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Evolution Of Biosimilar Landscape: A Global Perspective

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Abstract
Biosimilars, recognized as cost-effective alternatives to originator biologics while upholding safety and efficacy standards, are at the forefront of a transformative shift in healthcare. The article traces the historical development of biosimilars, emphasizing Europe's pioneering role in regulation and subsequent global expansion. It distinguishes biosimilars from generic drugs, highlighting their complexity. Key characteristics of biosimilars, including regulatory pathways, clinical trials, and their impact on therapeutic areas, are thoroughly explored. The evolving global biosimilar landscape is examined, with insights into regulatory processes in the US, Europe, and India. The article also addresses regulatory challenges and harmonization efforts, emphasizing global cooperation. Through case studies of successful biosimilar launches, it showcases their potential to reduce healthcare costs and enhance patient access. Looking ahead, the review anticipates a promising future for biosimilars, marked by expanding treatment options, cost savings, global expansion, and continued regulatory support, ultimately reshaping the healthcare ecosystem.

Keywords: Biosimilars; Regulatory Affairs; Generics; Safety; Approval

1. Introduction

The field of biopharmaceuticals has witnessed a remarkable transformation over the past few decades, with the advent of biosimilars emerging as a pivotal development. Biosimilars, also known as follow-on biologics, represent a category of therapeutic agents that have garnered immense attention due to their potential to provide cost-effective alternatives to originator biologics, while maintaining comparable safety and efficacy profiles. This dynamic evolution of the biosimilar landscape on a global scale has given rise to a complex and rapidly changing ecosystem, characterized by scientific, regulatory, economic, and clinical intricacies.

Understanding the evolution of the biosimilar landscape is of paramount importance for multiple stakeholders in the healthcare ecosystem. For healthcare providers and policymakers, this review offers valuable insights into the potential cost-saving opportunities and broader access to biologic therapies. Biopharmaceutical manufacturers can gain a deeper understanding of the evolving competitive landscape and regulatory requirements. Additionally, healthcare professionals and patients stand to benefit from enhanced knowledge of biosimilars' safety and efficacy, aiding informed decision-making in clinical practice. By synthesizing current knowledge and insights, we

aspire to provide a comprehensive overview of the biosimilar landscape's current state, highlighting key milestones, challenges, and opportunities.

1.1 Biosimilars: An Overview

The expiry of patents and/or data protection periods for a number of such biotherapeutics has ushered in an era of products that are designed to be highly "similar" to the corresponding licensed "originator" product. Based on a comprehensive head-to-head comparison and demonstrated high similarity, such products can partly rely for their licensing on safety and efficacy data obtained for the originator products. A variety of terms have been used to describe these products, including "biosimilars", "similar biotherapeutic products", "similar biological medicinal products" and "biosimilar products"(1).

1.2 Historical development of biosimilars

The concept of biosimilars began to take shape in the 1980s and 1990s with the growing use of biotechnology in drug development. This era laid the foundation for biosimilar development. Europe played a pioneering role in the regulation and approval of biosimilars. In 2006, the European Medicines Agency (EMA) issued guidelines for the approval of biosimilars. The inception of biosimilars commenced with the EU's historic approval of Omnitrope, a somatropin biosimilar, in 2006 (2). This landmark decision set in motion a sequence of approvals for various biosimilars within the EU. By August 2019, the landscape had evolved significantly, boasting a total of 61 approved biosimilars in the EU (3). Remarkably, these biosimilars, forged through extensive post-marketing surveillance spanning several years, were firmly established as possessing safety and efficacy profiles on par with their innovator reference counterparts.

During this evolutionary process, some biosimilars, even though containing the identical active substance, acquired distinct brand names or secured approval from multiple marketing authorization holders. The rationale behind these variations primarily revolved around commercial strategies and regional marketing allocation considerations.

Although there were instances of biosimilar products being withdrawn or facing rejection, it's notable that these actions were seldom connected to safety or efficacy concerns. Unfortunately, the specific reasons behind these decisions were not always made available to the public. Nonetheless, it's essential to underline that no biosimilar had been withdrawn due to safety or efficacy issues.

