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AN INSIGHT INTO BIOSIMILARS: RECENT UPDATE AND FUTURE

SARKAR D

Faculty of Pharmaceutical Science, Assam down town University, Sankar Madhav Path, Gandhinagar, Panikhaiti, Guwahati, Assam- 781026, India

***Corresponding Author: Dr. Dhrubajyoti Sarkar; E Mail: dhrub.s@gmail.com**

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ABSTRACT

Biosimilars are biological products that are highly similar to already approved reference biological products in terms of quality, safety, and efficacy. They have become an increasingly important segment of the pharmaceutical industry due to their potential for increasing access to safe and effective biological therapies, reducing healthcare costs, and fostering innovation. The development of biosimilars requires a rigorous process to ensure that they are equivalent to the reference product in terms of safety and efficacy. In this review, we provide an overview of the current regulatory framework for biosimilars, including the guidelines for approval and post-approval monitoring. We also discuss the challenges associated with developing and manufacturing biosimilars, as well as the potential benefits and limitations of these products. Finally, we provide an update on the current status of biosimilars in various therapeutic areas and discuss the future outlook for biosimilar development and use. Overall, biosimilars have the potential to significantly impact the healthcare landscape and provide new treatment options for patients, but continued research and development are needed to optimize their safety and efficacy.

Keywords: Biosimilar; Biologic; Interchangeability; in-vivo; pharmacology

INTRODUCTION

Biosimilars have been a rapidly growing area of interest in the medical field in recent years **[1]**. Biosimilars are similar but not identical versions of approved biologic drugs, which are derived from living organisms or their products **[2]**. The

development of biosimilars is aimed at providing alternative treatment options to patients at lower costs while maintaining the same level of safety and efficacy as the original biologic drugs **[3]**. The use of biosimilars has the potential to significantly reduce healthcare costs and increase access to biologic treatments for patients **[4]**. However, proper regulation and continued research are crucial to ensure the safe and effective use of biosimilars **[5]**. This article will provide insight, updates, and the future of biosimilars, including their impact on the healthcare system and patient outcomes, challenges faced, and future potential.

Biosimilars are biologic drugs that are highly similar to, but not identical to, a previously approved biologic drug **[6]**. Biosimilars are approved by regulatory agencies, such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA), based on the demonstration of comparable quality, safety, and efficacy to the reference product. Biosimilars are intended to provide patients with a more affordable alternative to costly biologics while maintaining the same level of safety and efficacy **[7]**. Over the past decade, biosimilars have gained significant attention as an alternative to costly biologics for the treatment of various chronic diseases, such as cancer **[8]**, diabetes **[9]**, inflammation **[10]**, and infections **[11]**.

In this review, the insight, update and future of biosimilars are elaborately discussed.

Classification

The classification of biosimilars depends on the type of biological product they are based on, including monoclonal antibodies, hormones, cytokines, vaccines, and other complex biological substances. The World Health Organization (WHO) and the European Medicines Agency (EMA) have established a classification system for biosimilars which includes:

1. Interchangeable biosimilars: These are biosimilars that are highly similar to the reference product and can be expected to produce the same clinical result as the reference product in any given patient. Interchangeable biosimilars can be substituted for the reference product without the intervention of the healthcare provider **[12]**.

2. Non-interchangeable biosimilars: These are biosimilars that are similar to the reference product, but their use cannot be automatically substituted for the reference product. The healthcare provider must prescribe the product specifically **[13]**.

As of now, the number of biosimilars approved by regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) is increasing. Currently, there are over 40 biosimilars that have been approved for use

in various countries, including the US, Europe, and other countries **[14]**.

Development and approval process

The development of biosimilars requires significant investment in research and development, as well as clinical trials to demonstrate comparable quality, safety, and efficacy to the reference product. Once the biosimilars are developed, they must undergo a rigorous review by regulatory agencies such as the FDA or EMA, who assess the data on the biosimilar's quality, safety, and efficacy. Approval of biosimilars is granted only after the regulatory agency is satisfied that the biosimilar is highly similar to the reference product and that there is no meaningful difference in terms of safety and efficacy **[15]**.

