UNIVERSIDADE D
COIMBRA

Marta Isabel Agostinho Cordeiro

A Regulatory Perspective on Biosimilar Medicines

Dissertação no âmbito do Mestrado em Biotecnologia Farmacêutica orientada pelo Professor Doutor João José Martins Simões de Sousa e pelo Professor Doutor Carlos José Manaia Sinogas apresentada à Faculdade de Farmácia da Universidade de Coimbra

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Hoje, termino aquele que foi um dos capítulos mais especiais da minha vida.

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"O sol de Coimbra é diferente do sol do resto do mundo",

e que bonito que foi vivenciar estes cinco anos neste canto do mundo.

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"O único homem que se educa é aquele que aprendeu como aprender: que aprendeu como se adaptar e mudar, que se capacitou de que nenhum conhecimento é seguro, que nenhum processo de buscar conhecimento oferece uma base de segurança."

Carl Rogers

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ABSTRACT

By definition, biosimilar medicinal products are biological medicinal products which correspond similarly to other biological medicinal products that are already on the market, called "reference medicinal products".

The access to biosimilar medicines, as available therapy and equitably framed in the pharmacology, is a current reality. However, to achieve this goal, it is extremely important to consistently and scientifically substantiate the regulatory requirements inherent to biosimilar medicines when accessing the market. Based on an analysis of the raw material, and the type of methods used in the manufacturing processes of biological medicines, it is known that this tends to be more complex for the quality of the finished product than the manufacture of molecules obtained through a chemical process. It is then relevant to highlight the main differences between both products: biological medicines manufactured using biotechnology and the current generics containing APIs obtained by synthetic processes.

Once arrived at the approval process of these medicinal products, it is intended to analyse the guidance documents and the regulatory framework which creates the rules that allow these biosimilar medicinal products to come to the market. This project will be based on the specific provisions of EU legislation, through the European Medicines Agency (EMA), as well as the legislation of the United States of America, through the Food and Drug Administration (FDA).

Focusing on a more practical aspect, this thesis aims to understand which criteria/parameters determine the positive evaluation of submission of a biosimilar medicine when facing an application for market authorization, as well as to differentiate the approval processes generated by different Regulatory Agencies.

Keywords: *Biosimilar medicines, regulation, assessment, biosimilarity, safety.*

RESUMO

Por definição, os medicamentos biossimilares são medicamentos biológicos que correspondem de forma semelhante a outros medicamentos biológicos que já se encontram no mercado, chamados de "medicamentos de referência".

O acesso a medicamentos biossimilares, como a terapia disponível e equitativamente enquadrada na farmacologia, é uma realidade atual. No entanto, para alcançar esse objetivo, é extremamente importante comprovar de forma constante e científica os requisitos regulamentares inerentes aos medicamentos biossimilares aquando da sua introdução no mercado. A partir de uma análise da matéria-prima, do tipo de métodos utilizados nos processos de fabrico de medicamentos biológicos, sabe-se que tal tende a ser mais complexo para a qualidade do produto acabado do que o fabrico de moléculas obtidas por processo químico. Deste modo, torna-se ainda mais relevante destacar as principais diferenças entre ambos os produtos: medicamentos biológicos fabricados por biotecnologia e os genéricos atuais contendo substâncias ativas obtidas por processos sintéticos.

Uma vez chegado ao processo de aprovação desses medicamentos, pretende-se analisar os documentos de orientação e o marco regulamentar que criam as regras que permitem que esses medicamentos biossimilares cheguem ao mercado. Este projeto será baseado nas disposições específicas da legislação da União Europeia, por meio da Agência Europeia de Medicamentos (EMA), bem como na legislação dos Estados Unidos da América, por meio da Food and Drug Administration (FDA).

Direcionando o trabalho para um aspeto mais prático, é pretensão desta Tese entender quais os critérios/parâmetros que determinam a avaliação positiva de uma submissão de um medicamento biossimilar ao se deparar com um pedido de autorização no mercado, assim como diferenciar os processos de aprovação gerados por diferentes de Agências Reguladoras.

Palavras-Chave: *Medicamentos Biossimilares, Regulamentação, Avaliação, Similaridade, Segurança.*

OUTLINE OF THE THESIS

Chapter I – Introduction

In this chapter, the concepts and principles of biosimilars are presented, from the clarification of the difference between biosimilar medicines and generic drugs, as well as certain characteristics important to provide some background to the dissertation.

Chapter 2 – Development of Biosimilars

The second chapter focuses on an explanatory approach about, firstly, the manufacturing and production process of the biosimilar, passing through cultivation and production, isolation and purification and, finally, the formulation, filling and final finishing itself. In the second part of this chapter, it is presented a wide range of issues inherent to similarity, immunogenicity, extrapolation, safety, comparability and interchangeability.

Chapter 3 – Regulatory Framework for the Development of Biosimilar

In the chapter, a regulatory framework is highlighted, giving the perspective of the approval process via the European Medicines Agency and the FDA. Other Regulatory Agencies, as also presented and analysed in the third chapter.