Building on the EU's pioneering efforts, other nations embraced the biosimilar paradigm, with this trend gaining momentum over time. This global expansion witnessed more countries adopting regulatory guidelines and swiftly moving toward the approval of biosimilars. Consequently, numerous biosimilar substances garnered approval in several countries, occasionally under different names, reflecting the international nature of this transformative healthcare advancement (4).

1.3 Biosimilars vs Genetic Product

The term "generic medicine" is usually used to describe chemical, small-molecule medicinal products that are structurally identical to an originator product whose patent and/or data protection period has expired (5). Demonstration of the analytical sameness and bioequivalence of the generic medicine to a reference product is usually appropriate and sufficient proof of therapeutic equivalence between the two (6). However, the approach established for generic medicines is not suitable for the development, evaluation and licensing of relatively large and complex proteins such as biosimilars. However, a biologic comes from a biologic (natural) source that cannot be copied exactly. These medicines come from very complex, living systems whose environments can change. So, while a

biosimilar is the same in the most important ways, it cannot be exactly the same in its structure. A biosimilar is highly similar to its brand name drug, but not an exact copy of it.

When a generic drug is approved by the FDA, it's usually automatically *interchangeable* with its brand name drug. There is no additional information needed by the FDA to show a generic drug is a safe and effective substitute for its brand name drug. Because its active ingredient has the exact same chemical structure, a prescription written for a brand name drug can usually be filled using a generic drug instead. So, a patient who is taking a generic drug can expect the same outcome as if they were taking its brand name drug, and can go back and forth between them (if needed) without seeing a difference. `

When a biosimilar gets its initial FDA approval, it's *not* automatically interchangeable with its brand name biologic. While biosimilars can be used to treat a disease once they get initial approval, they need another, special FDA approval to be considered interchangeable before they can be substituted automatically for a brand name biologic. If a biosimilar is not approved as interchangeable, it needs a prescription to be written specifically for the biosimilar to be used instead of its brand name biologic.

There are strict FDA rules that need to be met for a biosimilar to be approved as interchangeable. Any biosimilar that's approved for use has been shown in data from clinical trials to be as safe and effective in treating a certain disease as its brand name biologic. The company that makes the biosimilar may decide to only submit data to the FDA for this initial approval. But if the company wants their biosimilar to be considered interchangeable (and therefore able to be automatically substituted for its brand name drug), they must submit more information from clinical trials to the FDA (7).

1.4 Characteristics of biosimilars

1.4.1 Similarity to Reference Biologic: Biosimilars are designed to be highly similar to an already approved reference biologic, including the same active ingredient or molecule. However, they are not identical due to differences in the manufacturing process (8).

1.4.2 Demonstrated Equivalence: To gain regulatory approval, biosimilars must demonstrate that they are equivalent to the reference product in terms of safety, efficacy, and quality. This requires comprehensive comparative studies (9).

1.4.3 Regulatory Pathway: Biosimilars are approved through a specific regulatory pathway that differs from generic drugs. Regulatory agencies, such as the FDA in the United States and the EMA in Europe, have established guidelines and requirements for biosimilar approval (10).

1.4.4 Clinical Trials: Biosimilars typically undergo clinical trials to evaluate safety and efficacy in humans. These trials are designed to detect any clinically meaningful differences between the biosimilar and the reference product.

1.4.5 Immunogenicity: Biosimilars may have different immunogenicity profiles than the reference product, which can influence their safety and efficacy. Immunogenicity studies are an important part of biosimilar development.

1.4.6 Interchangeability: Some regulatory agencies may grant biosimilars an "interchangeable" designation if they meet specific criteria. This means that they can be substituted for the reference product without the need for the prescriber's intervention (11).

1.4.7 Cost Savings: Biosimilars are generally expected to be more cost-effective than their reference biologics. Their introduction into the market can lead to cost savings for healthcare systems and patients.

1.4.8 Therapeutic Options: Biosimilars provide additional therapeutic options for patients, potentially increasing competition in the biologics market and improving access to important treatments.

2. Therapeutic Areas Dominated by Biosimilars:

Biosimilars, which are highly similar versions of approved biologic drugs, have made a significant impact on various therapeutic areas, offering cost-effective alternatives to complex biologics, which are effective but expensive for the treatment of many illnesses. Dermatology, immunology, endocrinology, ophthalmology, and cancer are the therapeutic areas that have seen a quick improvement in patient care thanks to the usage of biosimilars (12). Inflammatory disorders, immunology, and oncology, which constitute the most lucrative therapeutic areas for sponsors of biosimilar development, are generally the therapeutic areas with the most biosimilar compounds available (4).

