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Development of Biosimilars: Engineering Challenges and Solutions

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ABSTRACT

Biosimilars have emerged as cost-effective alternatives to reference biologic drugs, providing broader patient access to essential therapies. However, their development poses significant engineering challenges due to the inherent complexity of biological molecules, stringent regulatory requirements, and the need for advanced manufacturing techniques. This paper investigates key engineering considerations in biosimilar development, including protein expression systems, purification methods, and analytical characterization techniques. Additionally, it discusses the regulatory landscape, clinical trial requirements, and emerging technologies shaping the future of biosimilars. Case studies highlighting successful biosimilar development further illustrate industry best practices. By overcoming these challenges through interdisciplinary collaboration and technological innovation, biosimilars can continue to revolutionize the biopharmaceutical industry, improving healthcare affordability and accessibility.

Keywords: Biosimilars, Biologic Drugs, Protein Expression, Biopharmaceuticals, Regulatory Challenges, Analytical Characterization, Bioprocess Engineering.

INTRODUCTION

Biologic medical products are an important, rapidly growing segment of modern therapy. It is estimated that by 2020 the best-selling pharmaceutical products in the world will be biologic drugs, with annual sales of about $200 billion. It is well known that biosimilars are medical products that are similar to other medical products that have already been approved by the corresponding regulatory agencies, contain similar medical substances, and have similar licensed indications. The active ingredient shall be an approved biotechnological product that has been granted marketing authorization on the European Community state level or which has been authorized in an analogous procedure under the Protocol on the patentability of biotechnological inventions to the European Patent Convention. The meaning of the term biotechnological product shall be based on the meaning contained in Art. 10.4 of Directive 2001/83/EC. The manufacture of the biosimilar must rely on current knowledge and technology. It is foreseen that manufacturing depends on recombinant DNA technology and controlled processes. The reference medical product must have been authorized at least 10 years before the submission of the application for marketing authorization of the biosimilar. 5 years of this period must have elapsed before the market introduction of a similar product in the European Community. The biosimilar must not contain the same active substances as the reference product. The mechanism of action, therapeutic indicators, and results must be understood because clinical trials depend on the present knowledge. The structure of the active substance contained in a similar medical product must be well known. In 2005 the European Agency for the Evaluation of Medical Products (EMEA) prepared guidelines on dossiers of biosimilar products. These guidelines list the necessary data that should be provided by the applicant and all the options with explanations on how to proceed [1, 2].

Definition and Importance

Biological products are crucial therapeutic agents for various diseases. The emergence of biosimilars, developed from living cells and mirroring reference biological products in safety and efficacy, follows the

expiration of patents on many existing products. It is vital to differentiate biosimilars from generic drugs, which are exact replicas of chemically synthesized medications, as the unique characteristics of biological products mean any modification can lead to adverse effects. Due to inherent variability from raw materials and manufacturing processes, biosimilars undergo rigorous regulatory evaluation. Their growing market presence, particularly since their introduction in the EU in 2006 and the US FDA endorsement in 2015, reflects increasing demand, especially after many drug patents expired in 2014. Fellows-in-training involved in patient care should familiarize themselves with brand names, active substances, and dosages of biosimilars for effective clinical practice. The rise of biosimilars has broadened healthcare options for chronic diseases, enhancing patient access to treatments since biopharmaceuticals emerged. The EU's biosimilar strategy focuses on Active Substance Groups, boosting market penetration and regulatory alignment, which has notably increased biosimilar applications. Market growth is linked to advancements in the biopharmaceutical sector and evolving surveillance policies. Historically, since 1984, pharmaceutical companies have developed low-cost versions of medicines, thereby significantly improving treatment affordability. For example, US patients can save up to four times compared to brand-name products. As chronic disease prevalence increases, effective biosimilar strategies are vital for addressing treatment costs and improving access to innovative therapies [3, 4].

Regulatory Landscape

After the initial regulatory approval of a biosimilar product in the EU and Australia in 2006, expectations rose for other regions to follow suit. The 2009 European Medicines Agency (EMA) guidelines for evaluating recombinant protein biosimilars established a crucial framework, subsequently adopted by the WHO in 2010 and the FDA later that year. These guidelines create a rigorous regulatory framework ensuring the safety, quality, and efficacy of approved biosimilars for patients, prescribers, and payers. In contrast to traditional generic medications, the distinctions regarding biosimilars can be more complex and less intuitive. Such misunderstandings often stem from the intricate molecular structures of biosimilars, which are more complicated than those of other drugs developed in the early 21st century. The regulatory framework for generics had been established much earlier, making it easier to understand over time. Additionally, biosimilars are typically developed by large pharmaceutical companies, fostering perceptions of them as distinct or superior to generics. The accumulated knowledge from monitoring synthetic pharmaceuticals provides a secure basis for developing new treatments, whereas insights about biosimilars continue to evolve alongside ongoing regulatory requirements [5, 6].

