Háskólinn á Akureyri
University of Akureyri

Production of biotech drugs in Iceland

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Auðlindadeild
Heilbrigðis-, viðskipta- og raunvísindasvið
Háskólinn á Akureyri
2025

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12 eininga lokaverkefni
sem er hluti af
Baccalaureus Scientiarum-prófi í líftækni

Umsjónarmaður lokaverkefna
Rannveig Björnsdóttir
Leiðbeinandi
Marco Fannar Schalk

Auðlindadeild / líftækni
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Titill: Production of biotech drugs in Iceland
Stuttur titill: Biotech production
12 eininga bakkalárprófsverkefni sem er hluti af Baccalaureus Scientiarum-prófi í líftækni.

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Abstract

We are currently experiencing a technological revolution in many respects, with the pharmaceutical group excelling in the use of biotechnology to produce drugs that deliver better results and ensure their safety. In an era of significant economic and demographic challenges, it is important for patients to obtain the highest quality outcomes and revolutionize treatments with new and effective drugs for acute and chronic diseases, known as biosimilars.

These biological products result from cutting-edge research that has changed the lives of many patients with novel treatments for various diseases, increasing survival in certain types of oncological diseases. That is why it is important to know what biosimilars are, how they are made, their characteristics, the respective uses that can be given to them, and the regulations regarding their safe use.

Keywords: Biosimilar, biotechnology, diseases, safety, industry, treatment.

I want to dedicate this work to all my teachers and study companions who supported me in one way or another on this long journey. I would also like to thank my dear family, especially my beloved husband, for his cooking and patience during my long nights of studying.

Introduction

As biotechnology advances, it is possible to use this technology in the pharmacological field, taking advantage of the situation when the patent periods and exclusivity of biological drugs draw to an end, opening the possibility of producing and authorizing drugs called biosimilars. Biosimilars are products that present a range of quality, safety, and efficacy similar to the reference precursor product. Despite their similarities to the reference items, biosimilars are not exact replicas and should not be thought of as generic alternatives to the original. (Ramanan and Grampp, 2014).

Developing and assessing biosimilars requires a long process that includes functional, analytical, non-clinical, and clinical trials. Comparable safety, effectiveness, and immunogenicity are the goals of these investigations. However, despite the increased knowledge about biosimilars, many disputes and misconceptions remain regarding their substitution, interchangeability, extrapolation, immunogenicity, and nomenclature. (Ramanan and Grampp, 2014).

The objective of developing biosimilar drugs gives us the opportunity to have greater competition in the market, contributing to the sustainability of health care and allowing greater access to these drugs to patients requiring treatment. To obtain these benefits requires the collaboration of regulatory bodies and producers to ensure that patients obtain benefits from the new therapeutic alternatives while, at the same time, maintaining the standards of quality, efficacy, and safety. (Ramanan and Grampp, 2014).

The creation of biological pharmaceuticals started in the 1980s, and a new class of medications made in living systems through the use of biotechnological techniques such recombinant DNA technology appeared. (Sekhon and Saluja, 2011).

Numerous illnesses, including diabetes, cancer, autoimmune diseases, and multiple sclerosis, are potentially fatal. With a sizable and expanding population, biologic medications'

value as a crucial healthcare technology has been established since they were first used to treat patients. With the end of patents for traditional medicines, biosimilars emerged as similar alternatives. To gain a foothold on the market, it is necessary to demonstrate that these drugs have a safety profile identical to that of their reference biologics. (Sekhon and Saluja, 2011).

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1 Biological medicines

The human body continuously produces hormones as well as enzymes, antibodies, and various endogenous substances that are important for its survival. Drugs that attempt to make up for the inadequacies that arise in particular diseases or disorders through particular methods have been produced for a long time. Biological medications were first put on the market more than 20 years ago. Unlike ordinary or generic medications, which are generated from chemical synthesis in a lab, they are made from living cells utilizing biotechnological procedures. As previously stated, biologic medications are essential for the treatment of numerous illnesses. (Blandizzi et al, 2017).

Biological drugs have a more complicated molecular structure that are larger in size compared to common drugs that have smaller molecules. They are currently seperated into three main categories: (Blandizzi et al, 2017)

a. They are products with a high connection to endogenous factors, often used as replacement therapy. (Blandizzi et al, 2017).

b. Monoclonal antibodies (mAbs) that bind to soluble targets and, in other cases, bind to the cell surface, obstructing cell signalling pathways and their respective functions. (Blandizzi et al, 2017).

c. Engineered proteins that copy soluble receptors, receptor antagonists, and fusion proteins. To be precise, biological drugs that are produced in the form of hormones, such as insulin, hormone deficiencies and growth hormones, mAb that is used for the treatment of autoimmune diseases and cancer, blood products such as hemophilia, immunomodulators such as interferon beta for multiple sclerosis, enzymes such as used for the removal of blood clots and vaccines that are used for the prevention of many diseases. (Blandizzi et al, 2017).

Most biologic medications are created with the help of genetically altered host cells that may originate from bacteria, yeast, plants, or animals. Every producer maintains its own collection of host cells, enabling it to create a different cell line. In addition, each producer is accountable for their specific method of production. Initially, the genetic sequence of the selected protein, which could be a hormone, an antibody, or a blood component, is determined, after which a complete DNA sequence is created. This newly generated genetic sequence is then introduced into various host cell lines, such as yeast or bacteria, to facilitate the production of this protein. The specific strain that produces the highest quality protein is chosen and cultivated in bioreactors, a method known as fermentation. After that, the protein is extracted, purified, and made stable outside of the bioreactor. Finally, it is developed into a medication. (Sekhon and Saluja, 2011).