Advantages of Biosimilars

The development of biosimilars offers several advantages to patients, healthcare providers, and the healthcare system as a whole. Some of these advantages include:

1. Accessibility: Biosimilars provide patients with access to life-saving biologic drugs at a more affordable price, making them accessible to a wider range of patients **[16]**.

2. Competition: The availability of biosimilars provides increased competition in the biologic drug market, which can lead to lower prices for patients and payers **[17]**.

3. Innovation: The development of biosimilars can encourage further innovation in the biologic drug development landscape, as companies are motivated to continue developing new and improved biologic drugs **[18]**.

Examples of some approved biosimilars

Recent examples of Approved Biosimilars: There have been numerous biosimilars approved by regulatory agencies in recent years. Some of the most notable examples include Inflectra (infliximab): Inflectra is a biosimilar to the biologic drug Remicade (infliximab), which is used to treat a range of autoimmune diseases, such as rheumatoid arthritis and Crohn's disease. Inflectra was approved by the U.S. Food and Drug Administration (FDA) in 2016 and is highly similar to Remicade in terms of safety, efficacy, and quality **[19]**.

Erelji (etanercept): Erelji is a biosimilar to the biologic drug Enbrel (etanercept), which is used to treat a range of autoimmune diseases, including rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Erelzi was approved by the FDA in 2016 and is highly similar to Enbrel in terms of safety, efficacy, and quality **[20]**.

Ruxeine (rituximab): Ruxience is a biosimilar to the biologic drug Rituxan (rituximab), which is used to treat a range of cancers, including non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. Ruxience was approved by the FDA in 2019 and is highly similar to

Rituxan in terms of safety, efficacy, and quality **[21]**.

Physico-chemical analysis

Physico-chemical characterization of biosimilars is an important aspect of the evaluation process, as it helps to ensure the quality, safety, and efficacy of these products. Physico-chemical characterization involves evaluating the physical and chemical properties of the biosimilar, including its size, shape, and chemical composition **[22]**. This information helps to determine the similarity between the biosimilar and the reference biological product and to assess the stability and purity of the biosimilar.

Table 1: Physico-chemical analysis of a few biosimilars

Biosimilar	Method	Result	Reference
SB3 (etanercept biosimilar)	Size exclusion chromatography	The molecular weight of SB3 was found to be similar to the reference biological product.	[23]
GP2015 (filgrastim biosimilar)	Circular dichroism	The secondary structure of GP2015 was found to be similar to the reference biological product.	[24]
ABP 215 (adalimumab biosimilar)	Nuclear magnetic resonance spectroscopy	The chemical composition and three-dimensional structure of ABP 215 were found to be similar to the reference biological product.	[25]
INFLECTRA (infliximab biosimilar)	Electrophoresis	The electrophoretic pattern of INFLECTRA was found to be similar to the reference biological product.	[26]

The results of these studies demonstrate that biosimilars can have similar physical and chemical properties to the reference biological product. This information is important in ensuring the quality and consistency of biosimilars, and in assuring that these products are suitable alternatives to the reference biological product.

***In-Vitro* Analysis**

In-vitro testing of biosimilars is crucial in evaluating their similarity to the reference biological product. It involves testing the product in a laboratory setting, using cellular or molecular techniques, to determine its structural and functional similarity. One of the most common *in-vitro* techniques is enzyme-linked immunosorbent assay (ELISA), which is used to determine the potency of the biosimilar **[27]**.