Chapter 4 – Pharmaceutical Market for Biosimilars

In chapter four, the current market for biosimilars in the European Union and the United States is presented. To give a more practical example of the regulatory framework of a biosimilar medicine, four biosimilars are selected from a previously approved reference medicine, indicating the differences between each one.

Chapter 5 – Challenges and Future Prospects

This chapter aims to reflect on biosimilar medicines, their benefits, risks, particularities from the regulatory point of view, and future perspectives, among other aspects relevant.

Chapter 6 – Final Considerations

The sixth chapter of this Master Thesis summarizes the concepts studied throughout this thesis in the world of Biosimilars, as well as a global perspective on the importance of this type of medicine, the impact they have on the health and well-being of individuals and society, ending with possible associated future perspectives.

Chapter 7 – References

The last chapter lists all the bibliographical references used throughout the document. This Dissertation was based on a specialised bibliographic review through the PubMed online database, guidelines from INFARMED, European Medicines Agency and Food and Drug Administration, as well as other regulatory documents. In addition to these aspects, and to increase the analysis, scientific books considered relevant to the objectives of this Thesis were used.

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ABBREVIATIONS

API – Active Pharmaceutical Ingredient

BAP – Biosimilar Action Plan

BGTD – Biologics and Gene Therapies Directorate

CHMP – Committee for Medicinal Products for Human Use

DNA – Deoxyribonucleic acid

EMA – European Medicines Agency

EU – European Union

FDA – Food and Drug Administration

GCP – Good clinical practice

ICH – International Council of Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

PD – Pharmacodynamics

PHS – Public Health Service Act

PK – Pharmacokinetic

PMDA – Pharmaceuticals and Medical Devices Agency

PRAC – Pharmacovigilance Risk Assessment

RMP – Risk Management Plan

TNF - β – Lymphotoxin

TNF- α – Tumour necrosis factor

USA – United States of America

CHAPTER I

General Introduction

1.1. Definition and Characterisation of Biosimilars

Biological medicinal products are defined as active substances obtained from a biological source, such as living cells or organisms, most of which are composed of proteins. In this sense, the manufacture of biological medicinal products is more complex than the manufacture of molecules obtained by a chemical process, since the process of the first case is obtained via biotechnology. This type of medication has a high and complex molecular structure, and still a certain degree of intrinsic variability. Of course, natural variability is intrinsic to all biological medicinal products, so strict quality and safety controls are carried out [1, 2].

Biological medicine contains one or more active substances produced or derived from a biological source. Reference biological medicines are approved based on complete technical-scientific documentation, in the areas of quality, safety and efficacy [3].

According to the European Medicines Agency (EMA), a biosimilar medicine is considered to be a medicine highly similar to another biological medicine that is already marketed in the European Union – a reference medicine. Since biosimilars are a type of biological medicinal product, all relevant characteristics of biological medicinal products apply to them. Biosimilar medicinal products are molecules of high molecular weight, with high complexity and produced in cells or transgenic organisms [1].

A biosimilar medicine is developed to be very similar to its reference medicine in terms of quality, safety and efficacy. Although there may be minor differences due to the complex nature and production methods, the active ingredients of a biosimilar medicine and its biological reference medicine are essentially the same biological substance [4].

In terms of similarity, the biosimilar medicinal product has physical, chemical and biological properties highly similar to the reference medicine, particularly in terms of safety and efficacy. Regarding their clinical performance, no differences are found, as these will not influence safety or efficacy. As for the existing variability, this may exist on a small scale, and it is crucial to demonstrate that it does not affect the safety and efficacy of a biosimilar. As for general standards, all biosimilar medicinal products comply with the same quality, safety and efficacy standards as any other medicinal product [1].

When the reference medicine is placed on the market, it has an associated patent that prevents other pharmaceutical industries from commercialising the same medicine. At the end of this market protection period, other companies are authorised to commercialise it. However, being biological products, there is an associated variability that prevents the biosimilar medicine to be exactly equal to the reference medicine. Table I shows the main differences between the two groups of medicines [5, 6].

For the safety and efficacy profile to be maintained, the legislation defines the studies to be conducted so that a biosimilar medicine can demonstrate similarities in terms of quality, safety and efficacy to its reference medicine and that there are no significant differences [7]. Table I shows the comparison between the data requirements for the approval of a biosimilar and a reference medicinal product.

Table I - *Comparison between the data requirements for the approval of a biosimilar and a reference medicinal product. (Adapted) [1].*

Reference medicinal product	Biosimilar medicinal product
Risk Management Plan	Risk Management Plan
Clinical studies: - Safety and efficacy - PK/PD - Immunogenicity	Clinical comparative studies: - Safety and efficacy - PK/PD - Immunogenicity
	Non-clinical comparative studies
Non-clinical studies	Comparative quality studies
Pharmaceutical quality studies	Pharmaceutical quality studies

It should also be noted that the clinical and non-clinical data required for the approval of a biosimilar are different from those required for the approval of a biological medicine with a new active substance. This is due to the fact that in demonstrating similarity, the biosimilar relies on the experience gained for the reference medicine with regard to efficacy and safety.