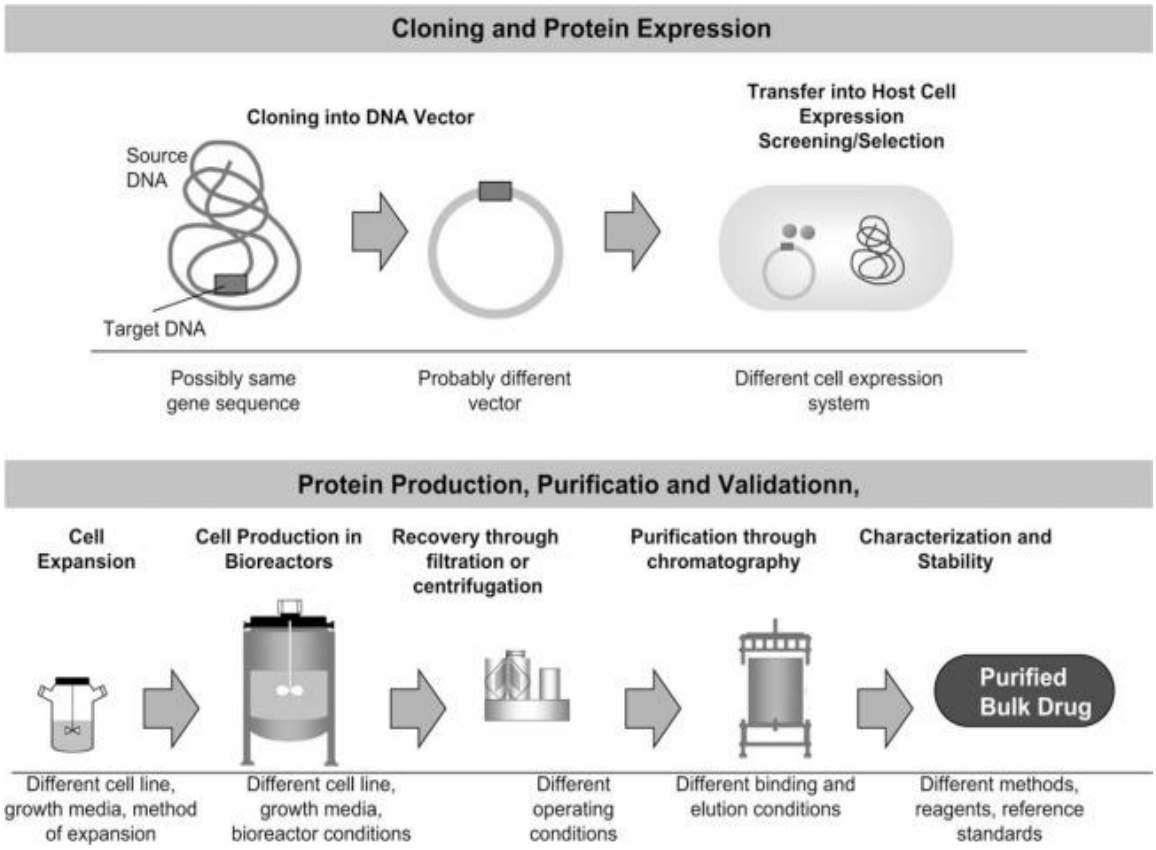

Figure 1: Recombinant protein production: sources of variation between manufacturers. (Mellstedt et al, 2008).

2 Biosimilar

In 2006, the first biosimilar drug was approved by the EMA (European Medicines Agency) called somatropin. Since then, the biosimilar market has been increasing considerably. In 2013, Europe granted approval for a monoclonal antibody biosimilar known as infliximab for the first time. 30 to 50% of the new drugs approved in the European continent are biosimilars. In the U.S. market in 2022, there were 1775 authorized biological products, 82 of which were biosimilars. (Millán et al, 2024).

The European Medicines Agency states that "a biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product- RP) in the European Economic Area (EEA)". (O'Callaghan et al, 2019).

To determine how comparable a biosimilar is to the original medication based on a variety of factors, including biological activity, safety, effectiveness, and quality, it is critical to look into whatever biosimilar is being assessed. The characteristics of the biosimilars in terms of pharmacokinetics and pharmacodynamics closely resemble those of a biological medicine that is currently authorized by the EMA and utilized within the EU. Based on the recognized treatment guidelines. Once the authorized biological drug is no longer under its exclusivity time frame, typically spanning a decade, or safeguarded by a patent, the introduction of a biosimilar medication becomes feasible. (Millán et al, 2024).

It is important to understand that a biosimilar is not the same as a generic medication according to the definition of generic. As we saw earlier, biosimilars and generics are variations of brand-name drugs that have already been approved and have different characteristics. Even though both biosimilars and generics are versions of existing brand-name medications, they have distinct qualities. Generics consist of chemically manufactured small molecules, rendering them chemically the same as the original products. Biosimilars, in contrast, are produced by a

biological cell. Even when two cells possess an identical sequence of amino acids in a protein, there can still be natural differences in the glycosylation or the way the protein is folded. This implies that it is impossible to create a biological medication that is identical to a reference product. However, a biosimilar with equivalent physiological and scientific effects might be created, ensuring its efficacy and safety. (Mascarenhas-Melo et al, 2024).

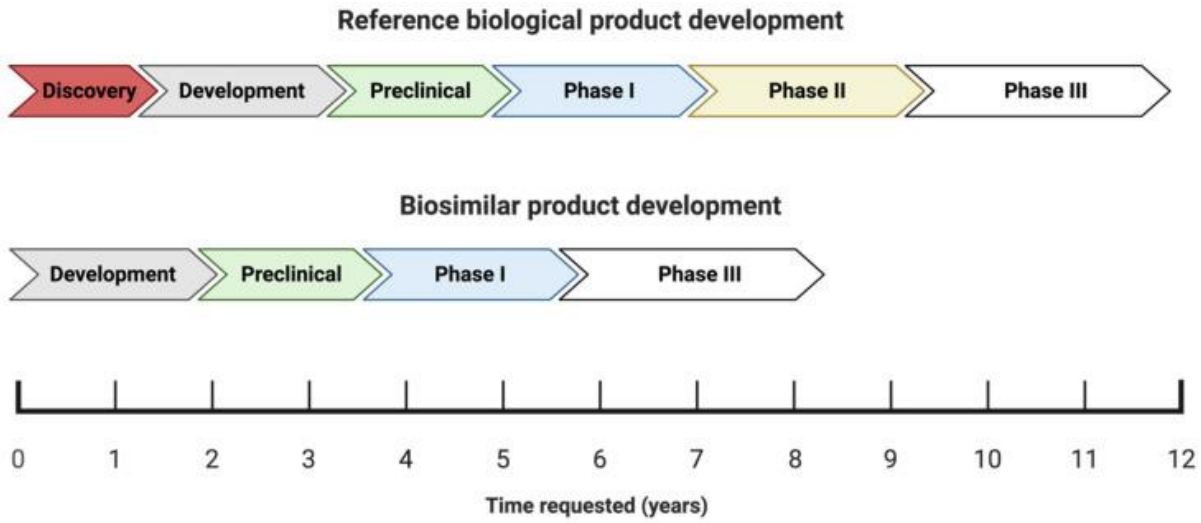

Figure 2: Schematic illustration of the phased and time-consuming development of reference biologics versus biosimilars. (Mascarenhas-Melo et al, 2024).