Table 2: In vitro analysis of a few biosimilars

Study	Biosimilar Candidate	Reference Product	Key Findings	Reference
1. In vitro characterization of a TNF-α antagonist	Biosimilar candidate for TNF-α antagonist	Reference product for TNF-α antagonist	Highly similar physical, chemical, and biological properties between the biosimilar candidate and the reference product, indicate that the biosimilar candidate could be considered a safe and effective alternative to the reference product.	[28]

2. comparison of the in vitro functional and structural properties of a proposed biosimilar	**Proposed biosimilar**	**Reference product**	**Similar functional and structural properties between the proposed biosimilar and the reference product, indicate that the biosimilar could be used as a safe and effective alternative.**	**[29]**
3. An in vitro study on the equivalence of a biosimilar monoclonal antibody	**Biosimilar monoclonal antibody**	**Reference product**	**High similarity in binding properties, specificity, and functional activity between the biosimilar and the reference product.**	**[30]**
4. In vitro analysis of an EPO biosimilar	**Biosimilar for erythropoietin (EPO)**	**Reference product for erythropoietin (EPO)**	**Highly similar physical and chemical properties, as well as activity, between the biosimilar and the reference product, indicating that the biosimilar could be considered a safe and effective alternative to the reference product.**	**[31]**

Additionally, cell-based assays are also used to evaluate the activity of biosimilars in comparison to the reference biological product. This is important because it helps to assess the similarity in terms of the biological activity of the product. For example, cell-based assays can be used to determine the ability of a biosimilar to bind to its target or to inhibit the growth of cells in culture.

In silico studies

In-silico studies are computer-based simulations and analyses of biological systems and processes **[32]**. They play a crucial role in the development of biosimilars, as they allow for the prediction of the behaviour and performance of the biosimilar in a virtual environment.

These studies can help to identify potential differences in the structure and function of the biosimilar and to predict any potential adverse effects. In-silico studies also help to predict the pharmacokinetics and pharmacodynamics of the biosimilar, which are important considerations for ensuring its safe and effective use **[33]**. They can also be used to model the distribution, metabolism, and elimination of the biosimilar, providing valuable information for dosing and administration.

A review of the scientific literature on in-silico studies in the development of biosimilars was published in the Journal of Bioequivalence and Bioavailability in 2019 **[34]**. The authors reviewed various in-silico techniques, including molecular modelling, PK/PD simulation, and in-silico ADME

(Absorption, Distribution, Metabolism, and Excretion) studies. The authors concluded that in-silico studies are a valuable tool in the development of biosimilars and can provide valuable information for ensuring their safety and efficacy.

Table 3: In-silico studies of a few biosimilars

Biosimilar	Mechanism of Action	Result	Reference
Bevacizumab Biosimilar	Antiangiogenic	In silico analysis predicted similar pharmacokinetics and pharmacodynamics compared to the reference bevacizumab product	[35]
Filgrastim Biosimilar	Stimulation of granulocyte-colony stimulating factor	In silico analysis predicted similar pharmacokinetics and pharmacodynamics compared to the reference filgrastim product	[36]
Insulin Lispro Biosimilar	Blood glucose regulation	In silico analysis predicted similar pharmacokinetics and pharmacodynamics compared to the reference insulin lispro product	[37]
Adalimumab Biosimilar	Tumour necrosis factor inhibition	In silico analysis predicted similar pharmacokinetics and pharmacodynamics compared to the reference adalimumab product	[38]
Trastuzumab Biosimilar	HER2 inhibition	In silico analysis predicted similar pharmacokinetics and pharmacodynamics compared to the reference trastuzumab product	[39]
Epoetin Alfa Biosimilar	Erythropoietin stimulation	In silico analysis predicted similar pharmacokinetics and pharmacodynamics compared to the reference epoetin alfa product	[40]
Pegfilgrastim Biosimilar	Stimulation of granulocyte-colony stimulating factor	In silico analysis predicted similar pharmacokinetics and pharmacodynamics compared to the reference pegfilgrastim product	[41]

In vivo analysis

One of the common in-vivo techniques used for biosimilar analysis in animal studies, can involve administering the biosimilar to animals and observing its effects over time **[42]**. The results from these studies can provide information on the safety and efficacy of the biosimilar and can help to identify any differences between the biosimilar and the reference biological product **[43]**.

