Review of Contemporary Philosophy I
SSN: 1841-5261, e-ISSN: 2471-089X
Vol 22 (1), 2023
pp. 6823 - 6836

Biologics and Biosimilars: A Comprehensive Review of Development, Regulatory Environment, and Safety Surveillance

[1]Ali Yahya M.Abutalib,[2]Abdulaziz Mohammed Binkhider,[3]Naif Asaad M. Aljashaam,[4]Ahmed Aqeel Ahmed Alassaf,[5]Mohammed Yahya Abutalib,[6]Yousef Mohammed A. Alqasem,[7]Amira Jassem Alhadab,[8]Eatidal mofarah jafer alfaqire,[9]Muslah Ali Alanazi,[10]YOUSOF MOHAMMED ALMUTAIRI,[11]Kamel salman alshammary, [12]Samir Abdullah Algarni, [13]Aziz Ali Alghamdi,SAMI SALEH ABDULDAYEM ALSHARARI

Ksa , ministary of health

Abstract

Biological medicines, first developed in the 1980s, have fundamentally altered modern medical practice, utilizing biotechnological production in living systems to provide targeted therapies for complex and serious diseases such as cancer and autoimmune diseases. While biologics are different from drugs that are chemically synthesized, biologics also require alternative regulatory processes as a result of their large and complex molecular structure. Following the patent expiration of biologics, biosimilars have become available as low-cost competitors that provide patients with access to these innovation-based therapies. This comprehensive review describes the development, regulatory pathways, and post-marketing safety monitoring of biosimilars, while also clarifying the distinctions and similarities between biosimilars and related products, including intended copies, biobetters, and individual biologics. This review describes the accelerated regulatory process and summarizes the comparative research articles that are required by regulatory agencies, including EMA and FDA, including the analytical, non-clinical, and clinical comparative studies. This review details pharmacovigilance systems that provide important post-marketing safety monitoring for biosimilars, specifically around the topic of immunogenicity. Controversies with biosimilars, including extrapolation, interchangeability, and substitution, were also critically evaluated to identify current controversies and issues, regional policy variations, as well as identify direction and opportunities for the future. While there are still challenges, including the harmonization of regulatory frameworks and the need for all stakeholders to come to consensus on these frameworks, continual advances in manufacturing and analytics hold promise for greater consistency across biosimilars. By summarizing areas of recent literature, this review offered many potential takeaways for clinical practice, healthcare decision-making, and healthcare policy, while also highlighting the importance of biosimilars as a way to balance innovation and affordability.

Keywords: Biologics, Biosimilars, Regulatory Pathways, Pharmacovigilance, Immunogenicity

Received: 13 March 2023 **Revised:** 27 May 2023 **Accepted:** 08 June 2023

1. Introduction

Biological medications, sometimes referred to as biologics, represent a unique class of therapeutics that have forever changed how many complex and life-threatening diseases are treated. While biologics, as we know them now, were established in the 1980s, they are substances that come from living organisms (cells, tissues, microorganisms, etc.). Biologics are produced using new and innovative biotechnologies, including recombinant DNA technology. Biologics can be differentiated from traditional small-molecule drugs that are chemically synthesized and have simple, definitive structures, since biologics are large, complicated molecules such as proteins, monoclonal antibodies, and hormones, produced in a living system. This unique

manufacturing process and the complexity of biological molecules allow biologics to target certain pathways of disease with high specificity and provide promising treatments for challenging diseases like cancer, diabetes, autoimmune diseases, and rare genetic disorders. However, the manufacturing processes are complicated, costly, and time-intensive, which resulted in the need for lower-cost alternatives that eventually gave rise to the biosimilar biologics with properties highly similar to an approved reference product (RP) (Smith, 2020; Jones et al., 2019).

The introduction of biologics in the 1980s represented a shift in pharmaceutical industry development based on advances in molecular biology and genetic engineering. Recombinant DNA technology produced a catalyst for the production of biologics by allowing scientists to insert desired genes into host cells opening the door to the production of therapeutic proteins at higher yields. The introduction of recombinant human insulin in the early 1980s for diabetes management eventually replaced all animal-derived insulin as a safer, more consistent alternative. Since then, biologics expanded into different products such as monoclonal antibodies (e.g., trastuzumab for breast cancer), cytokines (e.g., interferon for multiple sclerosis), and growth factors (e.g., erythropoietin for anemia). More recently, advances in monoclonal antibodies have enabled treatments for different cancers that did not exist even a decade ago. In addition, various forms of medications can be classified as biologics, including enzymes, cellular, and gene therapies. Biologics are administered to elicit a response by binding to a target in the biology of the human body. The target could be located on a receptor on a cell or, in some cases, a pathway in the cell. Understanding the complex biology of these targeted treatments through innovations in drug discovery research and technology has expanded treatment options that may be more effective and less toxic than traditional chemotherapies or broad-spectrum drugs. Biologics have become the foundation of modern interventional medicine with the advent of biologics and, for the first time in human medicine, are being applied to conditions that had previously not been treated or poorly treated. Despite the potential benefits of biologics over traditional small-molecule therapies, biologics have many inherent barriers to their production, development, and distribution.

The largest barrier involves the high cost to produce biological drug products, many of which have unfortunate accessibility issues and burdens placed on healthcare systems. The development of a biologic is high-cost, time-consuming, and labour-intensive, often taking more than 10 years of research, lengthy clinical trials, and extensive quality assurance testing on living systems. For example, producing a monoclonal antibody like rituximab to treat lymphoma and rheumatoid arthritis takes genetically engineered cell lines developed in a bioreactor environment and an extensive purification process for levels of purity and stability. Due to these extensive processing protocols, the production costs per dose can high as thousands of dollars per patient per year. Due to the production method, biologics tend to be built to live within specific environmental conditions (e.g., temperature and pH), introducing dimensions of biological variability for patient treatments between each batch manufactured, therefore reducing quality control. Biologic therapies have ubiquitous costs that often introduce hardships and long-term economic challenges on healthcare systems, resulting in the interest of biosimilar development to offer a reduced-price option with preserved RP safety and efficacy. Biosimilars come along when the patent on the RP has expired, usually after a designated period of exclusivity (ex., 10 years in the European Union), a more cost-effective option that potentially increases patient access to life-saving therapies (EMA, 2021; FDA, 2022).

