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Biosimilars-A Review

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Abstract

Recombinant human insulin, the first genetically designed biologic pharmaceutical product approved in the United States, was approved in 1982, and since then, innumerable biologic drugs have been approved to treat a variety of ailments, many of which are difficult to treat or treat efficiently. Their popularity has grown over time owing to its ability to cure serious and chronic diseases like cancer, inflammatory disorders, and diabetes. Biologics are significantly more complex to design and manufacture compared to small-molecule medications, and they are also significantly more expensive. Market forces combined with recent regulatory developments have led to the rise in interest and popularity of a new type of biologic drug: the Biosimilars. A Biosimilars, also known as follow-on biologic or a subsequent entry biologic, is a pharmacological product that is nearly identical to a distinct company's original product. Biosimilars are FDA-approved versions of initial "innovator" products which can be manufactured after the patent on the original product expires. The approval process includes a reference to the innovator product. Although Biosimilars are expected to reduce the cost of modern therapies, there are some issues that need to be discussed among physicians at this time, including the differences between Biosimilars and generics of traditional chemical drugs, the need for appropriate regulations, and the identification of potential Biosimilars problems. This review examines the differences between generics and Biosimilars, the current state of problems and opportunities, effects, as well as the attempt to demonstrate the difficulties in establishing regulatory guidelines and those associated with the introduction of these drugs into clinical practice.

Keywords: Pharmaceuticals; Biologics; Biosimilars; Generics; Innovators; Disorders

Introduction

Biopharmaceuticals are medications that incorporate active components obtained from biotechnology or biology (proteins or polysaccharides). Human erythropoietin, insulin, growth hormones, and cytokines are examples of recombinant DNA-produced proteins. Many disorders, including cancer, diabetes, hepatitis, multiple sclerosis, and anemia, have benefited considerably from these chemicals. Several biopharmaceutical patents have recently expired or will soon expire [1]. This has given pharmaceutical companies the opportunity to create and market Biosimilars,

also known as "similar biological therapeutic products." Biosimilars are also not replaceable with the actual product. The size of the active component, its complexity, and the nature of the production process all distinguish these medications from traditional generics [2]. Biosimilars have the potential to significantly reduce the cost and availability of key biologic medications in all markets. Approval of Biosimilars will improve patient access while also lowering costs, freeing up funds for the next generation of originator medications. The potential for price reductions compared to originator biopharmaceuticals has yet to be determined, as the benefit of a somewhat lower price could be overshadowed by the probable higher risk of side effects from Biosimilars molecules that are not perfect duplicates of their originators [3]. As a result, the introduction of Biosimilars may benefit patients, physicians, and healthcare providers by lowering healthcare costs and expanding access to these medicines. Important factors regarding the development, regulation, and usage of Biosimilars must be understood by all parties.

What are Biosimilars?

The expiration of patent protection and regulatory data protection for specific biotechnological drugs resulted in the rise of Biosimilars [4]. Biosimilars try to replicate the manufacturing method used to create the original revolutionary biotechnological treatment. The word 'Biosimilars' is used in the European Union, although the term 'follow-on biologics' is far more widespread in the United States. It is critical to note that Biosimilars are not the same as (bio) generics. Biosimilars are a type of biological medicinal product or protein medicine it attempts to replicate the properties of an existing biological medicinal product. The end product is not identical because they are made using a different cell line and a separate production and purification method [5]. Increasing use of biosimilars across major countries as more biological medicines lose their patents to improve patient access and care, free up funds to pay for new, more expensive biological medicines, aid in the sustainability of the healthcare system given the rising costs of new medications, and provide funding for more healthcare professionals (Table 1). A rising corpus of research demonstrating that biosimilars and original products are equally effective and safe will aid these efforts.

Given By	Definition
WHO	A biotherapeutic product similar to an already licensed reference biotherapeutic product in terms of quality, safety and efficacy [6]
US FDA	A product highly similar to the reference product without clinically meaningful differences in safety, purity and potency [7].
CANADA	A biologic drug that enters the market subsequent to a version previously authorized in Canada with demonstrated similarity to a reference biologic drug [6].
KOREA	Biological products which demonstrated its equivalence to an already approved reference product with regard to quality, safety, and efficacy [6].

Table 1: Various definitions of Biosimilars.

There are three factors in the definition of a Biosimilars product based on these various definitions:

- It must be a biologic product.
- The reference product must be a previously approved biologic product.
- High resemblance in terms of safety, quality, and efficacy must be demonstrated. Furthermore, it is widely acknowledged that similarity should be proved by a series of rigorous comparison activities at the quality, nonclinical, and clinical levels. Biosimilars are products that have been approved by this regulatory procedure for comparability.

How Biosimilars Differ from Generics?