This process to achieve approval of new biologic drugs would normally take 12 years. It is important to have a strict research and development phase that aims to produce an optimal molecule. In the preclinical stage, the molecule is then subjected to exhaustive analysis, at which point the drug production process is at a critical stage. The drug commercialization phase consists of several fixed processes which are I, II, III and IV. Then the drug is marketed and this starts in phase IV. (Agbogbo et al, 2019).

In contrast, this process is more straightforward for generic drugs since the molecule is already constituted and defined. As a result, the finished product's development and the bioequivalence verification are needed. Therefore, biosimilars are mainly reproductions of real molecules with properties of constituted products, in this case it is not necessary to perform

the initial phase of discovery or effectiveness, i.e. phase II, which gives us the advantage of reducing the production time to 8 years or less and reducing production costs by approximately 10-20%. (Agbogbo et al, 2019).

However, Figure 2 shows that the production of biosimilars is carried out in phase III. It is worth mentioning that in this phase, a clinical study is not carried out as we know it, but it is shorter and has the important objective of verifying safety and efficacy. During the production of biosimilars, we have to take into account a very important point, which is to demonstrate that the prepared biosimilar, when compared in its analytical and biological functions, is similar to the reference product. (Mascarenhas-Melo et al, 2024).

The production of biosimilar drugs falls in the middle of innovative and generic drugs. However, the molecule is constituted in the initial phase in the same way as for generics, its duplication and determination is a difficult phase, which constitutes an obstacle. For this reason, biosimilars producers have to face a great challenge in this phase of the production of the patented reference product, which means that the details of the same are not within the reach of the population. It is believed that the manufacture, administration, and formulation of biosimilars are similar to reference products, since in this case they do not depend on the common sense of the manufacturers. Likewise, the producer of the biosimilar must carefully examine the reference product and use a form of reverse engineering to achieve, as a result, a product that closely resembles the reference product. (Mascarenhas-Melo et al, 2024).

When a biosimilar is created, a concrete objective must be taken into account, developing step by step, assessing risks, and within kinetic principles. Then, “quality by design” (QbD) is a key instrument that allows the biosimilar to develop a closer resemblance to the corresponding reference product. It is important to choose a compatible reference product by obtaining the reference active principle recognizing the “quality target product profile” (QTPP) and the “critical quality attributes“ (Oliveira et al, 2022). (CQA) of the reference product, and to increase a production mechanism which has the quality to identify the characteristics of the reference product, in other words to develop this approach it is important to identify and level the QTPP. (Vulto and Jaquez, 2017).

The definition of the quality attributes (QA) of the reference product is important. It is also very important to calibrate the variation range of the quality properties that directly influence the efficiency and reliability of the reference product (CQAs). To achieve this, it is necessary to use different series of drugs to obtain the refinement of the target product condition of the chosen biosimilar. Therefore, the CQAs are biological, microbiological, chemical, and physical properties that are continuously evaluated and supervised in order to establish the clinical similarity. The initial stage in this procedure is choosing the expression technique. For instance, the CQAs of infliximab, the reference product of the biosimilar CT-P13, are numerous and include relationships with biology, function, structure, essence, and residues. At this point, we are at a critical stage given the power with which it can influence translation and post-translational modifications, and in turn, decide the proportion and properties of the contaminating residues that are present in the final product. (Vulto and Jaquez, 2017).

3 Post-translational modification (PTMs)

The resemblance observed in the proposed biosimilar, the reference product, and the PTMs can be damaged by many factors, and this is considered a challenge for pharmaceutical manufacturing. The genetic series dictates the order of the amino acids in the protein, but their functions, structure and stability will be determined by the PTMs. (Shrivastava et al, 2022).

Proteins experience post-translational modifications through the attachment of functional groups, cutting, or breakdown. Typically, recombinant monoclonal antibodies experience post-translational modifications, including changes to the N- and C-terminal, glycosylation, deamination, phosphorylation, glycation, sulfation, acetylation, methylation, alkylation, oxidation, proteolysis, variable S-S linking, and interruptions in processing. Glycosylation has the greatest effect on biological activity. (Shrivastava et al, 2022).

Proteins may withstand glycosylation, which occurs when carbohydrate fragments are bonded to the protein synosome in the cell's Golgi apparatus and endoplasmic reticulum. The two main forms of glycosylation that occur in proteins are O-linked and N-linked. “There are two significant glycosylation classes prevalent in proteins, namely O-linked and *N*-linked. Oligosaccharide moieties attached to serine or threonine amino acid residues via an oxygen atom (O) are classified as O-linked glycans. *N*-linked glycosylation starts by co-translational attachment of a common high mannose based structure to an asparagine amino acid residue in an Asn–X–Ser/Thr consensus sequence where X can be any amino acid except proline (Pro), that is modified downstream in the endoplasmic reticulum and in the Golgi apparatus“. (Shrivastava et al, 2022).

So-called N-linked oligosaccharides are observed in therapeutic monoclonal antibodies (mAb) in the most dominant aspect of glycosylation. N-glycosylation of therapeutic antibodies compromises PTMs that impair biological function and therapeutic effectiveness. The determination of these glycans is necessary because of the producers and the dependencies

they regulate by their complicated system, and diversity represents a challenge. (Shrivastava et al, 2022).

It requires several analytical tests that can confirm the equality of the protein in question, while maintaining a consistent production process that confirms the quality of the product. The single mistake in the transformation or in the mixture of the elements can cause unfavourable effects on the patient and also cause a decrease in the usefulness of the final product. Spectroscopy, electrophoresis, mass spectrometry (MS), and liquid chromatography (LC) are effective tools for checking biological equivalence, serial differences, and glycosylation patterns, as well as other PTMs and residues in antibody products. (Shrivastava et al, 2022).

The peptide mapping technique is used to study the primary configuration of a biopharmaceutical, which is accredited by the International Council for Harmonization Directive (ICHQ6B). This technique plays an important role in the biopharmaceutical industry by helping us to certify the similarity of a therapeutic protein and verifying the deterioration procedures, such as deamination or oxidation. Providing a complete study of the selected protein, making it a typical procedure for distinguishing mAbs. It is important to deeply study some differences in PTMs to protect the efficacy and safety of the selected biosimilar. (Mouchahoir and Schiel, 2018).

The target protein is metabolized with a particular enzyme for a particular sequence of cleavage sites. Likewise, because of the metabolization, peptides with a perfect molecular weight for the LC/MS study are manifested, making it possible to accurately define the molecular mass. A high percentage of the series can be achieved using the MS/MS (MSE) process. By mixing one or more enzymes, a total of 100% of the series can be achieved. This general approach not only simplifies the recognition of the various changes but also shows us the precise location within the protein series. (Mouchahoir and Schiel, 2018).