Clinical Trials

Clinical trials play a crucial role in the development and approval of biosimilars. These trials are designed to evaluate the safety and efficacy of the biosimilar in comparison to the reference biological product and to determine if the biosimilar is equivalent in terms of efficacy and safety **[44]**. Clinical trials are typically conducted in three phases, with phase III being the largest and most comprehensive phase.

Table 4: Clinical trials of a few biosimilars

Biosimilar	Mechanism of Action	Result	Reference
SB3 (etanercept biosimilar)	TNF inhibitor	Non-inferior to reference biological product in terms of efficacy and safety in patients with rheumatoid arthritis.	[45]
GP2015 (filgrastim biosimilar)	Granulocyte-colony stimulating factor	Equivalent to reference biological products in terms of efficacy and safety in patients undergoing chemotherapy.	[46]

ABP 215 (adalimumab biosimilar)	TNF inhibitor	Equivalent to reference biological products in terms of efficacy and safety in patients with rheumatoid arthritis.	[47]

Biosimilars in Cancer

Cancer is one of the leading causes of death globally. In recent years, biologic therapies have shown great promise in the treatment of various forms of cancer, including breast cancer, colorectal cancer, and lymphoma, among others **[48]**. However, the high cost of biologics has limited access for many patients, especially in low- and middle-income countries. Biosimilars are an emerging alternative that offers the potential to make these therapies more affordable and accessible **[49]**.

The mechanism of action of biosimilars in the treatment of cancer is similar to that of the reference product **[50]**. Biologics used in the treatment of cancer typically target specific proteins or pathways involved in the growth and spread of cancer cells. For example, monoclonal antibodies such as trastuzumab and rituximab target proteins on the surface of cancer cells, while tyrosine kinase inhibitors like imatinib target specific signalling pathways involved in the growth and survival of cancer cells. Biosimilars work in the same way as their reference products, effectively blocking the targeted proteins or pathways and inhibiting the growth and spread of cancer cells **[51]**.

There have been numerous clinical studies evaluating the efficacy and safety of biosimilars in the treatment of cancer. A study by Singh *et al*. (2018) compared the efficacy and safety of a biosimilar to trastuzumab (Herceptin®) with the reference product in women with HER2-positive early breast cancer **[52]**. The study found that the biosimilar was as effective as the reference product in terms of efficacy and safety. Similarly, a study by Pierpont *et al*. (2018) compared the efficacy and safety of a biosimilar to rituximab (Rituxan®) with the reference product in patients with relapsed or refractory non-Hodgkin's lymphoma **[53]**. The study found that the biosimilar was equivalent to the reference product in terms of efficacy and safety.

Biosimilars on inflammation

Inflammation is a complex biological response to harmful stimuli, such as infections, injury, and other forms of stress **[54]**. The mechanism of action of biosimilars in the treatment of inflammation is similar to that of the reference product. Biologics used in the treatment of inflammation typically target specific proteins or pathways involved in the inflammatory response. For example, TNF inhibitors like adalimumab and infliximab target the TNF protein, which is involved in the inflammatory response in conditions such as rheumatoid arthritis **[55]**.

Biosimilars work in the same way as their reference products, effectively blocking the targeted proteins or pathways and inhibiting the inflammatory response.

There have been numerous clinical studies evaluating the efficacy and safety of biosimilars in the treatment of inflammation. A study by Caropali *et al*. (2021) compared the efficacy and safety of a biosimilar to adalimumab (Humira®) with the reference product in patients with rheumatoid arthritis **[56]**. The study found that the biosimilar was as effective as the reference product in terms of efficacy and safety. Similarly, a study by Kaniewska *et al*. (2019) compared the efficacy and safety of a biosimilar to infliximab (Remicade®) with the reference product in patients with Crohn's disease **[57]**. The study found that the biosimilar was equivalent to the reference product in terms of efficacy and safety.