2.1 Autoimmune Diseases: Biosimilars have been widely adopted in the treatment of autoimmune diseases such as rheumatoid arthritis and psoriasis. For instance, biosimilar adalimumab (Humira) is used to manage these conditions, increasing accessibility (13).

2.2 Oncology: The oncology segment, which makes up 33.5% of these, dominates the market (14). Notable examples include biosimilar versions of trastuzumab (Herceptin) for breast cancer and bevacizumab (Avastin) for colorectal cancer treatment, offering more affordable options to patients. Additionally, biosimilars are becoming increasingly prevalent in the realm of cancer therapy, accounting for 61.8% of prescriptions for trastuzumab, 79.1% for rituximab, 35.5% for pegfilgrastim, and 76.7% for filgrastim (15).

2.3 Hematology: Biosimilars are utilized in hematological disorders, including biosimilar versions of filgrastim and epoetin alfa, which are critical for addressing anemia and neutropenia.

2.4 Diabetes: Biosimilar insulin products have emerged as alternatives to costly insulin therapies, supporting diabetes management and improving affordability

2.5 Growth Hormone Deficiency: Biosimilars for growth hormone therapy are available, providing more affordable treatment options for children with growth hormone deficiency.

2.6 Dermatology: Biosimilars in dermatology are used to treat conditions like psoriasis, offering alternatives to expensive biologic treatments.

3. Evolving Global Biosimilar Landscape

3.1 Key principles for the licensing of biosimilars by WHO

Following are the principle that are listed in the guidelines established by WHO for evaluation of biosimilars:

1. Quality Attributes Characterization: The initial step in biosimilar development involves the thorough characterization of the quality attributes of the Reference Product (RP). This provides the foundation for subsequent comparability exercises.

2. Structural and Functional Similarity: Biosimilars must demonstrate similarity to the RP in terms of structural and functional aspects. This is a prerequisite for establishing comparability. A tailored clinical data package may also be required as necessary.

3. Clinical Bioequivalence Trial: A clinical bioequivalence trial, incorporating pharmacokinetic (PK) and pharmacodynamic (PD) parameters and including an assessment of immunogenicity in human subjects, is typically a core component of the clinical comparability assessment unless scientifically justified.

4. Data Package Evaluation: The decision to license a biosimilar is based on a comprehensive evaluation of the entire data package generated during the overall comparability exercise.

5. Relevance of Differences: If relevant differences are identified between the proposed biosimilar and the RP at the structural, functional, or clinical level, the product is unlikely to qualify as a biosimilar.

6. Compliance with Guidelines: It is crucial to conduct comparability exercises according to established guidelines. Failure to do so means that the final product should not be referred to as a biosimilar.

7. Distinct from Generic Medicines: Biosimilars should not be confused with generic medicines. The authorization process for biosimilars is distinct from that of generics (16).

3.2 Recent updates in WHO guidelines for evaluation of biosimilars

The recently updated version of WHO guidelines for evaluating biosimilars has introduced in 2022 have several significant changes including:

a) Introduction Update: The document's introduction has been revised to reflect discussions held during the revision process, ensuring clarity and alignment with the latest developments.

b) Scope Expansion: The scope of the guidelines has been broadened to encompass the evaluation of biological products beyond biotherapeutics. Additionally, there has been a shift in terminology from "similar biotherapeutic product" to simply "biosimilar."

c) Terminology Change: The updated guidelines now use the term "reference product (RP)" instead of "reference biotherapeutic product (RBP)." Furthermore, considerations regarding the use of non-local RPs have been updated.

d) Quality, Nonclinical, and Clinical Evaluation: Extensive revisions have been made to these sections to align them with current industry practices and other relevant guidelines. Specific topics addressed include the use of WHO international standards and reference reagents, analytical considerations in quality evaluation, establishing similarity ranges for quality comparisons, determining similarity, and providing new guidance on the need for in vivo animal studies. The guidelines also emphasize implementing the 3Rs principles ("Replace, Reduce, Refine") to minimize animal testing and discuss the amount and type of clinical data required.

e) Pharmacovigilance and Labeling: Sections related to pharmacovigilance, prescribing information, and labeling have been updated with additional details and references (17).

