International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Biosimilars: A Game Changer in Future Therapeutics?

John SS, Adiga Sachidananda MN*

Department of Pharmacology, KS Hegde Medical Academy, Nitte (Deemed to be University), Deralakatte, Mangaluru, Karnataka, India 575018.

Abstract

Biologics (Biologicals) are medicines derived from blood, proteins, viruses, or other living things. The word "biosimilars" refers to a biologic product that is almost similar to another biological product that has been authorized by the Food and Drug Administration (as "reference product,") and hardly differs from the reference product in terms of safety or clinical efficacy in a meaningful manner. The expiry of a company's patent and intellectual property rights paves the way for development of cheaper biosimilars from biologicals by other firms. First biosimilar introduced in India was Biovac TM (hepatitis B vaccine, (Wockhardt). Biosimilars require a longer approval procedure and more information than other generic medications. The country specific regulatory agencies have put forth guidelines on comparable biologicals to address the issues and challenges surrounding the manufacture of comparable biologics. Biosimilars are already being used in the field of oncology, rheumatology, diabetes and cancer therapy induced bone marrow suppression. In this review article, we have made an attempt to discuss the history of development of biosimilars, how they are different from biologicals in terms of manufacturing method, approval process, nomenclature, efficacy, safety, cost, and business impact. We also tried to cover some important disadvantages with respect to their clinical utility, dilemma of physicians and future prospects in biosimilars utility in therapeutics.

Keywords: Biosimilars, Biologics, Nomenclature, Cost, Pharmacovigilance

Full length review article **Corresponding Author*, e-mail: adigapharma@nitte.edu.in

1. Introduction

1.1: Background*:* The term "biologics" (biologicals) refers to a class of medications that are produced using massive cell cultures of bacteria, yeast, plant, or animal cells before being purified. Monoclonal antibodies, growth factors, immune modulators, vaccines, items made from human blood and plasma will fall within the broad category of biological medicines. Biologicals are often proteins that are isolated from blood or live culture systems sets them apart from other medications [1]. Biologics are medicines derived from blood, proteins, viruses, or other living things. They are used to prevent, treat, and cure a variety of medical issues. Biologics are typically a lot more complicated than conventional drugs as for as manufacturing, processing and purification is concerned. Once these drugs are manufactured, they frequently become unpredictable and more susceptible to changes in temperature and light, biotechnologically produced biological products, notably those made under the use of heat, are subjected for frequent microbial contamination [2]. Use of aseptic principles from the first manufacturing processes is therefore required [3].The cell system in which a biologic agent is synthesized, the fermentation medium, or operational parameters may have an impact on the biologic agent's activity. It is very difficult to manufacture oral biological medications. The majority of them are offered as injections and infusions. However, they may occasionally be prescribed as an inhaled drug [4].

1.2: Limitations of Biologics*:* They are frequently less stable, can cost hundreds of dollars per month and require particular management. Biologics require a regulated environment for temperature and light, as well as safeguards against jarring when in liquid form. Several large proteins, for instance, cannot be reconstituted because shaking might damage the protein structure. Speciality pharmacies, which distribute complex-molecule goods for limited populations and have specialized handling, processing, and mailing procedures in place to accommodate these complicated pharmaceuticals. Biologics are viewed in many respects as designer pharmaceuticals that are aimed at individuals with rare diseases or genetic subclasses of people with diseases that are generally prevalent. The priciest medications available in the US are biologics. Biologics occupy top three most expensive brand-name medications available. So there is a need for similar molecules with comparable efficacy and safety with lower cost. The term “biosimilars” are versions of them that are considerably cheaper and quite similar in structure and efficacy [2].

2. Biosimilars:

2.1: Introduction: The word "biosimilar" refers to a biologic product that is highly similar to another biological product that has been authorized by the Food and Drug Administration (FDA), also known as the "reference product". It differs from the reference product neither in terms of safety nor efficacy. The complicated structure of homologous biologics, however, can be impacted by minute changes in sequences and posttranslational modifications, thus they are not completely identical to reference biologics [5]. The advent of biosimilars is a result of the high cost of biologics, which renders them prohibitive and unavailable to many patients, particularly in developing countries where a considerable percentage of the population lives in poverty and the notion of health insurance is still in its infancy. Biosimilars are anticipated to positively affect medicine pricing [5]. The usage of biosimilars, according to medical professionals and experts, may lower the price of biologics and eventually improve patients' access to these life-saving medications. According to research conducted in the United States, using biosimilars over a ten-year period might save the country 54 billion US dollars, demonstrating the biosimilars' enormous potential to lower healthcare cost [5].