Biosimilar medicines are approved by a shortened process that guarantees similarity, but not equivalences, to the pre-existing reference medicine. In this context, comparability studies make it possible to generate the evidence required to substantiate the similarity in the areas of quality, safety and efficacy, thus guaranteeing that the efficacy and safety identified for the reference medicine are recognised for the biosimilar medicine.

They are biotechnological when produced in a fermenter by cells usually modified by recombinant DNA technologies for the expression of the active substance. Biological medicines can be obtained through biotechnology or by extraction from a living organism. In the first case, production in a bioreactor may determine heterogeneities between medicines from different manufacturers or between several batches of the same medicine, which are the basis for adverse reactions, while in the second case, individual homeostatic control does not predict significant intra-individual, but rather inter-individual heterogeneities. Their proteinic nature, high molecular weight and the biological origin of the materials used in their manufacture may determine an intrinsic variability that may cause changes in the safety and efficacy profile that needs to be safeguarded, so this segment of medicines is considered a priority in terms of pharmacovigilance [4, 8-10].

1.2. Generic and Biosimilars Drugs

A generic drug differs greatly from a biosimilar drug due to several aspects when compared in terms of development and characteristics between them. Starting with its production process, the generic drug is produced by chemical synthesis while the biosimilar is based on biological production. In terms of reproductivity, in the case of biosimilar medicinal products, as its name implies, the molecule can be reproduced with a high degree of similarity, while generic drugs correspond to the same molecule. Associated with the production process, there is the ease of characterisation, being the molecules of generic drugs are much smaller, allowing a more accessible characterisation, and it is admitted that in the case of biosimilar drugs, in which the molecules are larger and much more complex at the structure level, several technologies are required for their characterisation [1, 9].

In terms of development, generic medicinal products are based on bioequivalence, demonstrating that the generic medicinal product and the reference medicinal product release the active substance into the body at the same rate and to the same extent under similar conditions. In the case of biosimilar medicinal products, these are based on comparability studies and complete direct comparison of the biosimilar with the reference medicine, in order to demonstrate the high similarity in terms of chemical structure, biological function, efficacy, safety and immunogenicity [1, 11].

The requirements for a biosimilar medicinal product are much higher and pharmacokinetic and pharmacodynamic studies also need to have data proving its safety and efficacy, due to the high complexity of this type of medicinal product.

A biosimilar medicinal product is a biological medicine containing a version of the active substance of a previously authorised "original" biological medicinal product, as it is the case with the reference medicinal product. The similarity to the reference medicinal product refers in terms of quality characteristics, biological activity, safety and efficacy, always based on a comprehensive comparability exercise that needs to be established in advance. In principle, the concept of similarity applies to the majority of biological medicinal product, and the development of a biosimilar will always depend on the ability to produce a medicinal product that is similar to the reference medicinal product and which demonstrates such similarity [1].

Thus, the demonstration of bioequivalence with the reference medicinal product, through appropriate bioavailability studies, applies to most chemically derived products, and this is not sufficient to demonstrate its similarity due to its complexity. This way, an approach based on a comprehensive comparability exercise should be followed, assessing the impact of changes in the manufacturing process of a biological medicinal product, as described in ICH Q5E. The applicability of this approach will always depend on the state of the art of analytical methods, manufacturing processes used, and the availability of clinical models to assess comparability [9].

This biosimilar approach is, however, more likely to be successfully applied to products that are highly purified and that can be fully characterised, as is the case with many biotechnology-derived medicinal products. For the active substance of a biosimilar, it should be similar in molecular and biological terms to the active substance of the reference medicinal product (*e.g.* for a substance which is a protein, the amino acid sequence is expected to be the same), the dosage and the route of administration should also be the same as the reference medicinal product. Obviously, all deviations from the reference product regarding strength, pharmaceutical form, formulation, excipients or presentation require justification, and, if necessary, additional data should be provided. However, any existing difference should never compromise security. The changes intended to improve efficacy (*e.g.* glycooptimization) are not compatible with this type of approach. However, any differences that may have an advantage with regard to safety should be addressed, never preventing similarity (*e.g.* for cases of low levels of impurities or lower immunogenicity). Finally, the biosimilar medicinal product must, concerning quality data, meet all the requirements for Module 3 [8].

For biosimilar medicines, it is essential to carry out extensive quality analysis and pre-clinically evaluate biosimilars. Thus, both the manufacturing process and the characterisation of critical quality attributes are described [12, 13].

As mentioned above, the amino acid sequence is exactly the same, differing in the biotechnological production aspect, hence the importance of demonstrating the comparability of quality attributes between the original and biosimilar biological medicine and also the impact on the efficacy and safety of the drug [14].