4. Evolution of Regulatory Pathways

4.1 FDA Biosimilar Approval Process

In 2009, the Biologics Price Competition and Innovation Act (BPCI), which was created by the US Congress, opened the door for the regulatory approval of biosimilars in the US (4).

According to current rules, whether a biologic product is licenced under the United States Public Health Service Act (US PHS) or is approved under the United States Food, Drug, and Cosmetic Act (US FD&C) determines whether it may be approved as a follow-on biologic. The BPCI Act amends the PHS Act to give the FDA the authority to approve follow-on biologics under a new section 351(k) of the PHS Act. This change applies to biologic drugs marketed under the PHS Act and establishes an expedited approval pathway for biological products that are substantially interchangeable with or very similar to an FDA-authorized biologic drug (18).

To date, the FDA has issued three guidelines (drafts) covering the requirements for biosimilar registration which covers the following topics-

- Scientific factors to examine while proving biosimilarity to a reference product.
- Qualitative aspects of proving biosimilarity to a reference protein product.
- BPCI Act of 2009 implementation-related queries and responses (19).

The FDA takes into account a number of factors when evaluating applications for biosimilars, such as the robustness of the manufacturing process, the demonstrated structural similarity, the degree to which mechanism of action was understood, the existence of valid, mechanistically related pharmacodynamic assays, comparative pharmacokinetics and immunogenicity, and the volume of clinical data and experience with the original products (18).

4.2 EMA Biosimilar Approval Process

The European Medicines Agency (EMEA, presently EMA), which approved the first biosimilar, Omnitrope, in 2006, was able to do so because to the regulatory approval procedure for biosimilar medications that was initially devised at the EU level in 2005 (20).

The EMA's biosimilar approval procedure is a thorough and well-organized system that strives to give patients access to high-quality, secure, and economically advantageous biological medicines while upholding strict criteria. The EMA's biosimilar approval process follows a series of step which includes scientific assessment, quality assessment, clinical and non-clinical studies, reference product bridging, immunogenicity assessment and proper review before giving approval to any biosimilar product (11).

Europe has expressed confidence in the reliability and calibre of its biologic goods, including biosimilars. Nicolas Rossignol, a former administrator of the Pharmaceuticals Unit of the European Commission, stated at the 2008 European Generics Medicines Association Biosimilars Symposium that "biosimilar products approved by the European Commission in accordance with EMEA guidelines should not be subject to unfounded questions regarding their safety" and "a biosimilar product is as safe and efficacious as any other product authorised by the European Commission in the EU" (21).

4.3 India's Biosimilar Approval Process

The Indian regulatory organisations have established strict rules for the clearance of Indian non-innovator/copy items. These have been released and may be found in Schedule Y of the Drug and Cosmetic Rules as well as on the website of the Central Drug Standard Control Organisation. These are based on suggestions made by a task committee on recombinant medicines that the Indian government accepted in January 2006. Guideline for similar biologics and regulatory requirements for market authorisation in India are published in 2016 (22).

Regulatory Process for Similar Biologics in India:

- The regulatory process for similar biologics in India involves obtaining marketing authorization based on comparability to an approved reference biological product.

- The guidelines require the generation of preclinical and clinical data for the similar biologic, including safety, efficacy, and quality aspects.
- The competent authorities involved in the approval process include the Institutional Biosafety Committee (IBSC) and the Institutional Animal Ethics Committee (IAEC) for evaluating the safety and procedures related to animal use.
- The quality attributes of the drug product, such as protein content and appearance, need to be tested to characterize the similar biologic.
- Comparative pharmacokinetic studies should be designed considering factors like half-life and linearity of pharmacokinetic parameters.

The Indian regulations for the biosimilar product approval procedure differ to some extent from those of the EMA and the recently released WHO regulations. The approval requirements for any biosimilar product are product development which requires approval from IBSC and DBT, Animal toxicity studies, clinical trials, submission of clinical trials report to DCGI and reviewing. None of the assessment includes any comparative testing at all (23).

4.4 Regulatory Challenges and Harmonization Efforts

A significant global concern is the regulatory obstacles and harmonisation initiatives for biosimilars. When creating and promoting highly sophisticated goods, the biosimilar business faces numerous difficulties and barriers.