Biological Drug Development Process

The process of developing and commercializing a biological drug, such as a biosimilar, is highly complex. The product is developed first in the laboratory using in silico, in vitro, and sometimes in vivo tools. Then the potential biosimilar is validated in laboratory and animal models to observe safety and activity preclinically. If successful, the potential biosimilar is transferred into a clinical setting and introduced to humans to evaluate safety and efficacy using a combination of bioavailability, dose-response, patient relevance, and clinical correlations. Developing a biological drug is generally more complex and expensive and requires a longer period of development than developing a small molecule, as it has a much higher order of complexity and requirements for development, manufacture, and validation. Biological drug development also requires a much higher level of innovation during the development process. Given the inherent challenges, it is also critical to plan for the future—antibiotics demanded robust development—yet evolving systems and requirements have led to repeated development failures as a result of overinvestment, underinvestment, and incompetence. The development of any drug can be roughly categorized into small molecules (generics) and biologicals. The multi-step path to the market of small molecules has been well established and streamlined by many decades of research and evaluation. Costs and time have been minimized in part due to the high degree of abstractions and simplifications involved with small molecules. Most recently, however, approvals of biological drugs have gained rapidly over small molecules. It has been noted that complexities legislate diversity of implementations and that over the last 20 years, a great diversity of therapeutic genomes has been encoded in drugs. Such diversity has abrogated the classification of biological drugs into simple households and led to long and expensive development and evaluation of biogenerics [7, 8].

Comparison With Small Molecule Drugs

The engineering of biological drugs, particularly biosimilars, differs significantly from small molecule drugs. Small molecules are typically synthesized through simple chemical processes and taken orally, while biological drugs consist of complex large molecules that require injection due to digestion issues.

Small molecules can be produced inexpensively with few steps (4 to 7) involving basic chemical reactions, whereas biological drugs are produced by living systems via cell cultures of genetically engineered organisms, taking weeks to months to manufacture. These biologics are delicate and easily damaged, and their manufacturing processes are closely guarded. For instance, a facility producing monoclonal antibodies cannot be repurposed to create insulin. Although biological products offer substantial therapeutic benefits, they are bulkier, complex, and costly to manufacture, necessitating specific storage temperatures, making them on average around 30 times more expensive than small molecules. For example, a year of treatment for Metastatic colorectal cancer costs about $30,000 with Avastin versus only $400 for Bevacizumab. Additionally, only 2 to 3% of biological drugs are off-patent, raising affordability concerns and enhancing interest in biosimilars over generics. The development of biosimilars faces numerous challenges, particularly in demonstrating biosimilarity. Unlike unchanging chemical molecules, biological ones are subject to variability inherent in living systems, influenced by the health of organisms and environmental factors, leading to potential differences in manufacturing each time, even for reference products. Analytical engineers strive to demonstrate comparability amid this variability [5, 9].

Challenges In Biosimilar Development

Biosimilars are biological products with similar protein structures and potency to their original innovative products, which have become publically available and produced commercially. Growing demand for biologics due to the higher efficiencies and milder side effects have led to the development of biosimilars; however, as the molecular structure of biosimilars is very complex, it is very difficult to produce them with similar protein structures, so they face several challenges during the engineering IDE's process. Biosimilars are therapeutic agents that are similar but not the same as the brand name biologics on which they are based. Because of their size and complexity, it is difficult to manufacture biological products such as mAbs and other glycoproteins, and the processes used to manufacture these products are often patented. In addition to engineering biologic expression systems, isoform patterns can be very sensitive to bioreactor parameters. Thus, even small changes in bioreactor parameters can affect the clinical performance of a potential biosimilar. Finally, the quality of biological products can be greatly affected by the events that occur throughout their production. For this reason, developers of biological products have a good practice of maintaining strict control throughout the manufacturing of biological products. Even minor changes such as buffering events, production freeze, etc., must be thoroughly evaluated and controlled as they are likely to lead to delayed adverse adaptations. These harmful events may not have any visible effects and may be exposed to the results of apoptosis assays etc [10, 11].