Overall, if we compare biosimilar medicines to both generic medicine and reference biological medicine, we come to several conclusions presented in the table below. The time to market is shorter for biosimilar medicines compared to reference medicines and much longer for biosimilar medicines comparing to generic medicines. The trials required by competent authorities on biosimilars are limited to comparative studies, as the information on the corresponding reference medicines already exists. As for the number of patients required for trials, this has also been reduced to approximately 500, compared to the reference ones. Finally, with regard to the post-marketing phase, the requirements are the same for biosimilars and reference medicines, as both require phase IV studies, and a risk management plan, including pharmacovigilance [1, 15].

Table 2 - *Comparison between the characteristics for the development of a generic, biosimilar vs reference biological product (Adapted) [1, 15].*

	TYPE OF DRUG		
	Generic	**Biosimilar**	**Reference**
Time to market (years)	2-3	7-8	8-10
Clinical Trials	Bioequivalence studies in healthy volunteers only. *Phase I:* not required *Phase II:* not required *Phase III:* not required	Comparative pharmacokinetic studies and phase III studies: *Phase I:* pharmacokinetic and pharmacodynamic studies *Phase II:* not necessary *Phase III:* in a representative indication ("sensitive")	Phase I-III efficacy and safety studies *Phase I:* full programme *Phase II:* in all indications *Phase III:* in all indications
Patients (n)	20-50	~500	800-1000
Post-marketing	Pharmacovigilance	Phase IV Risk Management Plan, including Pharmacovigilance	Phase IV Risk Management Plan, including Pharmacovigilance

CHAPTER 2

Development of Biosimilars

2.1. Development and Manufacture of Biosimilars Medicines

In terms of development, biosimilars cost about one hundred times higher than generic drugs, and the development period varies between seven to three years, as opposed to a period of two to four years for generic drugs.

The basis of the development of a biosimilar drug is thus an extensive structural and functional characterisation as well as the comparison of the biosimilar drug with the reference drug.

The development of a biosimilar medicine starts with defining the fingerprint of the reference medicine and its attributes and qualities. This makes it possible to define the limits of the potential variability of a biosimilar. Since the manufacturing process of the original molecule is not known, a new process must be developed to ensure that the biosimilar matches the fingerprint. Such a process requires that the cell culture and purification process conditions are continuously adjusted, investigating new cell lines throughout the development until the highest similarity is achieved. In the end, the potential biosimilar medicine can only enter clinical trials when the molecule is fully characterised, the process is well defined and the similarity between the molecules is effectively confirmed [7, 16, 17].

The development of biosimilars is quite complex, involving several steps, among them: selection of the cell line, cultivation and production, isolation and purification, and finally formulation, filling and finishing.

The first decision in the development of a biosimilar is about the **Cell Line Creation**, being such a decision important for the glycosylation patterns and the determination of the final profile of the biosimilar so that the protein of interest is expressed.

The relevant gene is then cloned into a complementary DNA vector, which may be human or microbial cell lines. Generally, the industry opts for Chinese hamster ovary cells for expression cells. This is because they have reliable folding, can grow in suspension, have a high yield and are stable to changes in pH and oxygen [18-21].

Then follows the clone selection, and the goal is to screen the clones in order to achieve the most similar product possible with the fingerprint [22]. It is important to mention that there are no two identical biologics because each product is produced using an exclusive cell line from the manufacturer [23, 24].