Chemical medications are generally simple to make because their structure is precisely defined and expressed by their chemical formula. Proteins' multi-dimensional structure and, as a result, their complex manner of action, are never completely repeatable. Biotechnological drugs can have variable pharmacokinetic and pharmacodynamic features, even if they have the same molecular weight and are made by the same sort of cells or microorganisms [1]. This was demonstrated in the instance of several α-epoetins, which are produced in many parts of the world in violation of patent restrictions [8]. Because they do not meet the regulatory approval standards, such compounds cannot be labeled Biosimilars. After the patent protection for original biotechnology products expired in 2006, the European Agency for the Evaluation of Medicinal Products permitted the first Biosimilars to access the market (EMEA). Omnitrope (a Geotropic Biosimilars) and Valtropin were the first Biosimilars [9,10]. However, the Biosimilars Alpheon (interferon-α) was recently rejected by EMEA due to a higher

number of side effects and more frequent disease recurrence in patients treated with Alpheon than with its reference product Roferon-A, as well as a lack of appropriate validation of the manufacturing process and the test used to evaluate a potential immunologic response to the drug. Despite South Korea's uneven product uptake rates, biosimilars quickly dominated the market. To foster price competitiveness and increase usage, preemptive policy measures are necessary to support the market's increased adoption of biosimilars and the resulting cost reductions [11]. Several Biosimilars drugs are also being developed for the European market, with the majority of them destined for the United States. (Table 2) outlines fundamental pharmaceutical differences between Biosimilars and generic [12].

Property	Biosimilars	Generic Drugs
Molecular Composition	High molecular weight, complex biologic agent	Small molecular weight, reproducible structure.
Comparison with reference drug	Same amino acid sequence. May have different posttranslational modifications, protein folding, excepient.	Identical active ingredient.Same bioequivalence, purity.
Manufacturing	Uses living cellular systems. Unique cell lines and production steps.	Chemically synthesized. Stepwise process of identified reactions.
FDA approval process	Biosimilars biologics license application. Demonstrates similar safety, purity, potency, and efficacy.	Abbreviated new drug application. Demonstrates bioequivalence.

Table 2: Comparison of Biosimilars and generic drugs.

Production Considerations

Biopharmaceuticals are big recombinant proteins that are often produced by living cells and undergo complicated post-translational modifications [13]. Compared to small-molecule medications, biologics are produced using more complicated methods. When drifting from batch to batch or in various production locations, they might even show to be labile. To meet the pertinent issues facing this industry, early regulation of the creation of new, similar biological products was implemented. As a result, there has been fierce competition in the pharmaceutical sector since 2006 when biosimilars were first brought to the biotechnology field [14]. Biopharmaceuticals (even originator drugs) are intrinsically changeable as a result of this. Studies on epoetins α and β, for example, have revealed that the active component is made up of multiple distinct isomers [15]. Biopharmaceuticals intricacy also means that manufacturing methods are more complicated.

Typical methods of manufacturing biopharmaceuticals:

- Confirmation of an appropriate host cell
- Establishment of a cell bank
- Protein production
- Protein purification
- Analysis of the product
- Formulation
- Storage and handling

Manufacturers of Biosimilars cannot completely replicate the manufacturing process of the reference product since manufacturing techniques are proprietary knowledge of the originator pharmaceutical business. Even if perfect duplication were attainable, innovator product producers change their manufacturing procedures, with the added obligation of demonstrating to authorities that the new process's product is similar to the old one. Biosimilars manufacturers must demonstrate that their product passes severe quality control criteria that apply to all biopharmaceuticals, in addition to comparability with the original product. These requirements may be established by a relevant pharmacopoeia monograph [16], a pharmacopoeial monograph contains specific guidelines for determining whether a pharmaceutical meets important quality attributes and can be lawfully marketed in any given nation. And they may also incorporate extra characteristics as required by regulatory bodies. Biopharmaceutical batches that do not match the required requirements, whether they are originator drugs or Biosimilars, are destroyed.

Nomenclature of Biosimilars

Biosimilars are named differently from small-molecule pharmaceuticals since small-molecule generic drugs must have the same non-proprietary name as the original chemical by definition [17]. It will be even more crucial to gather precise pharmacovigilance data that is attributable to the particular product as the number of biosimilar product approvals rises. Different nations and regions have adopted various strategies to guarantee precise product tracability. Meanwhile, the global naming of biosimilars has grown complicated and inconsistent. The non-proprietary

name should have a distinctive; four-letter suffix added to it, according to the FDA's newly released final guidance. Critics of this strategy claim that it will hinder prescribing by putting up an unnatural barrier and confusing prescribers [18]. Biosimilars nomenclature is a concern for regulators because it will be employed not just during Biosimilars distribution but also during pharmaco-vigilance [19]. In the United States, there is no guidance on naming conventions for Biosimilars. When implementing a system of nomenclature for Biosimilars, the FDA will consider several factors, including whether to:

- Assign unique, similar, or generic names (i.e., the same names as the respective reference biologic products)
- Consider structural relationships or classes when naming Biosimilars
- Make Biosimilars nomenclature systematic or predictable.