The following are some of the major obstacles and window of opportunity for regulatory harmonisation of biosimilars:

- Different regulatory systems in developing nations increase the expense of developing biosimilars and cause recurrent testing, which slows down the approval process (24).
- Regulatory issues including assessing biosimilarity, varying perspectives on interchangeability, and a lack of worldwide harmonisation of quality standards for biopharmaceuticals cannot be resolved by GMP alone (25).
- The interchangeability of biosimilars is not governed by regulatory criteria in the majority of nations (26).

WHO is providing considerable efforts for overcoming these regulatory challenges and for harmonisation of world for biosimilars. The following have been recognised as possibilities or answers for regulatory agencies to address the problems currently present:

(I) sharing product information with other regulatory agencies and accepting licenced and sourced reference products from abroad, thereby reducing the need for further (duplicative) bridging studies;

(II) applying the "reliance" concept and/or joint review to the evaluation and approval of biosimilars;

(III) conducting a review and re-evaluation of the products that had already received regulatory approval prior to the creation of a framework for biosimilar approval; and

(IV) establishing the necessary regulatory oversight for effective pharmacovigilance (26).

5. Successful Biosimilar Launches

Numerous case studies of effective biosimilar launches are available. The biosimilar UM programme is one illustration; it offers a thorough, cutting-edge, and multidisciplinary strategy to improve system-wide adoption of biosimilars. The health system was able to save USD 26.9 million as a result of this programme in just two years, and in November 2020, it adopted biosimilars on average at a rate of 62%, significantly above the national average (27).

Another illustration is the commercial success of the biosimilar drug filgrastim, which brought in about $1.2 billion in sales (28). Additionally, bevacizumab biosimilars have seen significant commercial success, with combined global sales exceeding $2.2 billion (29). Biosimilars of Rituximab like Ruxience and Truxima, shown significant success globally and have reduced the economic burden of autoimmune diseases and cancers. This has improved patient access to life-saving therapies.

Regulatory approvals by the FDA paved the way for trastuzumab biosimilars i.e., Ogivri, Herzuma, etc. in the U.S. These successful launches enhanced competition, lowered treatment costs, and improved treatment options for breast cancer patients (30). Despite these triumphs, biosimilar sales have been sluggish to take off in the US, and physician awareness of biosimilars is lagging. (31).

6. Future Prospects of Biosimilars

Expanding Treatment Options: As more biologics lose patent protection, the biosimilar market is expected to grow. This expansion allows for a wider range of treatment options, potentially leading to improved patient access to critical medications (32).

Cost Savings: Biosimilars often come at a lower cost than their reference biologics. This cost advantage is expected to drive their adoption in healthcare systems globally, reducing the financial burden on patients and healthcare providers. The availability and use of biosimilars have accelerated and are on track to reduce drug costs by $100 billion over the next five years (30).

Global Expansion: The biosimilar market is not confined to a single region. India, for example, is making significant strides in biosimilar production, contributing to the global market's growth. In comparison to the previous five years, savings are anticipated to practically double over the following five years as newly approved biosimilars go on the market and existing biosimilars continue to be used and experience price reductions (30).

Regulatory Support: Regulatory agencies like the FDA and EMA have established robust guidelines for biosimilar development and approval. This regulatory support ensures the safety and efficacy of biosimilars, further encouraging their market growth

7. Conclusion

It becomes evident that biosimilars have emerged as a promising solution to address the rising costs of biologic therapies while maintaining efficacy and safety standards. The biosimilars market has witnessed significant growth, with increasing competition and market entry of biosimilar products across various therapeutic areas. Regulatory agencies worldwide have played a crucial role in shaping the biosimilars landscape by establishing rigorous guidelines for approval, ensuring the quality and safety of these products. This has fostered confidence among healthcare professionals and patients alike.

As we move forward, it is clear that biosimilars will continue to be a key driver in improving access to biologic therapies globally, reducing healthcare expenditure, and enhancing competition within the pharmaceutical industry. Researchers, policymakers, and industry stakeholders must collaborate to further refine regulatory pathways, educate healthcare providers and patients, and ensure the continued success of biosimilars in the evolving healthcare ecosystem.

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