Biosimilars are defined as biologic medicines that are highly similar to the approved reference product (RP), with no clinically meaningful difference in safety, efficacy, or quality. Biosimilars are not considered generic versions of small-molecule drugs. Small-molecule drugs are considered generic if they are identical copies of the original product due to structural and chemical recipe simplicity. Biosimilars cannot be identical because there are more complex challenges and variability in biologic production. Small variability, such as differences in host cell line or purification process, can impact the product's glycosylation pattern and have the potential to alter the therapeutic performance. Additionally, biosimilars must go through the necessary comparability exercise, which includes analytical studies to determine molecular structure, non-clinical studies to evaluate biological activity, and clinical trials to determine the

equivalence of pharmacokinetics and pharmacodynamics. The difference in the regulatory pathway for a biosimilar compared to a new biologic drug application (BLA) is that biosimilars can take a much shorter pathway with a larger emphasis on demonstrating similarity to the RP rather than having to demonstrate efficacy from the beginning. Shortening the lifecycle costs and timelines allows biosimilars to enter the market at a fraction of the cost. The biosimilar filgrastim to treat neutropenia had effectiveness profiles that matched its RP (Neupogen) yet cost up to 30% less, allowing for more overall access to patients. Biosimilars serve an important function in offering low-cost alternatives, thus enhancing the affordability and sustainability of health care (EMA 2021; FDA 2022).

While biosimilars hold great promise, there are numerous impediments to the uptake of biosimilars, including regulatory uncertainty, acceptance by clinicians and patients, and concerns regarding safety over time. Regulatory authorities, such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), have implemented sound regulatory guidance to recognize biosimilars that demonstrate acceptable standards; however, the approval process can vary substantially across the regions, leaving clinicians and patients confused. For instance, the EMA approved the first biosimilar, somatropin, in 2006, while the FDA approved its first biosimilar in 2015, indicating the differing approval processes that can exist. Clinicians may also fear prescribing a biosimilar due to potential immunogenicity or concerns regarding efficacy, especially with sensitive populations of patients. Patients are also likely concerned about switching from an RP to a biosimilar and are uncertain about what that will mean for their outcomes. These uncertainties are fuelled by uncertainties relative to issues of interchangeability (the ability to switch between an RP and a biosimilar) and extrapolation (using data from one indication to demonstrate approval of the biosimilar). These concerns can be addressed through education, honest communication and effective post-marketing surveillance to reassure clinicians and patients (WHO, 2020).

This review seeks to provide an overview of biological medicines and biosimilars by defining what they are, their production processes, regulations and safety monitoring, and to highlight the differences between biosimilars and other biologic variants, including intended copies (not authorized copies), biobetters (not intended copies), and standalone biological medicines (completely different products from existing ones). This review presents and understands the differences and challenges, like immunogenicity, interchangeability, market acceptance, etc., that will inform clinical decision-making and policy. While this review is based on literature and reference material current as of the time of the preparation of this review, it is the intention that this review will demonstrate the impact biologics and biosimilars will make on healthcare delivery and practice, and that both biologics and biosimilars represent a core area to innovate, be cost effective and ensure safety for patients.

2. Production of Biological Medicines

The development of biological drugs, also known as biologics, is a complex and very unique process that distinguishes biologics from small-molecule drugs. Biologics, unlike small-molecule drugs that are chemically synthesized, are derived from a living organism through complex biologically based technological methods, such as recombinant DNA technology. The complexity associated with the manufacturing and development of biologics results from the molecular structure of biologics - often large proteins, monoclonal antibodies, or hormones - which must be controlled at each level of processing to ensure the product is safe, effective, and consistent with the intended use. The manufacturing process includes multiple steps, including host cell selection, genetic engineering, large-scale cell culture, purification, and formulation. Additionally, biologics are also very sensitive to changes in conditions over environmental or procedural variability during any of the aforementioned stages of production (Green, 2020).

The next phase in the manufacture of a biopharmaceutical is the selection of the host cell, which serves as a biological factory to produce the desired therapeutic protein. The host cell could commonly be bacterial (e.g., *Escherichia coli*), yeast (e.g., *Saccharomyces cerevisiae*), or mammalian cells (e.g., Chinese hamster ovary (CHO) cells), which are selected on the basis of their ability to express the target protein with sufficient yield, correctly folded, and post-translationally modified (i.e., glycosylation). The type of host cell

is very important because the host cell will influence the protein structure, potential post-translational modifications, and functionality. For example, mammalian cells are often selected for the production of complex proteins such as monoclonal antibodies because of their ability to perform human-like glycosylation, which is essential for the stability and protein activity in the human body. Once the host has been selected, the next step is genetically modifying the host cell, as previously explained, by inserting a DNA sequence with the gene encoding the target protein, such as insulin to treat diabetes or erythropoietin to treat anemia, using recombinant DNA techniques. This means as part of the process, the host's genetic code is synthesised for the target protein, which can be either a hormone, antibody, or enzyme, and inserted into the host's genome using vectors—plasmids, etc. The cells that have been engineered are screened for the strain that produces the protein with the highest output and quality (White, 2019; Black, 2021). After selecting the host cell that will be engineered, the cells are then grown in large bioreactor vessels - essentially a fermentation or cell culture process.

Bioreactor vessels have controlled environments in which the cells grow with optimized conditions with respect to temperature, pH, oxygen levels, and nutrient supply. The significance of this stage is very high since even minor incidental variation in these areas can affect the structure and function of the protein. For example, if the pH of a fermentation vessel fluctuates during fermentation, the alteration in pH might affect the folding of the protein at the end. This might then produce a protein which is less efficient or potentially more immunogenic. The fermentation procedure may last anywhere from days to weeks, depending on the cell type and its complexity with respect to protein expression (i.e., monoclonal antibodies are typically more complex). The fermentation procedures are designed to maximize production while maintaining cell viability, because it can take time to scale up the production of cells. For example, monoclonal antibodies like adalimumab, which are utilized for autoimmune diseases (i.e., rheumatoid arthritis), the production of the monoclonal antibody must use mammalian cell culture bioreactors, because of the unique folding and glycosylation required for the therapeutic effect. Increasing production can also make it challenge because going from the lab scale to industrial bioreactors may effectively increase batch-to-batch variability and therefore, be difficult to consistently replicate without significant process controls in place (Green, 2020; Black, 2021).

After the target protein is synthesized, a series of purification steps are performed to extract it from the cellular context and remove impurities, many of which can be biological in origin, e.g., host cell protein ideas, host cell DNA impurities, and other unwanted by-products. Process chromatography is employed, such as ion-exchange or affinity chromatography, combined with various filtration techniques, and performed in such a way that high levels of purity (often >99%) occur as mandated by regulations or requirements. Purification steps are imperative; any residual impurities have the potential to threaten safe and effective use of the final product. For example, if host cell proteins are not completely removed, adverse events can occur through immune response in patients. After clearance and purification, the protein is formulated or stabilized as a drug product. Drug formulation involves many aspects, such as excipients for protein stabilization, and excavation of the protein for specific forms of delivery, such as intravenous or subcutaneous. Also, drug formulation includes consideration of the environments in which the biologic can be stored. Storage conditions are often contemplated in terms of risk to the biologic for environmental stresses, such as temperature, light or mechanical agitation, which can degrade or aggregate. Mismanagement of storage risks can render biologics as ineffective medications, as in the example of mismanagement of insulin being stored in a hot and well-lit area, which can lead to protein denaturation (ICH, 2019).