Engineering Considerations in Biosimilar Development

As the biologic market continues to grow, biosimilars offer a competitive and cost-effective solution. With over ten patents set to expire, there is an industry focus on the development of biosimilars, providing patients with affordable monoclonal antibodies (mAb) and recombinant proteins. The development of biosimilar products, however, exhibits significant engineering challenges. These challenges include the selection of an expression system, a crucial step for a product's success as it determines yield and quality. Additionally, purification methods must be critically analyzed, as these techniques highly influence the final product's purity and functionality. The integration of technology and methodologies to streamline and reduce the cost of these processes is also a significant engineering challenge. Case study examples demonstrate the many challenges faced when developing a biosimilar candidate and highlight the importance of adaptability and the ability to develop turnkey responses to biological variability. To adapt to these changes, interdisciplinary groups must continually reassess strategies and provide their biological insights. As regulatory agencies are now increasing their emphasis on the physiochemical and biological characterization quality side of the regulatory review, engineering teams must work with scientists to adapt and recommend studies and characterization methods early in development. By fostering a collaborative relationship among cross-disciplinary teams, the engineering process may foster the most successful and innovative solutions developed for engineering challenges [12, 13].

Protein Expression Systems

The expression of a specific target protein is crucial in biosimilar development, as the choice of expression system significantly impacts protein production efficiency and quality. Various cell-based systems such as mammalian, yeast, and bacterial, along with cell-free protocols, offer different advantages in scale-up, protein folding, and post-translational modifications. Mammalian cells can produce proteins with eukaryote-specific modifications, closely resembling native human cytokines; however, they are labor-

intensive and costly compared to simpler systems. Yeast systems provide a compromise between cost and efficiency but fail to produce re-folded proteins typical of mammalian cells. Bacterial systems are fast and economical but often yield incorrectly folded proteins and lack essential modifications, posing challenges during purification. Achieving high yields of recombinant protein is critical for cost-effectiveness in biosimilar production, necessitating optimized expression conditions. The selection of the best expression system directly influences manufacturing outcomes. Each system presents unique challenges; bacterial systems, while efficient, require substantial downstream purification, and yeast systems risk contamination affecting growth and yield. Mammalian systems face contamination issues as well, demanding rigorous control over environmental conditions [14, 15].

Purification Techniques

Most of the complex biopharmaceuticals belong to the group of recombinant proteins either produced by prokaryotic or eukaryotic cellular processing. Owing to the complexity of the structure and function of a protein, most biopharmaceutical products exert their pharmacological activities by binding to the specific receptors present on the surface of target cells. Replacement of the binders with new produce, which may not bind the target cells, then acts as a new protein and the quality of the product would not be as expected. To overcome such kinds of impact, the regulatory body's approach is to make the producer develop a product, that has a structure closely similar to that of the reference originator product, thus developing a product is known as biosimilar. The process of developing biosimilars represents so many challenges in comparison to the exclusive development of a novel biotherapy. Most of these challenges come from different fronts, including the establishment of the physicochemical, preclinical safety, and structural and functional similarity to the reference product. Inter alia, the product characterization process represents a big challenge, in particular for complex biopharmaceuticals. Characterization is never exhaustive, and regulatory agencies request step by step a more and more comprehensive set of data. Besides, no analytical technique alone is enough to characterize the product in any given aspect. As an example, a comprehensive characterization of all active species in a solution for a protein would require their separation and definition single by single based on some relevant physicochemical feature. The second challenging aspect in biosimilar development is related to the production process by which the originator biopharmaceutical was made. In particular, upstream development is usually very time-consuming for the establishment of optimal growth conditions that, at a time, can both grant acceptable yield and host cell protein and DNA content as low as possible. Finally, the purification process has to be developed to guarantee a product with acceptable purity and potency within a quality-by-design (QbD) framework meeting regulatory requirements [16, 17].

Analytical Methods for Biosimilar Characterization

The use of biopharmaceuticals as safe and effective alternatives to chemical drugs is gaining ground in the medical field given their high specificity, low side effects, good effectiveness, and direct market value. However, a deeper understanding of these products has led to new regulations imposing stricter manufacturing requirements to help ensure their safety, quality, and efficacy. The development of biosimilars raises several new challenges compared to the production of classical generics. The molecular complexity of such drugs, the regulatory framework, and their production through living cells all represent obstacles that need to be overcome. This review addresses from a global view to specific ones, focusing on how topology engineering can be used to produce biologically similar products. Biosimilar products are developed with an ever-growing understanding of the biological and chemical nuances of drug products starting from replicated products, but the challenges arising from this have brought up new topologies. Rendering support to these changes, the possibilities of topological engineering as a means of manipulation of these very features are also discussed [18, 19].