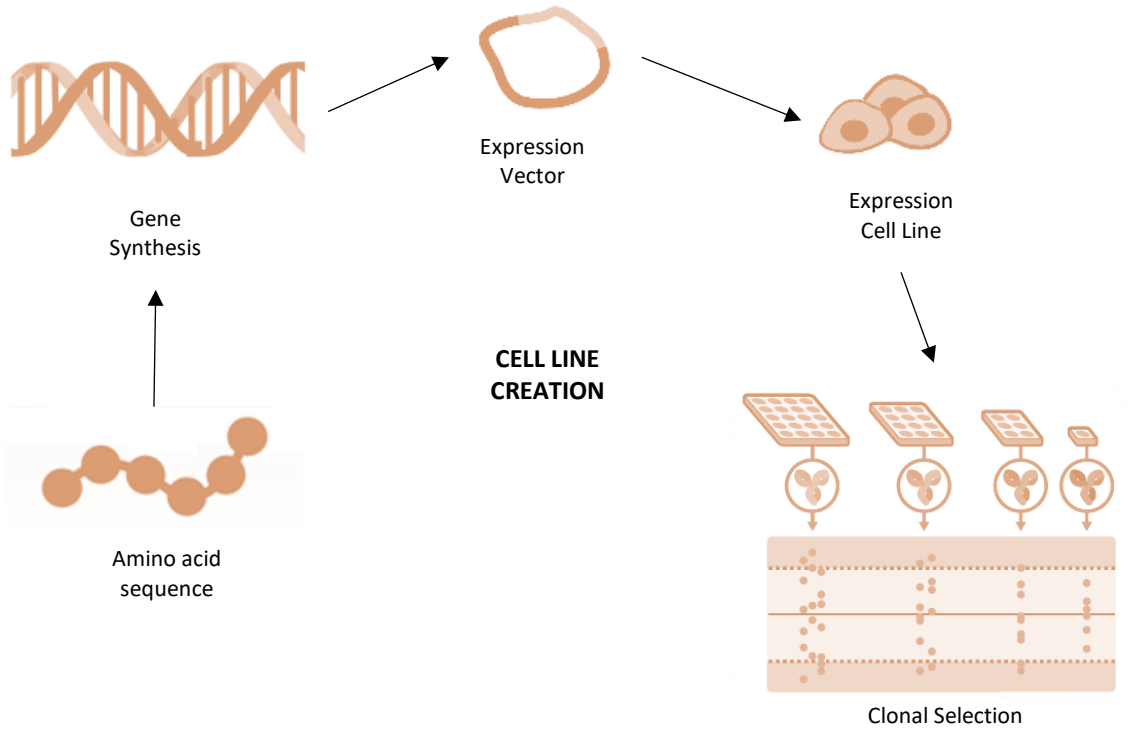


Figure 1 - *First step of development of a biosimilar: Cell Line Creation [25].*

Moving on to the second step in the development of a biosimilar - **Cultivation and Production** - the cell line that will produce the protein and originate the biosimilar medicine is expanded in a fermentation medium to obtain a batch of master cells, and these cells are then cultivated and produced in large-scale bioreactors [18, 19, 26, 27].

First, thawing of the cells occurs, followed by inoculation under agitation, increasing cell density. To ensure cell viability, the cells are maintained in a growth medium with nutrients and supplements [28].

Finally, it is also important to mention that throughout this process, parameters such as the amount of oxygen, lactate production, temperature, pH and osmolarity are controlled [24, 29].

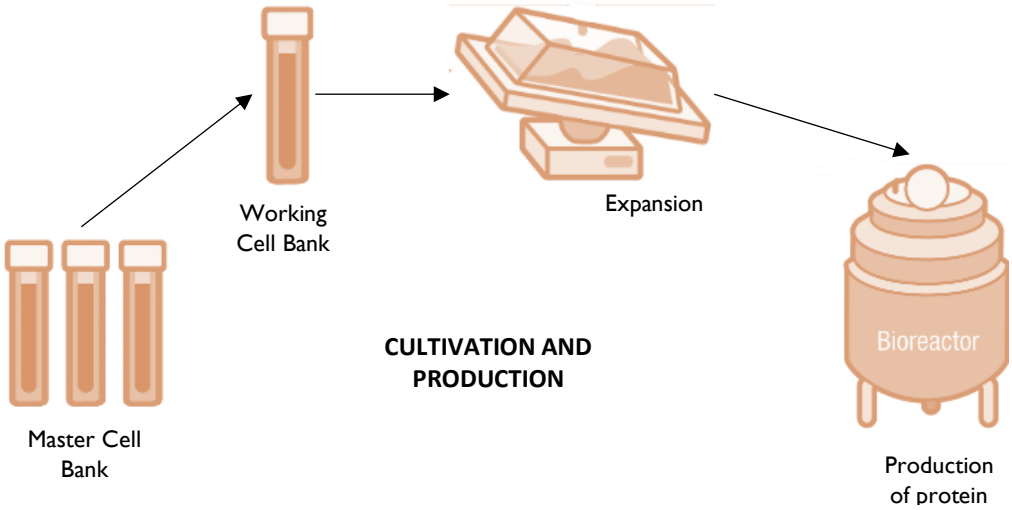


Figure 2 - *Second step of development of a biosimilar: Cultivation and Production [25].*

The third step consists of **Isolation and Purification** is intended to recover the target protein, discarding unwanted impurities, whether they are viruses, proteins, host cell DNA, aggregates or endotoxins [30].

At this stage, the protein of the biosimilar is excreted in the cell culture fluid by the mammalian cell, and it is necessary to recover it by removing cellular debris by centrifugation and filtration. In addition, cellular metabolites are also eliminated so that they do not generate immunogenicity [28].

Still, within the scope of purification, it is important to highlight that such a process depends on column chromatography and filtration to remove unwanted impurities, using the biochemical properties that are in favour of what is intended to be eliminated [31].

At this stage, the procedures are also constantly monitored, namely pH, conductivity and flow rate [24, 32].