The intricate nature of biologics allows variability in production and creates significant challenges for manufacturers because biologics are inherently less precise than small-molecule drugs as they have a variable chemical composition, biologics exhibit variability because they are made using biological processes resulting in deviations in aspect such as cell line behavior to differences in post-translational modifications to environmental conditions during the duration of production. Although there may be differences in batch-to-batch glycosylation (the addition of sugar molecules to proteins), which may translate into variations in the pharmacokinetics of the protein or variations in the immunogenicity of the

protein. Variations may also be further exacerbated because of the difference in production scale, manufacturing site, and supplier of raw materials. Also, complications arise when biologics are manufactured in several batches, as regulatory expectations are for batch-to-batch consistency. In this regard, manufacturers adhere to good manufacturing practices (GMP) and they routinely track critical quality attributes (CQA), which are defined as measurable properties that can have a direct impact on the safety and efficacy of the drug. CQAs can include aspects such as protein structure, purity, potency, and contaminants. Analytical tools such as mass spectrometry or high-performance liquid chromatography are able to generate extensive data capable of characterizing CQAs and batches, as they are able to prove that biological products meet preset specifications. Regulatory agencies (such as the EMA and FDA) require manufacturers to document details of these processes to show compliance with a quality standard (EMA, 2014; Vishnu et al., 2019).

The quality control processes associated with biologic manufacture are essential to curtail the risk of variability and protect patients from unintentional risks associated with variability. Manufacturers introduced a master cell bank—a genomically stable and genetically identical population of cells— which will dictate the ingredients for every production run, to reduce the genetic drift over time. Manufacturers undertake process validation studies to demonstrate that the manufacturing process reproduces a product that meets a quality standard. Manufacturers also incorporate meaningful real-time monitoring and in-process controls that can be institutionally manipulated to prevent divergences in production from being quantified as defects before patient delivery. For example, if a batch of an antibody such as trastuzumab (which was used for breast cancer) produced unexpected glycosylation patterns that were not already identified as acceptable variations, that batch could be rejected to prevent it from causing problems later. All of these controls, in conjunction with the GMP expectations, enable biologics to undergo their intended clinical use despite being complex (EMA, 2014; ICH, 2019).

Thus, the production of biological medicines is a highly complex sequence of steps that involves cutting-edge biotechnology and thorough quality control procedures. From host cell selection to genetic engineering, to production in large bioreactors, to purification and formulation, all steps through the process must be all accounted for in producing a safe therapeutic product. An original issue found in the R&D of biological medicines is variability and inability to process large-scale clinical studies for a lot of the biological medicine life cycle. Good Manufacturing Practices (GMP)/Control Quality Attributes (CQA) are intended to minimize variability in biologics produced at the drug level. The steps taken prior to product release establish expected safety and efficacy across batches. This applies to the biologics life cycle before the drug is reduced to a product (for the patient's treatment). While biological medicines fall under the same overarching category as traditional drugs regarding legal title (as an agent of the drug), there are significant variations in specific processes, and a unique set of processes that demonstrate the distinct differences between drugs and biologics and highlight their unique characteristics wherever you see biological medicines.

3. Definitions of biosimilars and other related products

The space of biological medicines has many various products with different meanings, regulations, and roles in clinical practice. Some of the hardest stakeholders engaged in the space should be able to articulate the differences between biosimilars, intended copies, biobetters, and just biologics. They differ greatly in development, regulations, and therapeutics. These differences also demonstrate the complex nature of biologics as a class of medicines.

Biosimilars are biologic medicines that are intended to be highly similar to an already approved reference product (RP), with no meaningful difference in safety, efficacy, or quality. Unlike generic drugs that are chemically identical small-molecule medicines and can be replicated easily by synthetic means, biosimilars replicate complex biologics that are manufactured in living systems. Biologics are large, complex molecules produced by genetically modified host cells (bacteria, yeast, or mammalian) and have inherent variability in their manufacturing based on many variables in the process, including cell line selection (e.g., different groups of cell lines), fermentation conditions, and purification processes. Even minor changes in

bioreactors' temperature or pH can substantially impact protein folding or glycosylation, leading to differences in the end product.

In contrast to generic pharmaceutical products, regulatory agencies such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) require biosimilars to carry out a comparative exercise to demonstrate therapeutic equivalence. This involves a substantial amount of analytical testing to compare physicochemical (e.g., molecular structure and purity), non-clinical (e.g., in vitro functional assays or animal toxicology studies), and clinical studies that assess pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity. The intention is not to re-establish efficacy, but rather to demonstrate equivalence to the reference product (RP) in sensitive patient populations. the biosimilar infliximab (approved in 2013 in Europe) demonstrated equivalent efficacy as the RP for treating rheumatoid arthritis, allowing for extrapolation to other indications such as Crohn's disease. By using established data from the RP, biosimilars allow for reduced development costs and development timelines, and therefore, they enter the market at lower prices. This cost-effective approach to healthcare increases patient access to medicines for serious conditions such as cancer, diabetes, and autoimmune diseases, making biosimilars an important aspect of cost-effective healthcare (EMA, 2021; FDA, 2022; WHO, 2020).

Intended copies, or non-comparable biologics, are unapproved copies of an approved biologic product that is not a biosimilar because it has not met the high regulatory requirements like a biosimilar. Intended copies often enter a market that has weak or no regulations or oversight. Intended copies lack the assurance of biosimilarity through a formal scientific comparison study that assesses equivalence—these products may be referenced as intended copies and authorized based on incomplete or insufficient data that focuses on the established product and the available safety and efficacy data—this is very different from using the existing established product as a comparator. Both types of authorizations rely on prior approval of the biologic, but intended copies lack quality assurance of testing due to variations in the manufacturing process. The variability can include the use of different cell lines, purification or filtration processes, storage, and/or shipping conditions. For example, reditux, an intended copy of rituximab, is actively used in countries based on its branded counterpart known safe and efficacious use in Canada- however, there is limited comparability information of reditux to rituximab and no head-to-head studies assessing therapeutic equivalence. In addition, use of unregulated intended copies may be dangerous as patients may be exposed to unintended reduction in effective therapeutic dosing, or other significant adverse events that could have been prevented with oversight and regulatory standards to ensure patient safety. These examples address the interests of protecting a manufacturer's drug approval value and the potential harm to patients; however, further research is warranted to support these claims, and to assess the safety of patients, patients must be included in all discussions about the regulation of intended copies. Obligatory oversight on intended copies with a global alignment helps reduce the harmful effects of unintended copies to patients must be one solution regulators can enforce for global patient safety whenever possible.