2.2: History: India was the first country to approve a biosimilars, much before the US and EU. First biosimilar introduced in India was Biovac TM (hepatitis B vaccine, Wockhardt) in 2000, subsequently by Wepox TM (epoetin alfa) in March 2001. Filgrastim-sndz (Zarxio®), which treats neutropenia caused by chemotherapy, was the first biosimilar drug to received approval in the United States. The EMA authorized the first biosimilars in Europe in 2006 (Nau, 2006). Somatropin is a recombinant human growth hormone with indications for pituitary dwarfism, Prader-Willi syndrome, and Turner syndrome. Omnitrope® was the first EMA-approved bio-similar for somatropin [6]. Pegfilgrastim-jmdb, the most recent one to receive approval in June 2018, was designed to lower the risk of infection after myelosuppressive chemotherapy [5]. When a company's patent and intellectual property rights expire after a predetermined period, it creates an opportunity for other firms to express interest in producing cheaper biosimilars than biologics, which is how biosimilars come into being[5]. There are now over 100 Indian biopharmaceutical businesses involved in the production and commercialization of biosimilars [7]. Table 1 denotes the reference drug used for the development of respective biosimilars. “Biosimilar” term is not used universally. Different countries are using unique terms for biosimilars which is mentioned in Table 2.

2.3: Development: Biosimilars require a longer approval procedure and more information than other generic medications. The Department of Biotechnology, India (DBT) and the Central Drugs Standard Control Organization, India (CDSCO) created Guidelines on comparable Biologics to address the issues and challenges surrounding the manufacture of comparable biologics. These regulations include the quality, safety, and efficacy of comparable biologics as well as the control of the production process. Additionally, it discusses the regulatory requirements for comparable biologics before and after commercialization [5]. Biosimilar drugs are developed over a period of nearly 8-10 years bypassing phase-2 trials as they are copies of marketed products with known product characteristics. They undergo meticulous analytical studies through toxicity and clinical studies to better understand the similarity of the biosimilar with that of reference product. It is advised to have a minimum of two clinical studies to demonstrate pharmacokinetic similarity and clinical equivalence between biosimilars and reference product [8]. In order to place more emphasis on the post-marketing studies, which CDSCO claims are meant "to further reduce the residual risk of the similar biologic," CDSCO has mandated that the biopharmaceutical company conduct a Phase IV study with a minimum of 200 patients within two years of receiving marketing authorization [5]. The average time spent in different phases of drug development with the total cost spent for overall drug development of a reference biological development is being compared with the biosimilars in Fig .1.

2.4: Nomenclature of Biosimilar: FDA states that “each biosimilar product will be a proper name that is a *combination of the core name and* a distinguishing suffix that is devoid of meaning and composed of four lowercase” [9]. The table 3 depicts the how different biosimilars were named and marketed for therapeutic uses.

2.5: Advantages of biosimilars: Unlike the reference product, biosimilars need less research and development time than the reference product therefore reduced cost is considered to be the main advantage of biosimilars. It also introduces competition in the market share thus increasing the patient’s accessibility to it. Another advantage noticed is that biosimilar drugs produce similar efficacy as that of reference product in comparative lower price. Additionally, patients attain knowledge by experimenting with new products that will aid them in choosing a course of therapy for themselves in terms of convenience, cost and accessibility [10].

2.6: Business impact: Recent times showed wide variation on uptake of biosimilars. This variation was mainly based on the molecule and the geography where they were introduced. In a global scale, biosimilars growth in the field of oncology has been faster in comparison to insulin glargine and insulin lispro, biosimilar used for diabetes. [9] In 2015, the market for Indian biosimilars was worth around $300 million USD. With a compound annual growth rate of 14%, domestic sales are approaching $250 million USD. The startling amount of US$51 million is the export of biosimilar or comparable biologics from India. India may one day dominate the market for biosimilar or comparable biologic [5].

2.7: Disadvantages of biosimilar: Lack of confidence in their safety and effectiveness is seen to be a major barrier to the use of biosimilars. Its restricted use is also a result of the healthcare system’s lack of understanding of its use and benefits[10]. Nocebo effect: This is the perception by patients that the offered treatment will have no impact. This is something that many patients who use biosimilars have encountered. This results in a negative response to the treatment, such as increased side effects and a lower response to therapy and is primarily caused by their concern about the new option and a lack of communication surrounding it [11].