Because this procedure involves sample processing steps, it should be taken into account that it is exposed to changes produced by different procedures or laboratories. The distinction across batches of articles or biosimilars can complicate the similarity and replication of the results obtained over a long period of time, which can affect the quality, safety, and efficacy of

the article, so that the sample processing situation should drive the reduction in the level of synthetically induced changes. (Mouchahoir and Schiel, 2018).

At the moment, there are several procedures available that apply the technology in the assimilation phase and decrease the time required for sample preparation for the use of peptide mapping. These processes provide us with a relevant increase in the capacity to reproduce the experiment, which leads to a minimum of errors and to a simpler analysis of the information. In order to accurately determine the protein in question, it is important to be informed in detail about its physiognomy and its own capabilities, which will contribute to an accurate peptide mapping. (Mouchahoir and Schiel, 2018).

4 Building the evidence for biosimilarity

Biosimilar research aims to demonstrate that the selected biosimilar has a safety and efficacy profile comparable to the reference product, without being definitively higher or lower. The approval of the biosimilar follows an approach sanctioned by the FDA and the EMA: First, a biological and physicochemical study of similarity (quality analysis); next, an evaluation of non-clinical similarity through in vitro and in vivo analysis; and finally, an assessment of clinical similarity, which includes a series of correlating steps that begin with pharmacokinetic (PK) analysis and may involve pharmacodynamic (PD) studies, followed by at least one clinical test for tolerance and efficacy. Moreover, in vitro quality tests are essential to confirm that any changes from a clinical perspective are minimal. (McKinnon et al, 2018).

It should be noted that the two products do not necessarily need to be identical; however, it is important to ensure that there are no clinically relevant changes. In other words, the desired biosimilar and the reference product should be similar. (Akiko and Takashi, 2019).

Quality Assurance (QA) is evaluated through analytical studies such as mass spectrometry, enzyme-linked immunosorbent assays (ELISA), surface plasmon resonance (SPR), and flow cytometry. The calculated GCs include biological activity capabilities, physicochemical properties, purity and impurities, immunochemical properties, resistance, quantity, oxidation, deamination, thermodynamic stability profiles, or other modifications The identification of a biosimilar mAb demonstrates its biological and physicochemical attributes: Fab (antigen binding fragment), Fc (crystallisable fragment), FcRn (neonatal Fc receptor), and FcγR (Fc-gamma receptor). (Akiko and Takashi, 2019).

Considering the safety and efficacy of the antibodies (mAbs), the difference is important as it relates to biological activity, particularly how the Fc regions may alter the ability of the mAb to function. Since the mAb exhibits ADCC activity, it is necessary to thoroughly examine the distinction in the FcgRIIIa interaction and ADCC activity. However, the mAb does not

inherently provide ADCC activity; for instance, a mAb contrasts with a soluble monomeric Ag, and ultimately, the distinction of the interaction does not significantly impact the efficacy and protection of the mAb. (Akiko and Takashi, 2019).

Antibodies (Abs) are big, pliable molecules made up of two identical light chains and two identical heavy chains connected by sulfur bridges, as seen by the structure and folding of the CH2 domain. The heavy chains have three constant domains (CH1, CH2, and CH3) that share identical amino acid sequences and are responsible for the immunoglobulin's effector action (CH2 and CH3), as well as a variable domain (VH) that exhibits significant variability in its amino acid composition. A constant domain (CL) and a variable domain (VL) are components of the light chains. VH, VL, CH1, and CL make up the Fab within the Fc region of IgG, which requires N-glycans collectively, whereas the CH2 and CH3 domains are found in the Fc region (crystallographic-effector fragment). Glycosylation enhances the equilibrium of the CH2 domains of IgG, in contrast to deglycosylation, which causes an imbalance, leading to a higher propensity for cleavage and disaggregation. Clearly, N-glycosylation influences ADCC and CDC activity by modulating the binding to the Fcγ receptor. Therefore, N-glycosylation is considered a critical quality attribute (CQA) and has the ability to change the therapeutic potential of monoclonal antibodies (mAbs) in a clinically meaningful way. (Wang et al, 2017).

5 Establishment of non-clinical biosimilarity

This exercise aims to make a non-clinical comparison to estimate the extent to which the biosimilar and the reference product may be similar regarding their active processes, effective action, and overall quality. During the PD analysis, physicochemical and in vitro laboratory tests are conducted in which ligands are attached to physiological targets, and the functional effects in the cells are estimated. This allows for stimulation or repression, consequently leading to an increase or decrease in cellular functioning. When we equate PK and PD at the preclinical stage, it helps reduce the excess uncertainty about their resemblance. (Declerck and Farouk, 2017).

The term "in vivo studies," which refers to the animal experiments used for these investigations, is still sensitive and contentious. Regulations recommend minimizing or eliminating their use in accordance with the 3Rs (Replacement, Reduction, and Refinement). It might be necessary to do complementary in vivo studies from a non-clinical standpoint, combining the findings from the analytical stage of the development of biosimilars. These tests are carried out to look into any notable discrepancies between the reference product and the biosimilar that were missed in the first study, like differences in composition or the usage of unusual excipients during production. (Declerck and Farouk, 2017).

In vivo evaluation is necessary to determine which research approach requires further information. This assessment should include a quantitative examination of the PK and PD aspects of the biosimilar, along with the reference product, including a concentration–response dose comparison. In this context, safety analysis considers apes to be a uniquely adaptive species, reflecting a tolerant perspective. Toxicity tests, specifically standard repeated dose toxicity tests, can be employed when developing a biosimilar in a new organism or cell by checking excipients' presence. Non-human primates should not, however, be used in these experiments. The quantitative and qualitative modifications related to the outcome, such as glycosylation that leads to hypersensitivity, should be evaluated clinically. Animal blood samples will probably be taken for continuous PK/toxicokinetic data calculation, even though

immunogenicity testing in animals do not reliably predict immunogenicity in humans. There is no need to look into carcinogenicity, reproductive toxicity, or pharmacological safety. Even though local tolerance tests are usually irrelevant, it is crucial to review them if there is inadequate information about the dose route of particular excipients. (Declerck and Farouk, 2017).