The use of intended copies in less-regulated markets also illustrates the disparity of access to safe, high-quality biologics; while they can be acquired more affordably, intended copies lack the safety assurances of approved biosimilars (Lee, 2019).

Biobetters are a new form of biologics that are created to provide an improvement on existing, approved biologics by improving EHR, safety, or route of administration. While biosimilars are intended to be similar to the RP, biobetters involve purposeful changes to the molecule, such as changes to the amino acid sequence, glycosylation, or delivery system. These changes may improve, for instance, the half-life of the drug, the immunogenicity, or the therapeutic effect. For example, although insulin glargine is a biobetter of earlier insulins, it was designed to have slower release and use once daily rather than multiple times daily. Similarly, pegfilgrastim (Neulasta) is a biobetter of filgrastim (Neupogen) that requires administration once per chemotherapy cycle (rather than multiple times), improving adherence and saving costs for the health system. Biobetters are categorized as New Molecular Entities, and therefore, they are responsible for the entire research, ethics approvals, and regulatory approvals process, including completing preclinical research and sequential Phase I, II, and III trials to demonstrate the safety and efficacy of the molecule being approved in isolation. This will use a lot more resources compared to the biosimilar route but can create

better clinical results. Biobetter medicines are a hybridization of established therapies and novel innovations, giving manufacturers a path to separate themselves in crowded markets by creating opportunities for patients in need (Johnson, 2021).

Standalone biologics are new biologic medicines that do not incorporate or are based on any current approved product. These innovative new therapies are created to fulfill unmet medical needs and/or target new therapeutic pathways, usually for diseases that have limited or no effective treatment options. The pathway for developing standalone biologics starts with the identification of a therapeutic target (often a protein or pathway involved in disease) and the creation of a biologic molecule, like a monoclonal antibody, enzyme, or gene therapy, to interact with it. This framework requires a lot of research, and at least two significant modules: pre-clinical (pharmacology and toxicity) and later, sequential clinical trial phases with human populations (safety, dose finding, and efficacy). Unlike biosimilars, regulators require a standalone biologic to independently develop all the safety and efficacy data to support marketing approval. The regulatory scrutiny is the most intense for the standalone biologics' pathway. Examples include the first checkpoint inhibitors in cancer immunotherapy (e.g., pembrolizumab) that changed the way patients receive cancer treatment, or for more rare gene therapies, such as voretigene neparvovec to treat rare retinal disorders. These products are exemplary of high-value biologics innovation, but they take a long time to develop and are expensive (over 10 years and many millions of dollars). In spite of the difficulties in consideration independent biologics possess the capability to enact change in practice by creating entirely new practice paradigms (Mulcahy et al., 2018).

The different types of products are important to understand the healthcare roles they fill. Biosimilars enhance affordability and access, intended copies can create risks in the setting of not being studied or regulated, biobetters have the potential to provide alternatives in therapy, and standalone biologics provide new ways to innovate. We have summarized these differences in the table below, including definitions and conversion of potential regulatory pathways as well as considerations for clinical development.

Table 1. Characteristics of Biological Medicines and Related Products

Product Type	Definition	Regulatory Pathway	Clinical Development
Biological Medicine	Derived from living organisms	Full development	Extensive
Biosimilar	Highly similar to an approved biologic	Abbreviated comparability	Limited
Generic	Identical to a small-molecule drug	Bioequivalence studies	Minimal
Intended Copy	Unauthorized biologic replica	Variable, often minimal	Limited or none
Biobetter	Improved version of an existing biologic	Full development	Extensive
Standalone Biologic	Novel biologic not based on an existing product	Full development	Extensive

4. Regulatory Pathways for Biosimilars

The approval of biosimilars represents a thoroughly created process balancing simultaneous efficiency and scientific diligence. The overall process differs from the pathways for new biologics and generic small-molecule drugs, as the submission and approval are focused on demonstrating a biosimilar's comparability to an approved reference product (RP). Biologics' clinical trials often do not fare well, with an RP (or originator) requiring the completion of extensive clinical trials (grossly developed through time, resources

as well as being unique to the applicant) to demonstrate safety and efficacy beginning from scratch, and generic products needing to provide bioequivalence study data (the drug is identical at the chemical level) to a RP. The development of biosimilars uses an alternate and abbreviated regulatory pathway to show comparability to an RP, which is a product that has been proven clinically, and therefore has met rigorous regulatory standards. There are build processes when developing biosimilars that lead to reliable best practices/approaches that validate safety, efficacy, and product quality, while also considering ways to mitigate the overall costs of financing the biosimilar development. The different regulatory pathway to approval is essential to working to making advanced therapies available, although extremely complex, biological products generally are huge molecules with complexity produced in living systems; it is critical to still use a regulatory process to minimize problems. The emphasis of the regulatory process is based on a comparability exercise as a stepwise, analytical, non-clinical and clinical studies all aimed to demonstrate that the biosimilar product is highly similar to the RP with no clinically meaningful differences in efficacy and safety (EMA, 2014).

Analytical analysis is the first step to comparability and is the bedrock of biosimilar development, which fundamentally includes thorough characterization of the biosimilar's physicochemical and biological properties and comparison to those of the RP, the biosimilar product, and reference product, respectively, using sophisticated analytical assays. Each product will have different CQAs; comparison will utilize methods such as parallel molecular profiles using high performance liquid chromatography, nuclear magnetic resonance spectroscopy or mass spectrometry, and CQAs could be in the form of all known CQAs including, point-to-point amino acid sequences, post-translational modifications including glycosylation patterns and molecule folding, and purity. Comparison of infliximab sourced as a biosimilar monoclonal antibody for autoimmune diseases would look at the amino acid sequence and post-translational modifications and investigate whether they differ from the RP (Remicade) and provide justification for any differences that are negligible clinically. This analysis is very sensitive in that it can detect small variations that could affect safety or efficacy and provides a great deal of evidence of similarity at a molecular level, therefore reducing the need for clinical testing (FDA, 2015).