3. Clinical Pharmacology:

3.1: Medical switching between biosimilars:

When a doctor decides to switch a patient's medicine, this is known as medical switching. A medical switch aims to maximize the patient's benefit from their treatment. Given that similar therapeutic benefits are typically anticipated from various formulations of the same reference product, a change in disease activity may be the driving force behind a medical cross-switch involving biosimilars, but this is unlikely. More likely, the decision will be made to address tolerability concerns and/or adverse events (AEs) (e.g., injection-related reactions) and/or for the convenience of the patient (e.g., device preference, frequency of dosing, storage requirements). Cross-switching may be medically advised or required in some situations to direct intolerance issues, such as avoiding an irritating excipient (citrate-free vs. citrate-containing biosimilars of adalimumab) or a prefilled delivery device for a biosimilar whereby a patient has heightened sensitivity (a latex-containing needle cover versus a latex-free needle shield). Other medical rationale for a biosimilar-to-biosimilar cross-switch could relate to adjustments to the volume in a prefilled syringe, the needle's length, or gauge, or both if doing so could improve patient satisfaction. In the event that a patient or their caregiver has a hand-eye coordination problem, to enable more precise administration of a lesser dose (a prefilled syringe to a biosimilar with the option of a single-dose vial). A medical cross-switch could also be necessary to accommodate the choice of one delivery method over another. The non-medical switching is for the goal of cost-cutting or to guarantee that the patient will have access to the same kind of medication. This type of switching is regulated mainly by either the payer who requires patients to adhere to the specific biosimilar listed on the healthplan's prescription formulary or based on an employer-sponsored benefit or by a pharmacist at a hospital to prevent supply-chain problems brought on by a faulty manufacturer, for patients who might be traveling or moving to a new place where the biosimilar might not be available [12].

3.2: Clinician's Dilemma: There are a few areas that need to be addressed at the level of treating physician to make biosimilars effective clinical use. The apprehension of compromised quality or substandard biosimilars products among the practicing clinicians. However, this is far from reality as the manufacturing process for biosimilars must fulfil the standard quality guidelines put forth by licensing authority. These products should also meet the standard production norms [13]. The term biosimilars itself is creating some skepsism among the stakeholders. We should first understand the fact that each batch of ordinator product is also not identical. This problem cannot be sorted out as with biotechnology we cannot produce two identical products. These two concerns can be addressed only with extensive and effective awareness program to the stakeholders. Another major concern is immunogenicity of biosimilars. With carefully designed administrative protocols we can effectively monitor and take remedial measures to address the issues arising with its clinical use.

3.3: Pharmacovigilance of biosimilar: Pharmacovigilance helps to recognize ADRs and risk factors that lead to ADRs. Due to the uncertainty in safety, immunogenicity and ADRs biosimilars might have, pharmacovigilance for biosimilars is the need of the hour. Comparing ADRs between biosimilars and reference products in terms of regularity and severity will help in understanding differences between the two. Because biosimilars are extremely temperature sensitive and have multiple manufacturing steps in arriving to a final product which might be highly prone to safety issues, pharmacovigilance in these areas is highly recommended. Post marketing surveillance will assist in identifying rare adverse events in a large number of patients utilizing biosimilars [14].

4. Patient Perspectives:

4.1: Cost of biosimilar: Biosimilars are considered to be a cost-effective substitute of biologics but are more high priced than generic drugs. A generic drug accounts two years for its development with cost of $1million to $4million in comparison to seven to eight years of manufacturing time with cost of $100million to $250million for a biosimilar. Using rituximab biosimilar saves about 44% to 69% of the total cost of reference drug. In John Hopkins study, patient spent 12% less when on infliximab biosimilar than when prescribed reference biologic. It was estimated to have a total savings of sum of 233-433million Euros over a span of 5 years when patients medication was interchanged from infliximab to biosimilar CT-P13 for treatment of rheumatoid arthritis. CT-P13 in 2014 provided 39% lower cost than the reference product followed by almost double the reduction in cost (69%) in 2015 [15]. The introduction of biosimilar into the market paved the way in the promotion of healthcare cost savings, availability of biological treatment and subsequent improvement in patient outcomes. The development of biosimilars is expected to witness more competition, and subsequently greater accessibility to cost-effective treatments [16]. The average cost of commonly used biosimilars is being compared with that of reference product is represented in table 4.