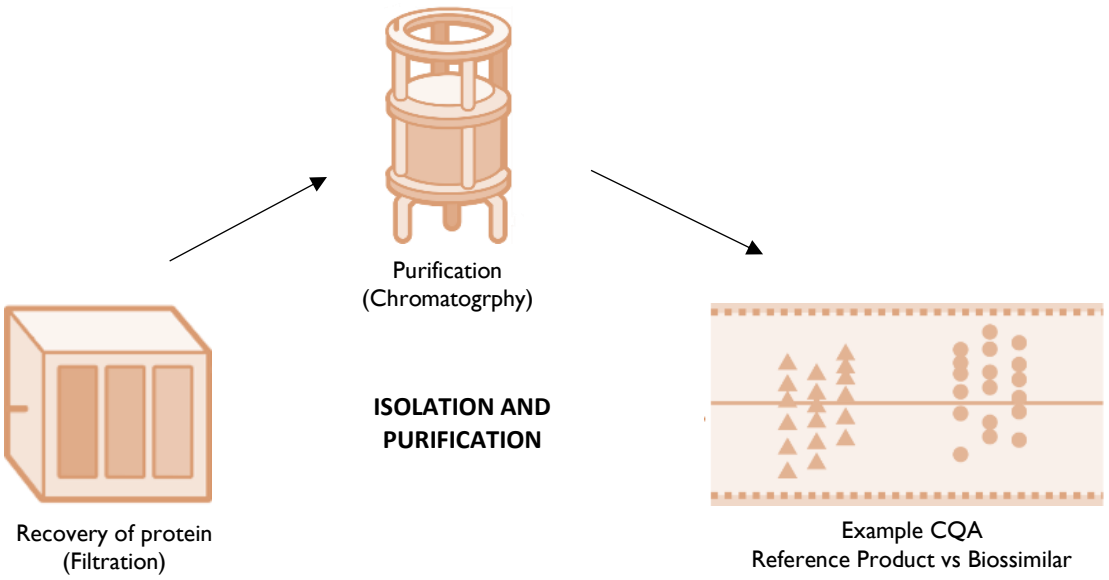


Figure 3 - *Third step of development of a biosimilar: Isolation and Purification [25].*

Finally, the last stage is concerning the following topics**: Formulation, Fill and Finish.**

The formulation of the product inevitably influences the mimicking of its degradation and the maximisation of its shelf-life, involving the optimisation of the buffer solution conditions, such as Ph, ionic strength, excipients and stabilisers [28].

Thus, the product in this phase is subject to specific conditions to assess its behaviour and stability, for example, subjecting the product to high levels of agitation or thermodynamic stress, such as high temperatures, freezing or thawing for long periods.

Concerning the final presentation of the drug, there are three possible forms: liquid, frozen liquid or lyophilised, with the preferred form being liquid, always depending on the stability of the product [7, 31].

Of course, in some cases, it may be necessary to freeze the product during storage in order to minimise chemical degradation. If, on the other hand, the lyophilised presentation is chosen, it requires some additional costs, as well as the need to use diluents for reconstitution.

If the frozen form is chosen, a cryoprotectant (*e.g.* sucrose) should be added to minimise cryoprecipitation or aggregation by cryoconcentration [24, 29].

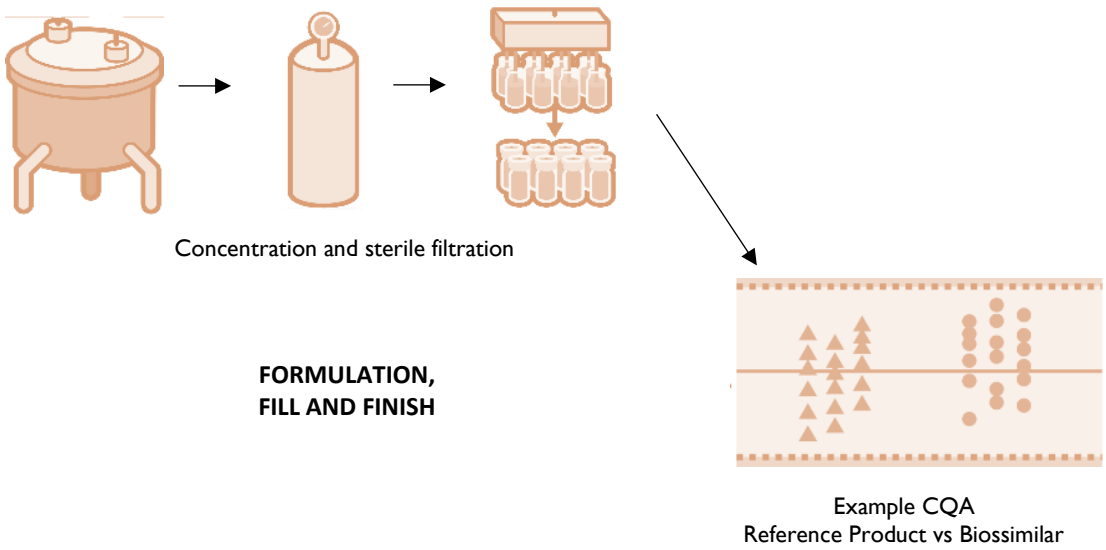


Figure 4 - *Fourth step of development of a biosimilar: Formulation, Fill and Finish [25].*

The manufacturer of the biosimilar medicine must develop the entire manufacturing process, from cell line selection to production. These activities are performed without full access to the development history of the reference medicine. Thus, the potential for differences between an innovative biological medicine and a biosimilar is necessarily greater than a biological medicine before and after the implementation of a change in its manufacturing. Therefore, any differences in safety/efficacy profile should always be justified. It should also be noted that modifications for the purpose of improving efficacy are not expected to be accepted, as distinct from the concept of a *biobetter*.