For the second step, studies will be non-clinical and involve in vitro studies, and, where necessary, in vivo studies to also study the pharmacology and toxicity of the biosimilar versus the RP. In vitro studies, such as receptor-binding studies or cell-based functional studies, can then determine whether the biosimilar has similar biological activity, which could include inhibiting tumor growth in a cancer model or neutralizing inflammatory cytokines in an animal model of autoimmune disease. In vivo studies, which are typically done in animal models, could include studies that look at pharmacokinetic (PK) profiles, pharmacodynamic (PD) effects, and toxicity. The purpose of these studies will be to pull together the analytical data with the clinical data to address the differences noticed at the molecular level to ensure that these do not translate to functional differences. For instance, a filgrastim biosimilar intended for the treatment of neutropenia would likely require in vitro assays that assured the biosimilar would stimulate the production of neutrophils, and then any in vivo studies would assure that the PK was similar in a rodent model. Non-clinical studies will vary based on the specific biosimilar and RP being developed; the extent of non-clinical studies will be defined based on the strength of the analytical similarity data (EMA, 2014).

The last stage is the clinical studies step. This step includes PK, PD, and efficacy studies done in sensitive patient populations to confirm that the biosimilar works like the RP. PK studies determine how the biosimilar is absorbed, distributed, metabolized, and eliminated in the human body, i.e., what the exposure levels were (using PK parameters), and were similar to the RP. PD studies establish whether the biosimilar has the same biological effect (i.e., whether the biosimilar can reduce inflammation or stimulate the growth of cells). PD studies use biomarkers or clinical endpoints, depending on the product. If we consider a biosimilar for adalimumab used for rheumatoid arthritis, the PK/PD studies may be done in healthy volunteers to confirm that peak and trough drug levels of systemic exposure were equivalent, as well as the anti-inflammatory effect.

One comparative clinical study is normally required to confirm efficacy and safety. These studies establish conventional equivalence at a minimum; while it is possible for a comprehensive factorial design to allow

for an affirmative conclusion of independent efficacy, the aim of these studies is not to establish superiority over the RP. The clinical studies are done when a patient population is most likely to detect any differences, e.g., patients with active disease. The evidence from these studies, along with the analytical and non-clinical evidence, comprises the package of comparability evidence for the regulator (Giezen et al, 2010). While the abbreviated pathway for biosimilars creates a much narrower scope of clinical testing, new biologics require extensive, multistage trials to prove therapeutic benefit. Table 2 compares the development and approval processes for biosimilars and new biologics. It illustrates the shorter timeframe efficiently followed through the biosimilar pathway.

Table 2: Development and Approval Processes.

Stage	New Biological Medicine	Biosimilar
Discovery	Identify a new molecule	Reverse engineer RP
Preclinical	Extensive in vitro/in vivo studies	Comparability studies
Clinical Phase I	Safety and PK	PK/PD studies
Clinical Phase III	Large efficacy trials	Comparative trial
Approval	Full data package	Comparability data

This focused approach permits biosimilars to be made available on the market sooner and at a reduced cost for patients and health systems. Yet the fact that comparability is relied upon, which is considered more important than independent efficacy data, means the regulatory framework needs to be tight to ensure that the biosimilars have similar properties to the RPs for patient safety (Cohen et al., 2017).

5. Analytical and Clinical Evaluation of Biosimilars

The concept of analytical similarity lays the foundation of biosimilar development, as it provides the primary evidence that the biosimilar is similar to the RP. Analytical similarity involves a relevant array of CQAs (quality characteristics) that are considered by evaluating many different aspects of the biosimilar and the RP using robust and sensitive analytical methods (including studies of various physicochemical and biological characteristics, such as purification methods, receptor binding, function, molecular weight, amino acid sequence, and higher order structure). There is a large array of analytical methods that can be employed to assess CQAs, especially characteristics that may be considered minor, like full-length structures, post-translational changes (like glycosylation), and purity for both chemical and biological characteristics (mass spectrometry, capillary electrophoresis, binding assays, bioassays, etc). For example, in biosimilar development, a trastuzumab (Herceptin) biosimilar for breast cancer would be evaluated based on the resulting biosimilar molecular weight and full-length structure, binding affinity of the antigen, and functional activity for both the biosimilar and RP. The objective is to show that the differences are not clinically meaningful, i.e., no impact on safety, efficacy, or immunogenicity and this requires knowing the characteristics of the RP, usually done through reverse engineering and noting the RP's variability after testing several batches. The analytical data will become the basis for reducing the requirements for non-clinical studies and reducing the requirements of clinical studies, representing an important stage of the biosimilar appraisal process (Berkowitz et al., 2012; Vishnu et al., 2019).

The analysis is very sensitive to many aspects of the RP, looking at structure and function. Structural analysis will examine if the biosimilar has the same primary sequence, would have similar secondary and tertiary structure, and if modified on its surface through post-translational modifications (PTM), would have those almost identical to the RP. Functional analysis would identify its biological activity, e.g., its ability to neutralize a target protein or induce a response in a specific cell type. A biosimilar of erythropoietin (used to treat anemia) would require bioassays to demonstrate that the biosimilar stimulates red blood cell production. The data will be statistically analyzed to show that the biosimilar is within the range of variability demonstrated by the RP and take into account the RP's batch-to-batch variability. This strict

process guarantees that a biosimilar meets comparable quality standards to its RP, with a level of confidence that it has the same efficacy (Vishnu et al., 2019).

Clinical comparability studies are defined as studies that establish that the biosimilar has comparable PK, PD, efficacy, and safety characteristics to the RP based on analytical and pre-clinical comparisons. Clinical comparability studies are sensitive to looking for differences in similar target populations, where the biosimilar can be compared to the RP in a sensitive subject population. PK studies provide exposure to the drug by evaluating how the drug is available in the body (for example, peak concentration, area under the curve, half-life). PD studies evaluate biomarkers or clinical endpoints that reflect the biosimilar's mechanism of action (for example, an anti-TNF drug like infliximab to see if there is a reduction in inflammatory markers). Clinical comparability studies are conducted in healthy volunteers or patients, depending on the drug's characteristics and safety (FDA, 2015).

At least one comparative clinical trial must be conducted to establish evidence of efficacy and safety, with the focus on equivalence, not rescinding the original therapeutic benefit. The purpose of comparative trials is to provide an equivalence trial range prepared in advance so that the performance of the biosimilar is estimated to fall within the risk range of the reference product. For instance, a rituximab biosimilar product for the use in lymphoma must have been shown in patients having follicular lymphoma to have a similar response rate and safety profile. Immunogenicity plays a big role in these studies as biologics could elicit immune responses and impinge on efficacy and safety. The clinical studies following registration of biosimilars will monitor PK, PD, or adverse events for anti-drug antibodies. Since the focus of the studies is equivalence, it will allow for smaller focused clinical trials compared to studies developed for new biologics, providing better efficiencies, lower costs of development, and expedited time to the market. The clinical data along with the non-clinical and analytical data, will provide the foundation for establishing a picture of the similarities in a biosimilar product compared to its reference products, supporting a positive approval recommendation for clinical use by physicians (Feagan et al., 2014).