Clinical Trials and Regulatory Approval

Following the expiry of patents on several first-in-class biologics over the past few years, there has been a rapid increase in the development of biosimilars—biological compounds highly similar to reference products that have already been authorized for use in the clinic. Although the manufacturing of biosimilars remains a complex challenge, the computer-aided design of antibody features and the incorporation of these features into biosimilar sequences offer the potential to streamline their industrial development. In light of this possibility, a new study explores how such design features modulate the cell metabolism of engineered CHO cells and how they can impact the drug's affinity towards its intended target. This study customizes the sequence of adalimumab, one of the best-selling biologics in the world, and a challenging template due to the asymmetry of its heavy and light chains. Using a combination of

experimental and computational support, 97 adalimumab variants are designed and two lead sequences are nominated containing fruited cell-line design features to maximize the productivity and to mimic the posttranslational modifications of the originator molecule. A better understanding of the interplay between protein sequence and cell-conditioning metabolites is provided, which can help design the next generation of high-performance biologics [20, 21].

Case Studies and Success Stories

Antecedent defenses of the use of biosimilars in the global market, the need for cost-effective alternative therapeutics, biosimilars in treatment landscapes, and lower subsequent procurement costs are often not discussed in narratives. This paper highlights illuminating case studies and success stories, focusing on approved biosimilars that are currently impacting the treatment landscape. These are detailed accounts of specific biosimilars that illustrate the factors contributing to their success and the challenges encountered during development. Outside-the-box approaches and innovative engineering is tackled, along with an in-depth analysis of regulatory and poetic factors that contributed to the success. A significant emphasis is placed on patient access and subsequently the overall cost savings as a result of these biosimilars. Biosimilars have been profoundly transformative in certain areas and represent the most significant recent cost savings in a specific market. Case studies are shared to demonstrate the impact of biosimilars and present a unique perspective on the biosimilar journey. Engineering and industry development short stories are critically evaluated and candidly shared. These are meant to be "positive examples" and do not diminish the representativeness of non-shared stories of difficulties. Yet, the stories shared are intended to inspire stakeholders, presenting best practices and sometimes out-of-the-box approaches, as a detailed view of the biosimilar journey. The hope here is that others will consider employing some of the innovative methodologies discussed and that a constructive conversation can be had among industry, regulatory bodies, and the healthcare community to collaborate on promoting biosimilars. Some biosimilars are beneficial to the global healthcare community, offering patients greater access to treatment, better health outcomes, and significant cost savings. Contributions to public health are made when patients stay healthy and return faster to work, and as such have far-reaching benefits. Biosimilars are a means of achieving these ends; however, biosimilars' success is fraught with complexities, not to mention the barriers put up by an uncritical, yet fierce, opponent [22, 23].

Future Directions and Emerging Technologies

In recent years, the biopharmaceutical landscape has witnessed the substantial growth of the biosimilars industry worldwide. This growth, however, comes with its own set of challenges that simultaneously require the support of different industries to resolve. As the industry becomes more complex, improvements, or at least modifications, of the current regulatory pathways are necessary. To ensure the optimized development of effective, high-quality biosimilars, these emerging trends and technologies must be carefully assessed and acted upon promptly, preferably in a collaborative effort. Thus, the continuous growth of the biosimilar industry can be ensured, keeping it up-to-date with the fast pace of biopharmaceutical development despite the associated limitations and barriers. Since the biosimilar industry is rapidly growing, several emerging technologies and trends have the potential to shape the industry landscape soon. Taking full advantage of a scientific library with artificial intelligence and machine learning technologies at its core could help molecular scientists design biosimilars at an earlier drug discovery stage to ensure rapid and efficient cell line development, upstream optimization, and in silico quality forecasting. Due to the "future-proofing" nature of biosimilars—being the current generation of innovator biopharmaceuticals after patents have expired—, there is an urgent need for novel industry 4.0 solutions that can bridge the critical gap between adaptable digital intelligence and resilient automated manufacturing of next-generation products. To enable this evolution, innovative partnerships and pilot studies will be needed to validate future biosimilar operation systems, including industrial data integration, AI-driven predictive maintenance, autonomous analytics, self-adaptive process control, digital twins, personnel skills advancement, secured connectivity frameworks, blockchain integrity, and distributed cloud-based infrastructures with data sovereignty [24, 25].

CONCLUSION

The development of biosimilars represents a significant advancement in modern medicine, offering cost-effective alternatives to biological drugs while maintaining safety and efficacy. Despite facing considerable engineering challenges, including complex manufacturing processes, regulatory hurdles, and rigorous analytical requirements, the industry has made significant strides in overcoming these barriers. Through

advancements in bioprocess engineering, protein expression systems, and purification techniques, biosimilars are becoming increasingly accessible to patients worldwide. The integration of artificial intelligence, automation, and predictive analytics further enhances the efficiency and reliability of biosimilar development. Moving forward, continued collaboration between researchers, regulatory agencies, and industry stakeholders will be essential to refining biosimilar production and expanding their impact on global healthcare.

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