Biosimilars are adapted to manifest the polypeptide chain of the reference product. It is possible to detect lower-level chain changes with the help of highly sensitive practical methods. These changes can come from variations in the DNA or from incorrect integration, caused by inaccurate conversion or inadequate tRNA reaction. Consequently, biological compounds are subject to PTMs in cellular expression, integrating N- or C-terminal changes such as polypeptide chain cleavage, thus methylation, N-acetylation, and most importantly, glycosylation that affect biological function. In conclusion, the quality of a product requires several elements, including the formulation, purification, and storage procedures, as well as the way the packaging is sealed. reference product producers use proprietary development and purification qualities, as well as cellular traits that have been specially adapted for their process. For biosimilars producers, knowledge of the protein chain or the cell group used is not enough to produce an exact biological product. Therefore, it is important to reduce the structural diversity between the biosimilar and the PR, since containing minute alterations can damage the PK, safety, efficacy, and immunogenicity of the product. (Declerck and Farouk, 2017).

6 Regulatory concerns

The EMA and/or FDA have approved nearly one hundred biosimilars in the last 15 years, and this number is expected to rise in the coming years. Therefore, it is crucial to ensure robust regulation for their approval. The primary responsibility for confirming that the proposed biosimilars closely resemble the reference product, in structure and function, falls to the manufacturers and the regulatory bodies. This responsibility is vital to prevent any negative effects on safety and efficacy. Continuous testing and verification are required to eliminate any structural changes that could influence clinical outcomes. (Agbogbo et al, 2019).

Regulations have been created that specifically and consistently outline the requirements for approval of the final result. However, there are disagreements among regulatory agencies regarding the number of biosimilars authorized in various markets, which are significantly different. One of the pioneers in establishing a set of biosimilar approvals was the EMA in 2003. The first biosimilar was approved in 2006 under the name Ominotrope. After adopting similar rules, a decade later, the FDA authorized its first biosimilar in 2015. The FDA and the EMA have recognized the difficulties in producing biosimilars, emphasizing that every potential biosimilar has different and special qualities. Thus, developing a specific plan for each biosimilar candidate is essential. The WHO has recommended promoting the global increase of these products, advocating for the minimum requirement of essential clinical criteria, along with pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, safety, and efficacy data to establish biosimilarity. (Agbogbo et al, 2019).

In this context, it would not be necessary to conduct effectiveness tests when assessing the fundamental similarity tests in the total preclinical data. However, additional toxicological and/or clinical tests may be requested to address any potential uncertainty and possible immunogenicity challenges if any changes are observed. (Patel et al, 2013).

The laws in both the USA and the EU specify that a reference product will be approved in accordance with the legislation of the local governments. In the US, the submitted biosimilar must demonstrate similarity to the approved reference product, while in the EU, it must be similar to the reference product ratified by the European Economic Area (EEA) to gain approval. Because of the challenges and expenses associated with producing biosimilars, regulatory bodies have set regulations to permit the use of foreign comparators in comparative clinical trials. The favorable structure of the "scientific bridge" is necessary for the clinical data produced by a foreign comparator to be considered safe from a regulatory and legal standpoint. (Markus et al, 2017).

The "scientific bridge" between domestic and international products entails a thorough evaluation of the proposed biosimilar's analytical similarities with both comparators. A three-arm PK similarity test ought to be performed as well. The test would verify that the submitted biosimilar and both arms of the comparator are bioequivalent with regard to the respective comparators. (Markus et al, 2017).

The U.S. has a distinct rule, known as the interchangeability provision. An interchangeable biosimilar is defined by U.S. rules as one that is biosimilar to the reference product and is presumed to produce the desired therapeutic effect in every patient .When a biosimilar replaces the reference product, the risk to effectiveness and credibility does not increase compared to not making a replacement. In EU regulations, no precondition for exchange is necessary. The European Medicines Agency is primarily responsible for accepting biosimilars, although each member state has specific rules. (Markus et al, 2017).

The international non-proprietary name (INN) is given a four-letter suffix to create unique names, which helps healthcare workers avoid errors by guaranteeing that adverse occurrences are correctly attributed to the right manufacturer. For biosimilars to be used safely and effectively, proper pharmacovigilance is essential. (Markus et al, 2017).

7 Post-marketing safety monitoring of biosimilars-pharmacovigilance

Pharmacovigilance, according to “Good Pharmaceutical Practice“, aims to evaluate, quantify, identify, and prevent potential hazards related to the use of marketed products, with the intent of increasing drug safety and protecting users and public health. The literature suggests that clinical studies are often insufficient to recognize rare adverse events, meaning that the clinical development project is somewhat inadequate for identifying tolerability risks since it is shorter than the reference product. Consequently, in clinical terms, continuous monitoring of the article's performance is essential during the post-marketing phase. For these drugs, it is crucial that their safety can be influenced by the potential for immune responses, counter-responses caused by hypersensitivity, and the likelihood of experiencing complementary adverse events due to their vulnerability to changes during the production phase. The manufacturer must have a pharmacovigilance system that can discover, assess, and prevent adverse events associated with the drug throughout its lifecycle. Therefore, pharmacovigilance groups should not limit their monitoring to the types and hazards of AEs, but should be robust enough to detect the frequency of recurrent AEs that occur over an extended period. Through these authorization methods, the applicant should provide a synthesis of the concept as well as a risk reduction plan that aligns with valid EU regulations and pharmacovigilance recommendations. (Ramanan and Grampp, 2014).

It is also necessary to argue that other traceability requirements obligating the reference product must be properly maintained in the biosimilar pharmaceutical custody project, and immunogenicity requires careful consideration of this situation. (Beninger, P., 2017).

When the product enters the market, the EMA has established appropriate pharmacovigilance projects to monitor adverse events. EudraVigilance is the EMA-developed system for exchanging and assessing reports of adverse events that occur both during and after

marketing authorization. The safety of medicines is ensured through information collected from voluntary reports by healthcare professionals and patients. To enhance these results, the data must provide a clear and specific assessment, capturing the essence of the AE along with detailed drug information such as trade name, INN, batch number, and dosage administered. However, calculations may be complex because patients using biopharmaceutical therapies might also be undergoing polytherapy and may have serious or severe diseases. AEs are often not fully reported or may not be reported at all, and these reporting regulations vary from one state to another. (Ingrasciotta et al, 2018).

In general, the Summary of Product Characteristics (SmPC), and the Information Leaflet (IF) should include a section that helps people report suspected adverse events (AEs), utilizing the national communication programs or official resources available online. Meanwhile, a new concept has recently been introduced by EU legislation on veterinary medicinal products (VMPs), which has published a list of medicinal products that are subject to supplementary supervision for a specified period. For this reason, these medications are identified by a black triangle-shaped symbol, as well as relevant wording on the SmPC and IF. According to this new viewpoint, trust, communication, and transparency are improved by visualizing the consolidation of the pharmacovigilance (PV) of all medications. (Beninger, P., 2017).

