ema/index.jspcurl=pages/medicines/general/general_content_001832.jsp&mid=WC0b01ac0580bb8fda
[5] Kang HA, Knezevic I (2018) Regulatory evaluation of biosimilars throughout their product life-cycle. Bull World Health Organ 2018(96):281–285. https://doi.org/10.2471/BLT.17.206284
[6] Sekhon BS, Saluja V. Biosimilars: An overview. Biosimilars. 2011;1:1-11
[7] Leader B, Baca QJ, Golan DE. Protein therapeutics: A summary and pharmacological classification. Nat Rev Drug Discov 2008;7(1):21-39
[8] Revers, L, Furczon E. An introduction to biologics and biosimilars. Part II: Subsequent entry biologics: Biosame or biodifferent? Can Pharm J 2010;143:184-91
[9] Scitable by Nature Education. Recombinant DNA technology.
http://www.nature.com/scitable/definition/recombinant-dnatechnology-dna-cloning-gene-cloning
[10] Revers L, Furczon E. An introduction to biologics and biosimilars: Part I: Biologics: What are they and where do they come from? Can Pharm J 2010;143:134-9
https://www.fda.gov/drugs/biosimilars/biosimilars-basics-patients
[11] Current Scenario of Biosimilar. Narayan, D.: Biosimilar – Pros, Cons, Global Status and Future, http://www.biotecharticles.com/Healthcare-Article/Biosimilar-Pros-Cons-Global-Status-and-Future-3087.html
[12] Rcgm SOF, DBT C. Guidelines on similar biologics, 2012
[13] Zelenetz AD, Ahmed I, Braud EL, Cross JD, Davenport-Ennis N, Dickinson BD, et al. NCCN biosimilars white paper: Regulatory, scientific, and patient safety perspectives. J Natl Compr Canc Netw 2011;9 Suppl 4:S1-21
[14] Vulto AG, Jaquez OA (2017) The process defines the product: what really matters in biosimilar design and production? Rheumatology 56:iv14–iv29
[15] European Medicines Agency. Guideline on similar biological medicinal products. Committee for Medicinal Products for Human Use; 2005 Oct; London. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: Non-clinical and clinical issues. Committee for Medicinal Products for Human Use; 2006 Feb; London.
[16] European Medicines Agency. Annex to guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: Non-clinical and clinical issues. Committee for Medicinal Products for Human Use; 2006 July; London23
[17] Frost and Sullivan, 2011. Strategic Analysis of the Indian Biosimilar Market. Research and Markets.
[18] Generics and Biosimilars Initiative. Development of biosimilars. [Online]. GaBI Online 2010 July 2
[19] European Medicines Agency. Guidance on similar biological medicinal products, 2006.
[20]European Medicines Agency. Guidance on similar biological medicinal products, 2005.
[21] Schiesttl, Zabransky M, Sorgel F. Ten years of biosimilars in Europe development and evaluation of the regulatory pathways. Drug Des Devel Their, 2017; 11: 1509-15.
[22] https://www.ema.europa.eu/en/human-regulatory-overview/biosimilar-medicines-overview
[23] Sheridan C First generic biologics finally approved. Nat Rev Drug Discov, 2006; 5: 445.
[24] https://www.fda.gov/drugs/biosimilars/biosimilar-product-information
[25] US Food and Drug Administration Drug filgrastim-sndz, 2018 July 25
[26] FDA approves first biosimilar to Neulasta to decrease the risk of infection during cancer treatment, 2018 July 2.
[27] Llano A, Fisher M, McKay G. Biosimilar insulin the current landscape. Pract Diabetes, 2017; 34: 51-4.
[28] Ferrando M, Bagnasco D, Braido F, Varricchi G, Canonica GW. Biosimilar in allergic disease. Curr OpinAllergy Clin Immunol, 2016; 16: 68-73.
[29] El Zorkany B, Al Ani N, Al Emadi S, Al Saleh J, Uthman I, EL Dershaby Y, et al. Bioimilar in rheumatology: recommendations for regulation and use in middle eastern countries. Clin Rheumatol, 2018; 37: 1143-52.

[30] https://www.fda.gov/drugs/biosimilars/biosimilar-product-information
[31] Desai, J.P. 2009. Bridges to bloom: The future of Indian biosimilars. Available at: http://www.universalconsult
[32] Brennan Z, India Release New Biosimilar Guidance, Regulatory 2018 June 23.
[33] https://www.centerforbiosimilars.com/view/global-biosimilar-market-projected-to-reach-1-3-trillion-by-2032
[34]https://purplebooksearch.fda.gov/patent-list