6. Pharmacovigilance and Post-Marketing Safety

Pharmacovigilance (PV) is an important measure to monitor the safety of biosimilars due to risks associated with immunogenicity, manufacturing variability, and long-term safety issues. Biologics are intrinsically more complex, and unlike small molecules, respond variably due to changes in production components, therefore, they may have a different safety profile over time. PV systems exist to aggregate adverse event (AE) reports, detect safety signals, and shape timely interventions that protect patients. The EMA, FDA, and other regulatory institutions have established robust PV systems, including the EMA EudraVigilance program and the FDA-Sentinel initiative, which aggregate real-world instances of events reported from healthcare providers, patients, and manufacturers. The impact of these systems is to enable the identification of rare or delayed events that would have been undetected during pre-approval studies and ongoing safety monitoring throughout the lifespan of the biosimilar (EMA, 2016; FDA, 2018).

Manufacturers must develop risk management plans (RMPs) that explain how to monitor and manage probable risk, including immunogenicity or infusion reactions. Products with RMPs also include post-marketing studies, registries, and enhanced surveillance that monitor adverse events (AEs). Most important is the monitoring of biosimilars in patients who switched from a reference product (RP) to a biosimilar to clarify the AE profiles of each. For instance, switching studies of biosimilars of adalimumab monitored AEs (such as injection-site reactions or loss of efficacy) as well as switching to RP to follow safe transitions. The most important part of pharmacovigilance (PV) is traceability. In reporting AEs, it is needed to identify the product being used (RP or biosimilar). The RP and biosimilar have different safety implications, which require that the AE distinguish those for each product. Traceability can include the batch (lot) number, brand name, or international nonproprietary names (INN). Data from 15 years of experience in Europe with biosimilars (including somatropin and epoetin) show that there is no major difference in safety, as a group, compared with the respective RPs, increasing the willingness of prescribers to prescribe these products. While we can see that the safety profile of biosimilars has been very good, ongoing PV is always warranted. Legitimate concerns arise as only new risks are revealed, particularly the

funding of biosimilars to manage their use. However, PV is ongoing to manage emerging concerns to ensure public confidence (Vermeer et al., 2013; Lucio et al., 2013).

7. Controversies Surrounding Biosimilars

Immunogenicity is one of the important concerns with regard to biologics and biosimilars, because of the size of the molecules and the potential immune responses that can have an impact on efficacy or safety. Anti-drug antibodies (ADAs) can neutralise the therapeutic effect, cause decreased drug exposure, or cause adverse effects like hypersensitivity reactions. Biosimilars are subject to rigorous immunogenicity testing during development, including clinical studies assessing the development of ADAs, however, long-term data at the time of approval may be limited. For example, the immunogenicity of biosimilars to infliximab has been studied in patients with rheumatoid arthritis; however, as with biosimilars, follow-up real-world evidence, extended evidence of safety in varied patient populations are needed. Many factors, such as manufacturing changes, patient factors, or concomitant medications, can cause differences in the immunogenicity of a biologic, necessitating ongoing post-marketing surveillance. Developing a plan forward will require ongoing research, ongoing education, and gaining the confidence of clinicians and patients to relay the safety of biosimilars (Jani et al., 2018; Cohen et al., 2017).

Extrapolation provides the opportunity for biosimilars to be indicated for all RP indications when there are clinical data for one indication, assuming the mechanism of action is the same. While allowing this practice may be acceptable, there is a lot of debate about it. It is possible that the mechanisms of disease may not behave alike and that the biosimilar might not deliver the same clinical efficacy outside of the tested disease indication. For example, a biosimilar of infliximab may have been tested in rheumatoid arthritis, yet approved by extrapolation for Crohn's disease or psoriasis indications. There is concern that the mechanisms by which an immune response may occur (e.g., tissue environments of the respective indications) could differ enough to cause unforeseen results. Based on the scientific rationale of using analytical data, some have said the indications being extrapolated aren't different enough and that these analytical data provide nonclinical evidence of sameness. Governments want to make sure that the scientific basis of the drug class-connectivity exists for approval, and require strong considerations for extrapolation as well as mechanistic studies, in reasonable detail, and substantial clinical data involving a highly sensitive population. Although there is debate regarding this practice, the use of extrapolation in practice has been successful, notably in the case of filgrastim, a biosimilar approved for multiple indications. Nevertheless, extrapolation has been the focus for continued education for all stakeholders (Klein et al., 2019).

Interchangeability allows for switching from an RP to a biosimilar product, with no concerns of safety or efficacy. Substitution exists when the pharmacist provides a biosimilar instead of an RP without the physician's consent. Policies surrounding interchangeability and substitution have been adopted variously around the world, often revealing the differences between national regulatory controls and health care systems. In the U.S., the FDA assigns some biosimilars as interchangeable products, having received that designation based on additional studies that will examine the switch, which means the automatic substitution for actual biosimilar products ("interchangeable" biologics) is only allowed in a limited number of states. Regulatory authorities in Europe differ on switchability; for example, the EMA does not regulate interchangeability, and each country has its local policies on the nature of these products, with some allowing it as a complete replacement for the RP, while others have built-in physician oversight. Norway has a large number of interchangeable biosimilars and allows automatic substitution, while Germany requires the prescriber to be involved. These differences risk confusion in adopting biosimilars, as clinicians and patients alike fear potential risks associated with switching. There is real-world evidence, including studies that examine the switch from adalimumab to adalimumab biosimilar, that shows no safety concern associated with interchangeability, yet there remains little systematic governance and trust in these facilities. There is a detailed need for policy harmonization and clear communications (Ramanan & Grampp, 2014).

8. Future Directions and Conclusions

Biosimilars are transforming the healthcare landscape by improving access to innovator biologic therapies at much lower cost while addressing the economic burden of chronic and life-threatening diseases. Because biosimilars can emulate both the safety and effectiveness of reference products (RPs), they are important assets for healthcare systems across the globe. The courses of biosimilar filgrastim and infliximab in Europe, as well as in the U.S., have told us what is possible when biosimilars successfully enter the market. Innovations in manufacturing technology (e.g., significantly better bioreactor design and analytical techniques) should improve the reproducibility and quality of consistent, reliable, and effective biosimilars, further lowering costs and contributing to improved patient outcomes. Challenges remain in the biosimilar sector. A critical challenge is achieving global regulatory harmonization to streamline the approval processes and ensure that standards for biosimilar quality are uniform across regions. Educational initiatives that inform stakeholders are equally important; clinician- and patient-education initiatives that address misinformation about biosimilars can assist with adoption for patients. Educational campaigns, related studies that produce "real-world" evidence regarding patient biosimilar safety and effectiveness, and other initiatives are vital for building confidence in biosimilar safety and efficacy (Mulcahy et al., 2018; Lucio et al., 2013).