The preventive qualities of these products have not changed significantly since the first biosimilar was introduced in Europe more than 20 years ago. However, as the risks and related morbidity differ for children and adults, attention is still essential, especially in pediatrics. There are currently over 20 biosimilar drugs accepted in the European Union, categorized into three groups based on their active ingredients: Epoetins (alpha and zeta), filgrastim, and monoclonal antibodies (rituximab, trastuzumab, and bevacizumab). (Santos et al, 2019).

Wealthy countries are experiencing a healthcare spending squeeze due to the production of new, high-cost cancer-fighting biologics and population growth. However, since biosimilar drugs represent a new category of medications, this advancement will be more complicated than simply replacing generics. (Cornes, P., 2012).

8 Use of biosimilars; controversies

Biosimilars offer many advantages; however, significant disparities exist in their use, particularly regarding market share and cost savings. This discrepancy prompts many questions about the effectiveness, safety, and interchangeability of these drugs. (Ascef et al, 2020).

8.1 Immunogenecity

The ability of a certain element to cause an adverse reaction due to different agents is known as immunogenicity. T cells are activated or the innate immune response is triggered by this complex reaction, which also results in the production of antibodies. The quality of the immune response is critically linked to the regulatory approval of biosimilars; a fundamental aspect can reveal the similarity of the biosimilar to the proprietary reference product, which is assessed through rigorous clinical and non-clinical quality control tests. As mentioned earlier, biological proteins are more complicated in structure and have a higher molecular weight. The effectiveness of the treatment may therefore be jeopardized when these medications are given to patients since they may cause undesirable immune responses and the production of anti-drug antibodies, or ADA, which can result in delayed hypersensitivity and anaphylactic events. However, the essence of this reaction is influenced by additional factors, such as variations in the production of the product, the protein's properties during equilibrium and storage, as well as factors related to the dosage form- whether subcutaneous or intravenous. Other factors to consider include the patient's condition or sickness, including age, genetic background, immune system health, and the coordinated use of drugs. Last but not least, producers, physicians, and pharmacists must guarantee that immunogenicity maintains full traceability after permission. (Kabir et al, 2019).

8.2 Extrapolation

Biosimilars can integrate clinical information from the reference product without needing to conduct clinical tests for the same data. This capability provides us with extrapolation, which is a crucial concept in their acceptance and process. (Declerck et al, 2017).

Therefore, to validate the extrapolation, the information must come from studies employing a clinical model with a high degree of sensitivity to detect any potential differences in safety, efficacy, or immunogenicity between the reference product and the possible biosimilar. (Declerck et al, 2017).

According to regulations certified by the EMA for indicated biologic medicinal products, all information from the clinical study is included in the SmPC (Summary of Product Characteristics). Thus, the extrapolation between the PR and the biosimilar is authorized, provided it is backed by scientific examinations and an evaluation of clinical, non-clinical, and analytical information. Consequently, neither restriction nor extension of indications should be accepted, as non-approved indications will be regarded as such off-label. (Declerck et al, 2017).

8.3 Interchangeability and substitution

When a regulatory agent authorizes a biosimilar, it is prescribed with endorsement of effectiveness and protection in all recommendations outlined in the SmPC. For this reason, when initiating a patient's therapy, a physician may include a reference product or a biosimilar. However, the following questions arise: Can physicians substitute the reference product administered with a biosimilar, or can the reference product and biosimilar be used interchangeably? It is important to clarify the distinctions between substitution and interchangeability to answer these questions, as they may be similar but represent very different concepts, thus avoiding any confusion. (Cazap et al, 2018).

Replacement or substitution refers to a pharmacist's activity of changing one drug for a similar one without the physician's approval or the patient's consent. This practice assumes that frequent switching between two drugs does not pose additional risks and that the treatment's effectiveness remains intact. Only a few European countries depend on the

knowledge and expertise of healthcare professionals to prevent incorrect substitutions. (Cazap et al, 2018).

In the USA, the term “interchangeability” refers to the qualification that allows automatic replacement if permitted by state laws. In the EU, however, interchangeability means the exchange of one drug for another, which can be done by switching, a decision made by the physician, or replacement, which is carried out by pharmacists. (Lyman et al, 2018).

When it comes to choosing the best medication for a patient, doctors are crucial and the last person in the decision-making process. Regulatory bodies must, however, adopt a position on interchangeability and put in place rules that outline the manner and timing of replacement in order to select and recommend the best course of action. According to regulatory bodies and scientific associations, biosimilars are recommended for patients who have never received a biologic treatment before (known as naïve primary patients), those who have received a biologic treatment and then gone through a wash-out period, or those who have benefited from biologics to manage a chronic illness. In January 2017, the FDA became the first regulatory body to formally define interchangeability.. (Lyman et al, 2018).

8.4 Nomenclature

Throughout the drug's shelf life, the nomenclature is crucial for controlling usage and allowing for continuous monitoring of side effects. Accurate differentiation is guaranteed at the next stage of commercialization to avoid confusion between the biosimilar and its reference product or between the biosimilar and other biosimilars. (Blandizzi et al, 2017).

The organic articles are quite complex, making it challenging to use abbreviated, useful, and defined names. The active elements are named based on their configuration, acceptance, and mode of commercialization. This isn't always the case with biopharmaceuticals, though, as their names can indicate differences in the real substance. Therefore, depending on the individuality and innovation of the article, it is important to assign a new name. Opinions vary on this matter; some groups believe that having a new formulation, an inspected production phase, a recent license, and a different commercial title qualifies as a new product. (Blandizzi et al, 2017).

WHO and INN specialists are closely involved in selecting a unique and globally recognized title for each functional origin marketed as a pharmaceutical product. However, to achieve the desired goal in further commercializing biologics and biosimilars, INNs are hindered by being used as the sole means of biologic recognition. Since INNs are less effective for biopharmaceuticals and more effective for generic medications it is important to keep in mind that even comparable distinct. products are perceived as different. To clarify the relationship of AEs, the INN should incorporate the trade title. Otherwise, a blend of the INN and a singular marker, such as a Greek letter, is a prudent choice in reference to biopharmaceuticals. Meanwhile, new alternatives have emerged, with the WHO proposing to use a biological qualifier consisting of a four-digit code to differentiate biosimilars from PRs. Few regulatory bodies suggest abandoning the INN method for biosimilars. The use of brand names is necessary to appropriately indicate the similarity of biologics, according to Directive 2012/52/EU published by the European Commission. This principle is regarded as relevant for biosimilars. (Blandizzi et al, 2017).