4.2: Future prospects of biosimilars: Due to decrease in developmental span of a biosimilars and huge savings, biosimilar continues to show an exponential growth. Industry is expected to double its profits from an estimated $15 billion in 2020 to more than $30 billion in 2025 [17]. However, to attain maximum benefit from biosimilars, a holistic approach is required from physicians, developers and manufacturers. A proper understanding of biosimilars by physicians and effective communication to patients on the same will help patients to embrace biosimilar as their therapeutic option in future. Such partnerships will also guarantee future success in the biosimilar market, help in decreasing overall financial burden and in implementation of alternative treatment plans in healthcare system [18]. The success of biosimilars greatly depends on acceptance by patients, attitude of physicians towards biosimilars, cost effectiveness and number of losses of protection events for originator brands. The loss of protection events and other alternatives to reduce medical cost will expand usage of biosimilars in the near future [9].

Table 1: Reference drug for different biosimilars approved.

BIOSIMILAR	REFERENCE DRUG	APPROVAL YEAR
Yuflyma	Humira	2023
Fylnetra	Neulasta	2022
Alymsys	Avastin	2022
Yusimry	Humira	2021
Rezvoglar	Lantus	2021
Riabni	Rituxan	2020

Table 2: The synonyms used for Biosimilars in different parts of the world. [8]

Countries	Terminology used
European Union	Biosimilars
United States	Follow-on –pharmaceuticals
Canada	Subsequent entry biologics
Mexico	Biocomparables

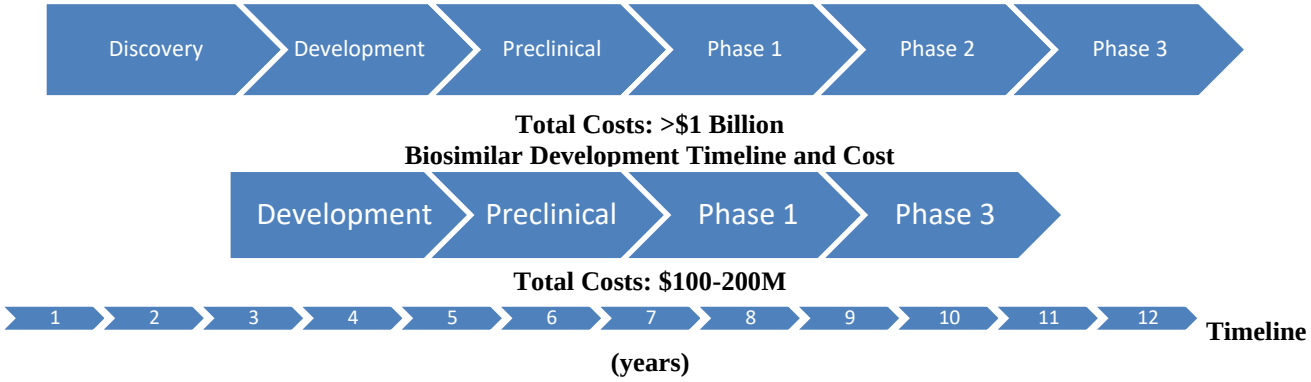

Figure 1: Showing the comparative timeline and cost of development for reference and Biosimilars
Reference Biological Development Timeline and Cost

Table 3: Nomenclature **of biosimilars**

REFERENCE PRODUCT	BIOSIMILAR
Neulasta (pegfilgrastim)	Fylnetra (pegfilgrastim-pbbk)
Avastin (Bevacizumab)	Alymsys (bevacizumab-maly)
Humira (Adalimumab)	Yusimry (adalimumab-aqvh)
Lantus (Insulin Glargine)	Rezvoglar (insulin glargine-aglr)

Table 4: Cost comparison between reference and biosimilars.

Drug	Reference Product	Cost	Biosimilar	Cost (INR)
Pegfilgrastim	Neulasta	₹5,55,080 6mg/0.6ml	Fylnetra	₹2,16,689 6mg/0.6ml
Bevacizumab	Avastin	₹32250 /100mg	Alymsys	₹2400/100mg
Adalimumab	Humira	₹5,67,813/carton	Yumisry	₹81,620/carton
Insulin Glargine	Lantus	₹2136 100IU/ml	Glaritus	₹2101 100IU/ml
Rituximab	Rituxan	₹ 3,85,304/500mg	Riabni	₹2,94,000/500mg

5. Conclusions

Understanding whether biosimilars are a blessing or a scourge requires careful assessment. Biosimilars have a significant positive financial and healthcare impact. Utilizing them will widen the scope of the treatment plan and assist patients in saving money, both of which will improve patient compliance and adherence. For definite use, evaluation in the areas of production practices, safety and quality concerns, immunogenicity, and resemblance to reference products must be carefully taken into account. Additionally, improving doctor-patient communication, creating a positive mind in patients on biosimilars will lessen the most likely cause for discontinuing biosimilars, which is the nocebo effect that trickles down to the sufferer from the treating physician's lack of understanding and confidence in biosimilars. In conclusion, effective cooperation between all parties is necessary to achieve the ultimate goal of biosimilar development, which is to provide patients with the clinical advantage of biologic therapy without compromising the sustainability of the healthcare system.