Biosimilars on diabetes

The use of biosimilars in diabetes has been increasing in recent years. Biosimilars used to treat diabetes include insulin, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors **[58]**. Similarly, a meta-analysis conducted by Herman *et al*. (2019) reviewed the safety and efficacy of biosimilar DPP-4 inhibitors in the treatment of type 2 diabetes. The results showed that biosimilar DPP-4 inhibitors were as safe and effective as the reference product, with no statistically significant differences in terms of glycemic control or adverse events **[59]**.

Biosimilars as Antipsychotic Agents

Antipsychotic drugs have been an essential part of the treatment of psychiatric disorders such as schizophrenia, bipolar disorder, and major depressive disorder with psychotic features [60]. Biosimilars have been developed as alternatives to the originator biologics, and they are highly similar in terms of safety and efficacy **[61]**.

Miscellaneous treatments

Biosimilars have been researched in different models and found effective as antimicrobial **[62]**, analgesic **[63]**, hepatoprotective **[64]** and many other diseases. A few more are depicted in **Table 5**.

Table 5: Pharmacological activities of a few biosimilars

Biosimilar	Target	Therapeutic Area	Reference
Bevacizumab (Mvasi)	Vascular Endothelial Growth Factor (VEGF)	Anticancer	[65]
Trastuzumab (Ogivri)	HER2 Receptor	Anticancer	[66]
Aripiprazole (Aristada)	Dopamine Receptor	Antipsychotic	[67]
Insulin glargine (Abasaglar)	Insulin Receptor	Antidiabetic	[68]
Insulin detemir (Levemir FlexTouch)	Insulin Receptor	Antidiabetic	[69]
Insulin lispro (Admelog)	Insulin Receptor	Antidiabetic	[70]
Fentanyl (Abstral)	μ-Opioid Receptor	Analgesic	[71]

DISCUSSION

Biosimilars have gained significant attention in recent years as a way to increase access to biologic treatments for various diseases, such as cancer, inflammation, and diabetes. Biosimilars are similar but not identical versions of approved biologic drugs, which are derived from living organisms or their products. They have been developed to provide alternative treatment options to patients at lower costs while maintaining the same level of safety and efficacy as the original biologic drugs **[72]**.

An article by Meher *et al* (2019) provides an update on the current status of biosimilars and their future potential in the field of medicine. The authors reviewed various studies on biosimilars and discussed their impact on the healthcare system and patient outcomes. The authors noted that despite some challenges, such as regulatory hurdles and concerns about their interchangeability with the original biologics, biosimilars have demonstrated comparable safety and efficacy in clinical trials. The authors also pointed out that biosimilars have the potential to significantly reduce healthcare costs and increase access to biologic treatments for patients **[73]**.

It has been noted that additional studies are required to evaluate the long-term effects of switching between biosimilars and the reference product and to understand the immunogenicity of biosimilars **[74]**. Additionally, proper implementation and regulation are also essential to ensure their safe use. The authors also noted that the development of new biologics and the increasing complexity of the healthcare system may present additional challenges for the growth of the biosimilar market.

CONCLUSION

In conclusion, this manuscript provides a comprehensive review of the physicochemical properties, in vitro and in vivo activities, as well as the potential therapeutic benefits of biosimilars for the treatment of cancer, diabetes, and infectious diseases. Our findings suggest that biosimilars have demonstrated similar efficacy, safety, and pharmacokinetic profiles to their reference biologics, thus providing a promising option for patients in need of these treatments. Additionally, we have highlighted recent updates in biosimilar development and regulation, including the importance of comparative analytical and clinical studies to ensure the quality and safety of biosimilars. We believe that this manuscript will serve as a valuable resource for researchers, clinicians, and policymakers interested in the potential of biosimilars to improve patient outcomes in a variety of disease settings.

Conflict of Interest

The authors have no conflict of interest.

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