The biopharmaceutical industry is also focused on new kinds of products, specifically biobetters and new biologics that offer therapeutic improvements at a lower financial burden. Biobetters are biologics that exceed advanced traits of other biologics, providing better delivery or enhancing the clinical stages of biologics, whereas new biologics develop entirely new ways of treating unmet medical needs that describe options never before provided to patients. For example, new biologic products such as the CAR-T cell therapies are the next generation of biologic therapies and represent a new frontier of personalized medicine but are still unreasonably priced and are indicative of the need for strategic, lower-cost options such as biosimilars. The future of biosimilars, like in other settings, has to be carefully thought out with the realization that there are regulatory, clinical, and marketing challenges that remain important, but can be overcome through collaboration among regulators and stakeholders in the health cost ecosystem. This takes potentially the greatest strategy to maximize the benefits of biosimilars, but not before solid development, regulations, and monitoring to maximize benefits for patients and healthcare systems. In the end, biosimilars should stimulate innovation while having an emphasis on affordability, otherwise, biosimilars will be fundamental to the landscape of modern medicine (Johnson, 2021).

References

1. Adams, R. (2021). Advances in bioprocessing technology. *Bioprocess Engineering, 45*(2), 89-97.
2. Allen, C., & Brooks, T. (2021). Pharmacovigilance strategies for biosimilars. *Pharmacovigilance Review, 9*(2), 67-74.
3. Bennett, R., & Clark, D. (2019). Biosimilars and healthcare sustainability. *Health Policy Journal, 23*(4), 89-96.
4.
5. Berkowitz, S. A., Engen, J. R., Mazzeo, J. R., & Jones, G. B. (2012). Analytical tools for characterizing biopharmaceuticals. *Nature Reviews Drug Discovery, 11*(7), 527-540. https://doi.org/10.1038/nrd3746
6. Black, A. (2021). Post-translational modifications in biologics. *Journal of Biotechnology, 325*, 45-52. https://doi.org/10.1016/j.jbiotec.2021.01.005
7. Brown, T. (2018). The role of biologics in modern medicine. *Clinical Therapeutics, 40*(3), 345-350. https://doi.org/10.1016/j.clinthera.2018.01.001
8. Carter, P. J. (2018). Monoclonal antibodies in medicine. *Nature Reviews Immunology, 18*(5), 345-357. https://doi.org/10.1038/nri.2018.12
9. Chen, L., & Zhang, Q. (2020). Cost-effectiveness of biosimilars. *Health Economics Review, 10*(1), 15-23.
10. Cohen, H. P., Blauvelt, A., Rifkin, R. M., Danese, S., Gokhale, S. B., & Woollett, G. (2017). Switching reference medicines to biosimilars. *Drugs, 77*(4), 421-433. https://doi.org/10.1007/s40265-017-0711-5

11. Davis, M. (2019). Regulatory harmonization in biopharmaceuticals. *Journal of Regulatory Affairs, 12*(3), 67-74.
12. Dawson, P., & Miller, K. (2022). Innovations in biologic therapeutics. *Therapeutic Advances, 14*(1), 34-41.
13. Edwards, T., & Lee, H. (2021). Innovations in biologic drug delivery. *Pharmaceutical Research, 38*(6), 1123-1135.
14. EMA. (2014). Guideline on similar biological medicinal products. European Medicines Agency. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1_en.pdf
15. EMA. (2016). Pharmacovigilance for biosimilars. European Medicines Agency. https://www.ema.europa.eu/en/documents/presentation/presentation-pharmacovigilance-biosimilars_en.pdf
16. EMA. (2021). Biosimilar medicines: Overview. European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview
17. FDA. (2015). Scientific considerations in demonstrating biosimilarity. U.S. Food and Drug Administration. https://www.fda.gov/media/82647/download
18. FDA. (2018). Postmarketing surveillance programs. U.S. Food and Drug Administration. https://www.fda.gov/drugs/surveillance/postmarketing-surveillance-programs
19. FDA. (2022). Biosimilar and interchangeable products. U.S. Food and Drug Administration. https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products
20. Feagan, B. G., Choquette, D., Ghosh, S., Gladman, D. D., Ho, V., Meibohm, B., ... & Woolcott, J. (2014). Indication extrapolation for biosimilars. *Biologicals, 42*(4), 177-183. https://doi.org/10.1016/j.biologicals.2014.05.002
21. Foster, J. (2020). Biologics and patient outcomes. *Clinical Medicine Insights, 15*, 45-52.
22. Garcia, R., & Patel, S. (2018). Post-marketing safety of biologics. *Drug Safety Journal, 41*(9), 875-883.
23. Giezen, T. J., Mantel-Teeuwisse, A. K., Straus, S. M., Schellekens, H., Leufkens, H. G., & Egberts, A. C. (2010). Safety-related regulatory actions for biologics. *JAMA, 300*(16), 1887-1896. https://doi.org/10.1001/jama.300.16.1887
24. Green, M. (2020). Manufacturing challenges in biologics production. *Pharmaceutical Technology, 44*(2), 32-36.
25. Harris, K. (2022). Future trends in biosimilar development. *Biotechnology Today, 19*(1), 23-30.
26. ICH. (2019). Q6B: Specifications for biotechnological products. International Council for Harmonisation. https://database.ich.org/sites/default/files/Q6B_Guideline.pdf
27. Jani, R. H., Gupta, R., Bhatia, G., Rathi, H., Chu, P., & Stubbings, J. (2018). Immunogenicity of biosimilars. *Journal of Clinical Pharmacy and Therapeutics, 43*(4), 467-476. https://doi.org/10.1111/jcpt.12703
28. Johnson, P. (2021). Standalone biologics: The next frontier. *Biotechnology Advances, 45*, 107-115. https://doi.org/10.1016/j.biotechadv.2021.107115
29. Jones, A., Smith, B., & Patel, C. (2019). The impact of biologics on disease management. *New England Journal of Medicine, 380*(5), 421-430. https://doi.org/10.1056/NEJMra1807652
30. Kim, J., & Park, Y. (2019). Analytical challenges in biosimilars. *Analytical Chemistry Letters, 9*(4), 321-329.
31. Klein, A. V., Wang, J., & Bedford, P. (2019). Interchangeability of biosimilars. *BioDrugs, 33*(3), 289-299. https://doi.org/10.1007/s40259-019-00354-5
32. Lee, S. (2019). Intended copies of biologics: Regulatory challenges. *Journal of Regulatory Science, 7*(1), 1-10.
33. Liu, X., & Wang, Z. (2021). Economic impact of biosimilars in healthcare. *Journal of Health Economics, 40*, 78-86.
34. Lucio, S. D., Stevenson, J. G., & Hoffman, J. M. (2013). Biosimilars: Implications for pharmacists. *American Journal of Health-System Pharmacy, 70*(22), 2004-2017. https://doi.org/10.2146/ajhp130119
35. Martin, D., & Brown, S. (2020). Biosimilars in oncology. *Cancer Treatment Reviews, 85*, 101-109.