Safety Problems with Biosimilars

Biosimilars will, by definition, be similar but not identical to the product they are attempting to duplicate. Each product in biotechnological medicine has a distinct safety profile based on its mechanism of action, manufacturing technique, and content (including byproducts and impurities). The recently licensed Biosimilars growth hormone Valtropin contains distinct precautions and warnings than its reference product Hum trope, which is the finest example of how the Biosimilars safety profile will differ from that of the reference medication. This is most likely due to the fact that both medications are made from different cell lines (yeasts in the case of Valtropin and Escherichia coli in the case of Hum trope). Appropriate pharmacovigilance is required to reduce the risk of such unexpected effects. Although the issue of pharmacovigilance is not unique to Biosimilars, their introduction has undoubtedly emphasized and aggravated it [20]. The products traceability should be ensured through pharmacovigilance. Companies and regulatory bodies should be able to distinguish between the products of different manufacturers. If Biosimilars have the same international non-proprietary name (INN) as the originator, this becomes more complicated. Furthermore, adverse event reports are frequently incomplete. This is especially true when an automatic substitute is used. Although it is evident that modifications are unavoidable or essential in chronic therapy, uncontrolled replacement will confuse accurate pharmacovigilance. Only 2% of all prescriptions in the US are biologics, which are medications manufactured from living cells and given via injection or infusion. These medications account for 40% of the skyrocketing drug expenditures in the US. As more biologic drugs are approved, these costs are predicted to skyrocket. For example, the recently approved Alzheimer's medicine is anticipated to raise Medicare spending by 50% and cost individuals 40% of their annual income. These medications are costly because they cannot be mass-produced; making them unaffordable for many Americans who need to use them to treat diseases like cancer and arthritis (Herceptin and Humira, respectively). Fortunately, there are less expensive biosimilars of original biologics that are permitted under an accelerated regulatory approval procedure that reduces the need for expensive brand-name drugs. [21] Some approved Biosimilars are mentioned below in the Table 3.

Biosimilars	Reference	Approved Year
Omnitrope	Somatropin	2006
Valtropin	Somatropin	2006
Binocrit	Epoetin α	2007
Epoetin α Hexal	Epoetin α	2007
Abseamed	Epoetin α	2007
Silapo	Epoetin zeta	2007
Retacrit	Epoetin zeta	2007
Filgrastim	Filgrastim	2008
Ratiograstim	Filgrastim	2008
Biograstim	Filgrastim	2008
Tevagrastim	Filgrastim	2008
Filgrastim hexal	Filgrastim	2009
Zarzio	Filgrastim	2009
Nivestim	Filgrastim	2010
Shankinase	Streptokinase	2013
Razumab	Ranibizumab	2015
Krabeva	Bevacizumab	2017
Riabni	Rituxan	2020
Hulio	Humira	2020
Nyvepria	Neulasta	2020
Yusimry	Humira	2021
Rezvoglar	Lantus	2021
Byooviz	Lucentis	2021
Semglee	Lantus	2021
Fylnetra	Neulasta	2022
Alymsys	Avastin	2022
Releuko	Neupogen	2022

Table 3: Timeline of approved Biosimilars.

Comparison of Biosimilars between Different Countries

According to the survey taken by WHO on 2010, three major challenges of Biosimilars are revealed they are,

- Appropriate comparability studies had not been recommended by regulators in some countries;
- Some products had been inappropriately called biosimilars without conducting full comparability studies for their approval;
- The term bio generic products were prevalent and in use along with inappropriate use of the term biosimilar in some countries.

As April 2021 will mark the quinquennial of the initial biosimilar's approval in Europe and, consequently, the rest of the world. The first biosimilar was subsequently approved in the US in 2015. Biosimilars, which are approved in accordance with the same criteria of pharmaceutical quality and have equivalent efficacy and safety in patients, are very similar to the original biological therapies. Since their commercialization has been proved to lower costs and expand patient access to crucial and frequently expensive biological medicines, biosimilars provide significant social advantages. Biological medicines currently make up around 40% of all pharmaceutical spending in Europe, and this percentage is expected to increase during the ensuing years. In order to manage this expanding market and increase the affordability and accessibility of biological medicines for patients and our healthcare systems, the introduction of biosimilars to the market is a crucial and required step [22-24]. As such, different countries have their own perspective over Biosimilars.

Conclusion

Biotechnological medications will play a significant role in the future of healthcare. Biologics and properly regulated Biosimilars will become more widely available, providing patients and clinicians with more treatment alternatives and, most likely, lowering the direct costs of medicines and expanding their availability to patients. Physicians should be aware that in the case of biotechnological medications and Biosimilars, quality, safety, and efficacy issues are critical and far more difficult than with standard generics. Because Biosimilars and originator products are never identical, substitute regulations must be different than in the case of generic substitutions. For patient safety, understanding the differences between original biotechnology therapies and Biosimilars is critical.

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