9 Use of biosimilars; economic aspects

During the last few years, public spending on inpatient and outpatient drugs has increased by 30%. Biosimilars are a valuable option in this regard, promoting competition, providing easy access, and maintaining beneficial quality, making these therapeutic options cost-effective. (Mascarenhas-Melo et al, 2024).

It has been estimated that the EU and the US will save 49 billion Euros and 98 billion Euros between 2016 and 2020. Introducing biosimilars in the pharmaceutical markets has reduced healthcare costs and provided us with therapeutic alternatives. Therefore, their use increases patients' competition for biologic treatment. Introducing biosimilars on the market can help alleviate expensive healthcare budgets, and the savings generated from this can create new budgetary space for recent therapeutic alternatives. Furthermore, the introduction of biosimilars can enhance patients' access to biologic therapies. Biosimilars use is a boost not only in an economic framework but also in a social framework, especially in public health. (Mascarenhas-Melo et al, 2024).

In Europe, the increase in biosimilar drugs has been revealed; these drugs now account for more than 7% of the market. This increase is due to the development of the biosimilar market in the immunology and oncology sectors. The experience with biosimilars in Europe spans over 15 years, and with more than 2000 billion patients treated per day, we can assure that these drugs demonstrate a high standard of safety, efficacy, and quality, having been adequately approved by the EMA at the European level. Significant savings will arise from the FDA's regulatory specificity regarding biosimilars. The conventions of competition, payment, and approvability contribute to the potential for considerable savings in the short term; however, long-term benefits will accrue to patients and taxpayers. (Mascarenhas-Melo et al, 2024).

10 Conclusions and future perspectives

New avenues for the development of biologic medications are made possible by biotechnology. Biosimilars are acknowledged and regularly included into clinical settings, acting as useful tools to improve patients' access to advantageous medications and treatments. These medications also have the benefit of being substantially cheaper than reference biologics, which helps healthcare provider organizations financially. As a result, more patients can benefit from these novel medicines because they are more advantageous while being comparable in terms of efficacy, protection, and quality. (Janjigian et al, 2014).

For manufacturers, especially, biosimilars present challenges different from those of generic drugs. The high cost of the clinical process poses an obstacle, as this process requires substantial funding and technical expertise. Additionally, because biosimilar legislation is still relatively new in most markets, there is a difference in the current acceptability of legislation between generics and biosimilars. However, in order to dispel skepticism and prove the goods' safety, it is critical that patients and medical professionals begin to trust them. To achieve this, it is essential to finance marketing groups, and simultaneously, the growth of this biosimilars market necessitates constant regulatory and scientific updates, which companies are obliged to implement. (Janjigian et al, 2014).

All stakeholders must effectively carry out their responsibilities in order to maximize the use of biosimilars. To increase their trust while prescribing them, doctors should be aware of their use. As a result, it's critical that patients and doctors are aware of any side effects and have a strategy in place to deal with them and reduce adherence to the treatment. Producers must adapt to market variations and remain cost-competitive; the efficient cooperation of all stakeholders is crucial to the evolution of biosimilars. The main goal is to provide the clinical benefits of biologic therapies to patients and ensure, at the same time, that the healthcare system can be sustainable for the long term. (Peyrin-Biroulet et al, 2017).

The importance of regulatory administrations lies in establishing a comprehensive set of rules that are scientifically sound and capable of addressing existing challenges. This includes adopting a common approach to nomenclature, terminology, abbreviations, and more. (Mascarenhas-Melo et al, 2024).

So, we can think that Iceland has the potential to produce biosimilars and biotechnological drugs. Its natural environment contains a great variety of microorganisms that can help us in the research of new drugs. Besides, it has the great advantage of having pure water and the low cost of electricity. The environment for patents is very favorable, and the country is located between the two largest markets for the pharmaceutical industry worldwide, between Europe and the United States.

The other major advantage is its human resources, as the high level of education and the advancement of the pharmaceutical industry have allowed for experienced people in this field. Recent science graduates and those who have studied abroad can get a job in one of the pharmaceutical companies or biotech drugs, here we can cite as an example the biotech drug company, Alvotech.

Bibliography

Agbogbo, F.K., Ecker, D.M., Farrand, A., Han, K., Khoury, A., Martin, A., McCool, J., Rasche, U., Rau, T.D., Schmidt, D., et al. (2019). Current perspectives on biosimilars. *J. Ind. Microbiol. Biotechnol*, 46, 1297–1311. https://doi.org/10.1007/s10295-019-02216-z

Akiko, Ishii-Watabe., Takashi, Kuwabara. (2019). Biosimilarity assessment of biosimilar therapeutic monoclonal antibodies, *Drug Metabolism and Pharmacokinetics*, Volume 34, Issue 1, Pages 64-70, I SSN 1347-4367. https://doi.org/10.1016/j.dmpk.2018.11.004

Ascef, B.d., Lopes, A.C.d. and de Soárez, P.C. (2020). Health technology assessment of biosimilars worldwide: a scoping review. *Health Res Policy Sys* 18, 95 https://doi.org/10.1186/s12961-020-00611-y

Blandizzi, C., Meroni, P. L., and Lapadula, G. (2017). Comparing Originator Biologics and Biosimilars: A Review of the Relevant Issues. *Clinical therapeutics*, 39 (5), 1026–1039. https://doi.org/10.1016/j.clinthera.2017.03.014

Beninger, P. (2018). Pharmacovigilance: An Overview. *Clinical therapeutics*, *40*(12), 1991–2004. https://doi.org/10.1016/j.clinthera.2018.07.012

Blackstone, E. A., and Joseph, P. F. (2013). The economics of biosimilars. *American health & drug benefits*, *6*(8), 469–478. Available online: The Economics of Biosimilars - PMC

Cazap, E., Jacobs, I., McBride, A., Popovian, R., Sikora, K. (2018, October). Global Acceptance of Biosimilars: Importance of Regulatory Consistency, Education, and Trust, *The Oncologist*, Volume 23, Issue 10, Pages 1188–1198. https://doi.org/10.1634/theoncologist.2017-0671

Cornes, P. (2012). The economic pressures for biosimilar drug use in cancer medicine. *Targ Oncol* 7 (Suppl 1), 57–67 https://doi.org/10.1007/s11523-011-0196-3

Declerck, P., Danesi, R., Petersel, D. *et al.* (2017). The Language of Biosimilars: Clarification, Definitions, and Regulatory Aspects. *Drugs* 77, 671–677. https://doi.org/10.1007/s40265-017-0717-1

Declerck, P., and Farouk Rezk, M. (2017). The road from development to approval: evaluating the body of evidence to confirm biosimilarity. *Rheumatology (Oxford, England)*, *56*(suppl_4), iv4–iv13. https://doi.org/10.1093/rheumatology/kex279