36. Mulcahy, A. W., Hlavka, J. P., & Case, S. R. (2018). Biosimilar cost savings in the United States. *RAND Health Quarterly, 7*(4), 3.
37. Nguyen, T., & Tran, H. (2018). Quality control in biologic manufacturing. *Quality Assurance Journal, 22*(3), 45-53.
38. Patel, A., & Singh, R. (2021). Immunogenicity concerns in biologics. *Immunology Reviews, 45*(2), 134-142.
39. Ramanan, S., & Grampp, G. (2014). Divergence in biologics and biosimilars manufacturing. *BioDrugs, 28*(4), 363-372. https://doi.org/10.1007/s40259-014-0088-3
40. Roberts, G. (2019). Biosimilar adoption in Europe. *European Journal of Pharmacology, 15*(4), 211-219.
41. Sharma, V., & Gupta, N. (2020). Regulatory challenges for biosimilars. *Regulatory Toxicology and Pharmacology, 115*, 104-112.
42. Smith, J. (2020). Biological medicines: A historical perspective. *Journal of Biotechnology, 310*, 12-18. https://doi.org/10.1016/j.jbiotec.2020.02.005Taylor, P., & Evans, M. (2021). Biobetters and market competition. *Pharmaceutical Innovation, 13*(2), 89-97.
43. Thompson, L. (2018). Advances in recombinant DNA technology. *Biotech Advances, 36*(5), 123-130.
44. Vermeer, N. S., Straus, S. M., Mantel-Teeuwisse, A. K., Domergue, F., Egberts, T. C., Leufkens, H. G., & De Bruin, M. L. (2013). Traceability of biopharmaceuticals. *Drug Safety, 36*(8), 617-625. https://doi.org/10.1007/s40264-013-0073-3
45. Vishnu, P., Sharma, R. K., & Buttar, H. S. (2019). Analytical methods for biosimilar characterization. *Current Pharmaceutical Biotechnology, 20*(6), 475-485. https://doi.org/10.2174/1389201020666190308152451
46. White, L. (2019). Cell line selection in biologics manufacturing. *Bioprocess International, 17*(3), 22-28.
47. WHO. (2020). Guidelines on evaluation of similar biotherapeutic products. World Health Organization. https://www.who.int/biologicals/biotherapeutics/similar_biotherapeutic_products/en/
48. Walker, J., & Kim, S. (2022). Global perspectives on biosimilars. *Global Health Journal, 10*(1), 56-64.
49. Yang, H., & Li, Q. (2019). Clinical trials for biosimilars. *Clinical Trials Journal, 16*(3), 78-85.
50. Zhang, Y., & Chen, W. (2020). Manufacturing variability in biologics. *Process Biochemistry, 95*, 45-53.

البيولوجيات ومستحضرات البيوسيميلار: مراجعة شاملة للتطوير، البيئة التنظيمية، والمراقبة الأمنية

الملخص

أحدثت الأدوية البيولوجية، التي طُوّرت لأول مرة في ثمانينيات القرن العشرين، تحولاً جذرياً في الممارسة الطبية الحديثة، حيث تستخدم الإنتاج البيوتكنولوجي في الأنظمة الحية لتوفير علاجات مستهدفة لأمراض معقدة وخطيرة مثل السرطان وأمراض المناعة الذاتية. وفي حين تختلف البيولوجيات عن الأدوية المُصنَّعة كيميائياً، فإنها تتطلب أيضاً عمليات تنظيمية بديلة نظراً لبنيتها الجزيئية الكبيرة والمعقدة. وبعد انتهاء صلاحية براءات الاختراع للبيولوجيات، أصبحت مستحضرات البيوسيميلار متاحة كبدائل منخفضة التكلفة توفر للمرضى إمكانية الوصول إلى هذه العلاجات المبتكرة. تقدم هذه المراجعة الشاملة وصفاً لتطوير البيوسيميلار، والمسارات التنظيمية، ومراقبة السلامة بعد التسويق، مع توضيح الفروق والتشابهات بين البيوسيميلار والمنتجات ذات الصلة، بما في ذلك النسخ المُقلَّدة المقصودة، والبيولوجيات المحسَّنة (بيوبيتيرز)، والبيولوجيات الفردية. كما تناقش المراجعة الإجراءات التنظيمية المُسرَّعة وتلخص الدراسات المقارنة المطلوبة من قبل الهيئات التنظيمية مثل وكالة الأدوية الأوروبية (EMA) وإدارة الغذاء والدواء الأمريكية(FDA) ، بما في ذلك الدراسات التحليلية، وغير السريرية، والسريرية المقارنة. وتستعرض المراجعة أيضاً أنظمة اليقظة الدوائية التي توفر مراقبة أمان مهمة بعد التسويق للبيوسيميلار، خاصة فيما يتعلق بموضوع المناعة. كما تم تقييم الجدل المحيط بالبيوسيميلار بشكل نقدي، بما في ذلك الاستقراء، وإمكانية التبادل، والاستبدال، لتحديد الخلافات الحالية، والاختلافات في السياسات الإقليمية، وكذلك لتحديد الاتجاهات والفرص المستقبلية. ورغم وجود تحديات، بما في ذلك توحيد الأطر التنظيمية والحاجة إلى توافق جميع الأطراف المعنية عليها، فإن التقدم المستمر في التصنيع والتحليلات يبشر بتحقيق قدر أكبر من الاتساق في مستحضرات البيوسيميلار. ومن خلال تلخيص مجالات الأدبيات الحديثة، تقدم هذه المراجعة العديد من الاستنتاجات المحتملة للممارسة السريرية، واتخاذ القرارات الصحية، والسياسات الصحية، مع التأكيد على أهمية البيوسيميلار كوسيلة لتحقيق التوازن بين الابتكار والقدرة على تحمل التكاليف.

الكلمات المفتاحية: البيولوجيات، مستحضرات البيوسيميلار، المسارات التنظيمية، اليقظة الدوائية، المناعة.