The comparative studies between the biosimilar biological medicine and the reference medicine include the criteria of quality, safety and efficacy, in order to demonstrate that the manufactured medicine is under the approved legislation [10].

Pharmaceutical quality then focuses on characterisation at the structural level, through physicochemical properties, which encompasses control and production standards and product preparation and processing. In addition, purity must also be controlled, so that it does not exceed the established limit. Other data concern the biological activity, the excipients and starting materials, the dosage and formulation, the control of the manufacturing process and the actual stability of the active substance and the final product [1].

2.1.1. Immunogenicity

In terms of immunogenicity, for example, proteins have an intrinsic ability to provoke an undesirable response. In rare cases, this response can cause a serious adverse reaction or even reduce efficacy, however, this type of reaction is very rare. This is because the immunogenicity itself is influenced by the characteristics of the drug and external factors related to the treatment or even related to the patient himself or the disease in particular [1, 33]. It is known that there are quality problems that affect immunogenicity, such as the introduction of new production methods, new formulations and new packaging, which can affect the characteristics of the drug and the content of impurities. But these changes should not affect the efficacy and safety of the medicine itself [34, 35].

It is very unlikely to occur a harmful immune response after the introduction of such a change, since comparability studies reveal whenever the batch obtained has the same quality, is free of impurities or aggregates, among others. In addition, regulatory authorities monitor the immunogenicity of biosimilar medicinal products [1]. This monitoring can be clarified through comparability between different batches and using physicochemical and structural analyses, allocated to functional *in vitro* assays [33, 36].

The immunogenicity data required for the approval of a biological medicinal product for approval purposes, includes the incidence, titration and persistence of antibodies against the biological medicinal product, neutralisation tests, clinical impact assessment and measures to manage the risk of immunogenic potential.

Nevertheless, these data always depend on the type of biological medicine and its intended use, the characteristics of the product itself. In this context, analyses of changes in the structure or variability of protein ("micro-heterogeneity"), In addition to these aspects, we highlight all previous knowledge about immunogenicity, namely the fact that for biological medicinal products, there is a prolonged follow-up of patients with intensive clinical monitoring and specific studies after authorisation [1, 37].

The new analytical and production technologies, which are used in the manufacturing process of biosimilars, guarantee a higher purity and quality than the reference medicines of their approval [1, 14].

2.1.2. Extrapolation

Extrapolation emerges as a perfectly consolidated scientific principle. The objective will be to assess where the biosimilar is highly similar to a reference medicinal product and has comparable safety and efficacy in a therapeutic indication, so that it is possible to extrapolate these data to other approved indications for the reference medicinal product. In practical terms, this means that in some situations few clinical studies with biosimilars may be carried out since this extrapolation is always supported by scientific evidence from comparability studies. At extrapolation, some criteria are distinguished: mechanism of action, relevant study population, different clinical contexts, safety data and immunogenicity data [1, 38].

Concerning the mechanism of action of the active substance, it should be mediated by the same receiver, and further studies may be needed to prove that the behaviour is similar. Depending on the clinical context, the mode of action, dosage or pharmacokinetics may be different, which means further studies will again be required as the data for a given indication is subsequently not applicable, at least from the direct outside. At this stage, it is essential to determine a safety profile that is comparable to a therapeutic indication and only after this time can the safety data be extrapolated. Finally, regarding immunogenicity data, this issue becomes more complex, since it is a specific criterion which always needs to be substantiated [1, 39].

2.1.3. Safety

About the safety of biosimilar medicinal products, there are several important considerations to be had in this context, from a sound regulatory framework, a risk management plan always in place, post-authorisation safety studies and continuous safety monitoring. In addition to these considerations, and knowing that most adverse drug reactions due to biosimilar medicinal products can be predicted from pharmacological action, it is always sought to spontaneously collect adverse drug reactions and subsequent presentation of periodic safety reports, as well as the existence of additional monitoring and long-term adverse events or with long latency periods [1].

The European Union has a consolidated system of monitoring, reporting, assessing and preventing adverse drug reactions, so the authorities continuously assess the risk-benefit ratio of all medicines and take the necessary measures. When an undertaking applies for the marketing authorisation, it shall submit a risk management plan including a pharmacovigilance plan, as well as any risk minimisation measures to identify, characterise and minimise risks. When talking about a Risk Management Plan (RMP) for a biosimilar medicine, it will always be based on the knowledge and experience already gained with the reference medicine. For post-authorisation studies, it has been made possible to monitor known risks and detect adverse drug reactions that only arise after a large number of patients receive treatment over a substantial time period. In addition, it is noteworthy that toxicity studies are used to carry out this safety assessment of biological medicinal products. The main mechanisms of adverse effects of biological drugs are related to exaggerated pharmacology. However, if comparable pharmacological activity has been established *in vitro*, there is no need to confirm these mechanistic properties *in vivo* [40].