Ingrasciotta, Y., Cutroneo, P.M., Marcianò, I. *et al.* (2018). Safety of Biologics, Including Biosimilars: Perspectives on Current Status and Future Direction. *Drug Saf* 41, 1013–1022. https://doi.org/10.1007/s40264-018-0684-9

Janjigian, Y. Y., Bissig, M., Curigliano, G., Coppola, J., and Latymer, M. (2018). Talking to Patients about Biosimilars. *Future Oncology*, *14*(23), 2403–2414. https://doi.org/10.2217/fon-2018-0044

Kabir, E. R., Moreino, S. S., and Sharif Siam, M. K. (2019). The Breakthrough of Biosimilars: A Twist in the Narrative of Biological Therapy. *Biomolecules*, *9*(9), 410. https://doi.org/10.3390/biom9090410

Kijanka, M., Dorresteijn, B., Oliveira, S., and van Bergen en Henegouwen, P. M. (2015). Nanobody-Based Cancer Therapy of Solid Tumors. *Nanomedicine*, *10*(1), 161–174. https://doi.org/10.2217/nnm.14.178

Peyrin-Biroulet, L., Lönnfors, S., Roblin, X., Danese, S., Avedano, L., (2017). Patient Perspectives on Biosimilars: A Survey by the European Federation of Crohn's and Ulcerative Colitis Associations, *Journal of Crohn's and Colitis*, Volume 11, Issue 1, 128–133. https://doi.org/10.1093/ecco-jcc/jjw138

Lyman, Gary H. et al. (2018). American Society of Clinical Oncology Statement: Biosimilars in Oncology. *JCO* 36, 260-1265DOI:10.1200/JCO.2017.77.4893

Markus, R., Liu, J., Ramchandani, M., Landa, D., Born, T., and Kaur, P. (2017). Developing the Totality of Evidence for Biosimilars: Regulatory Considerations and Building Confidence for the Healthcare Community. *BioDrugs: clinical immunotherapeutics, biopharmaceuticals and gene therapy*, *31*(3), 175–187. https://doi.org/10.1007/s40259-017-0218-5

Mascarenhas-Melo, F., Diaz, M., Gonçalves, M. B. S., Vieira, P., Bell, V., Viana, S., Nunes, S., Paiva-Santos, A. C., and Veiga, F. (2024). An Overview of Biosimilars—Development, Quality, Regulatory Issues, and Management in Healthcare. *Pharmaceuticals*, *17*(2), 235. https://doi.org/10.3390/ph17020235

McKinnon, R. A., Cook, M., Liauw, W., Marabani, M., Marschner, I. C., Packer, N. H., and Prins, J. B. (2018). Biosimilarity and Interchangeability: Principles and Evidence: A Systematic Review. *BioDrug: clinical immunotherapeutics, biopharmaceuticals and gene therapy*, *32*(1), 27–52. https://doi.org/10.1007/s40259-017-0256-z

Mellstedt, H., Niederwieser, D., and Ludwig, H. (2008). The challenge of biosimilars. *Annals of oncology: official journal of the European Society for Medical Oncology*, *19*(3), 411–419. https://doi.org/10.1093/annonc/mdm345

Millán-Martín, S., Zaborowska, I., Jakes, C., Carillo, S., Bones, J. (accessed on 7 February 2024). Comparability Study for the Determination of Post-Translational Modifications of Biotherapeutic Drug Products and Biosimilars by Automated Peptide Mapping Analysis.

Available online: https://assets.thermofisher.com/TFS-Assets/CMD/Application-Notes/an-21850-lc-ms-comparability-biosimilars-an21850-en.pdf

Mouchahoir, T. and Schiel, J. E. (2018). Development of an LC-MS/MS peptide mapping protocol for the NISTmAb. *Analytical and bioanalytical chemistry*, *410*(8), 2111–2126. https://doi.org/10.1007/s00216-018-0848-6

O'Callaghan, J., Barry, S.P., Bermingham, M. *et al.* (2019). Regulation of biosimilar medicines and current perspectives on interchangeability and policy. *Eur J Clin Pharmacol* 75, 1–11 https://doi.org/10.1007/s00228-018-2542-1

Oliveira, N., Cádiz-Gurrea, M. d. l. L., Silva, A. M., Macedo, C., Rodrigues, F., & Costa, P. (2022). Development and Optimization of a Topical Formulation with *Castanea sativa* Shells Extract Based on the Concept "Quality by Design". *Sustainability*, *14*(1), 129. https://doi.org/10.3390/su14010129

Patel, M. M., Shah, P. J., and Patel, B. M. (2013). Insights of biosimilars through SWOT analysis. *Expert Opinion on Biological Therapy*, *14*(2), 139–144. https://doi.org/10.1517/14712598.2014.849689

Ramanan, S., and Grampp, G. (2014). Drift, Evolution, and Divergence in Biologics and Biosimilars Manufacturing. *BioDrugs* 28, 363–372. https://doi.org/10.1007/s40259-014-0088-z

Santos, S. B., Sousa Lobo, J. M., and Silva, A. C. (2019). Biosimilar medicines used for cancer therapy in Europe: a review. *Drug discovery today*, *24*(1), 293–299. https://doi.org/10.1016/j.drudis.2018.09.011

Sekhon, B. S., and Saluja, V. (2011). Biosimilars: an overview. *Biosimilars*, 1, 1–11. https://doi.org/10.2147/BS.S16120

Shrivastava, A., Joshi, S., Guttman, A., Rathore, A.S. N-Glycosylation of monoclonal antibody therapeutics: A comprehensive review on significance and characterization. *Anal. Chim. Acta.* 2022;1209:339828 https://doi.org/10.1016/j.aca.2022.339828

Simoens, S. (2011). Biosimilar medicines and cost-effectiveness. *ClinicoEconomics and Outcomes Research*, *3*, 29–36. https://doi.org/10.2147/CEOR.S12494

Vulto, A. G., & Jaquez, O. A. (2017). The process defines the product: what really matters in biosimilar design and production?. *Rheumatology (Oxford, England)*, 56(suppl_4), iv14–iv29. https://doi.org/10.1093/rheumatology/kex278

Wang, T., Chu, L., Li, W., Lawson, K., Apostol, I., and Eris, T. (2017, mars 21) Application of a Quantitative LC-MS Multiattribute Method for Monitoring Site-Specific Glycan Heterogeneity on a Monoclonal Antibody Containing Two N-Linked Glycosylation Sites. *Anal. Chem*. 89, 3562–3567. https://doi.org/10.1021/acs.analchem.6b04856