Acknowledgment: None

Conflict of Interest: None

References

[1] M. Nowicki. (2007). Basic facts about Biosimilars. Kidney and Blood Pressure Research. 30(5)267-272.

[2] H. Mellstedt, H. Ludwig, H. (2008). The challenge of biosimilars. Annals of Oncology. 19(3), 411–419.

[3] G.B. Kresse.(2009). Biosimilars-science, status, and strategic perspective. European Journal of Pharmaceutics and Biopharmaceutics.72(3), 479–486

[4] A. Anselmo, Y. Gokarn, S. Mitragotri, S. (2019). Non-invasive delivery strategies for biologics. Nat Rev Drug Discov. 18, 19–40. https://doi.org/10.1038/nrd.2018.183

[5] B.R.Meher, S.Balan, R.R. Mohanty, M. Jena, S. Das. (2019). Biosimilars in India; Current Status and Future Perspectives. J Pharm Bioallied Sci. 11(1): 12–15.

[6] B. Oza, S. Radhakrishna, P, Pipalava, V. Jose. (2019). Pharmacovigilance of biosimilars – Why is different from generics and innovator biologics? J Postgrad Med.65(4):227–32.

[7] R. Kumar, Singh. (2014). Biosimilar drugs: Current status. Int J Appl Basic Med Res. 4(2):63–6.

[8] F.K. Agbogbo, D.M. Ecker, A. Farrand, K.Han, A. Khoury, A.Martin, J. McCool 3, U. Rasche , T.D. Rau , D.Schmidt , M. Sha , N.Treuheit. (2019). Current perspectives on biosimilars. J Ind Microbiol Biotechnol. 46(9):1297–311.

[9] Biosimilars to continue rapid growth over the next decade [Internet]. [cited 2023 Jun 23]. Available from: https://www.iqvia.com/blogs/2021/12/biosimilars-to-continue-rapid-growth-over-the-next-decade

[10] K.Sarnola, M.Merikoski, J.Jyrkkä, K.Hämeen-Anttila. (2020). Physicians' perceptions of the uptake of biosimilars: a systematic review. BMJ Open.5; 10(5):e034183.

[11] H.Kim, R Alten, L.Avedano, A.Dignass, F.Gomollón, K.Greveson, et al.(2020).The Future of Biosimilars: Maximizing Benefits Across Immune-Mediated Inflammatory Diseases. Drugs. 80(2):99–113.

[12] E. Mysler, V.F. Azevedo, S. Danese, D. Alvarez, N. Iikuni, B. Ingram, M.Mueller, L.P.Biroulet. (2021). Biosimilar-to-Biosimilar Switching: What is the Rationale and Current Experience? Drugs.81 (16):1859–79.

[13] U.S. Food and Drug Administration. Draft guidance on biosimilar product development. http:// www.fda.gov/Drugs/DevelopmentApproval Process/ How Drugs are Developed and Approved/ Approval Applications/Therapeutic Biologic Applications/ Biosimilars/ default.htm. Accessed October 20, 2012.

[14] B.S.Sekhon, V.Saluja. (2011). Biosimilars: an overview. Biosimilars. 15;1:1–11.

[15] T.K. Kvien, K.Patel, V.Strand. (2022). The cost savings of biosimilars can help increase patient access and lift the financial burden of health care systems. Semin Arthritis Rheum.1; 52:151939.

[16] E.R.Kabir, S.S.Moreino, M.K.S.Siam. (2019).The Breakthrough of Biosimilars: A Twist in the

Narrative of Biological Therapy. Biomolecules. 9, 410; doi: 10.3390/ biom9090410

[17] C.Ying, M. Alex, D.S.Jorge Santos. An inflection point for biosimilars | McKinsey [Internet]. [cited 2023 Jun 23]. Available from: https://www.mckinsey.com/ industries/life-sciences/our-insights/an-inflection-point-for-biosimilars.

[18] J.S.Smolen, J.Goncalves, M.Quinn, F. Benedetti, J.Y.Lee. (2019). Era of biosimilars in rheumatology: reshaping the healthcare environment. RMD Open.5(1):e000900.