However, examples of unexpected toxicity are scarce. Often, these functional differences between these antibodies have a structural basis based on variations in the amino acid sequence. These differences are not integrated into the development of similar biological medicines, because the amino acid sequence should be the same as that of the reference medicine [41].

Thus, although unexpected toxicity can be found in preclinical animal studies during the development of new biological medicinal products, it has never been shown that this may occur with biosimilars [14].

2.1.4. Comparability

The fundamental principle of developing a biosimilar is based on the comparability exercise that is carried out between the reference biological medicine and the biosimilar medicine.

For such a comparability exercise to be undertaken, comprehensive analyses of the proposed biosimilar and the reference product are required, using sensitive methods. Thus, the main objective is the demonstration that the biosimilar and the reference product are similar at a finished medicinal product level [10].

In this context, several important pillars arise when comparing the reference medicine and the biosimilar medicine: Target/Quality by Clinical Trial design, Quality (data set for stand-alone) Biological and Physicochemical Comparability, Comparative Pre-clinical Trials, Comparative Clinical Trials and a Risk Management Plan [11]. The comparability exercise is carried out in several steps, namely Quality Comparability, Non-Clinical Comparability and Clinical Comparability.

In the first step - **Quality Comparability** - a full characterisation approach needs to be undertaken to compare the physicochemical and biological quality attributes, for instance the purity of the potential biosimilar medicine. This is done using a wide range of different state-of-the-art analytical tests, as no single method can characterise all aspects of a product. The development process is also to be modified, if there are significant differences found in the analyses until the product generated has a profile that matches the reference product profile. Continuous modification at each stage of the development process so that the final biosimilar medicine corresponds to the quality of the reference medicine concerning all the criteria required by the European Medicines Agency when submitting the documentation for assessment and marketing authorisation.

Then, it is the second step - **Non-Clinical Comparability** - in which non-clinical studies, sometimes called pre-clinical studies, need to be conducted for biosimilar medicines before any clinical trial begins. Generally, non-clinical data for a biosimilar is generated through an abbreviated testing programme or *in vitro* animal studies, as required by the European Union guidelines. On the other hand, non-clinical studies usually include repeated dose toxicity studies as well as pharmacokinetic and pharmacodynamic (PK/PD) studies along with local tolerance testing. For this type of study, similarity criteria should be pre-defined and scientifically justified in order to allow comparability of the support with the reference and detect potential differences between them.

Finally, it comes the third step - **Clinical Comparability** - clinical tests are also considered comparative in the case of the development of a biosimilar medicinal product. However, such clinical tests are not required to the same extent as would be necessary for a new active substance, taking into account the clinical experience gained from the use of the reference medicinal product. Therefore, it is crucial to consider the nature and characteristics of the medicinal product as well as the therapeutic indications. Another key aspect is to understand how comparable the profile of the biosimilar is to that of the reference product. The closer the biosimilar and reference profiles are, and the greater the similarity demonstrated (through appropriate studies such as comparative quality, biological and receptor binding activity analyses, and animal testing), the more easily the clinical trial programme will be accepted by the Regulatory Authorities.

In summary, the clinical comparability exercise starts with pharmacokinetic and/or pharmacodynamic studies, and comparative clinical efficacy and safety trials may still follow. An important step is also to present the side effects, not least because the evaluation of immunogenicity comparable profiles for the biosimilar and the reference are also encompassed in the clinical safety data [42, 43]. In addition to the comparability of the quality attributes of two medicines, the similarity of the biological activity and safety of the biosimilar should be determined using *in vitro* assays that are relevant and sensitive to identify pertinent differences in allosteric mechanisms between the two medicines and for all approved indications, as presented in Table 3 [44].

Table 3 *- Critical Attributes of Quality and Similarity's demonstration products [14, 44].*

Critical Attributes of Quality	Similarity Demonstration
Protein structure and production quality	Extensive laboratory analysis for all molecular characteristics (multiple lots)
Pharmacokinetics, Pharmacodynamics and Animal Toxicity	*In vitro* and *in vivo* assays (carried out on relevant animal species, if further confirmation scans are required for laboratory studies)
Pharmacokinetics, Pharmacodynamics and Animal Toxicity	Phase I clinical studies
Clinical Efficacy and Safety	Phase III clinical studies
Safety in clinical practice	Risk management plan Phase IV studies Pharmacovigilance

2.1.5. Interchangeability

The term interchangeability emerged in the context of the possibility of exchanging a reference biological medicine for its biosimilar, or a biosimilar for another biosimilar, hoping to obtain the same therapeutic effect produced by the option initially used [1, 45].

This exchange can occur in two distinct ways: "switch" or (automatic) substitution. As for the "switch" option, this occurs when the prescribing physician decides to exchange one medicine for another that has the same therapeutic purpose. Automatic substitution, on the other hand, refers to a practice carried out at the pharmacy level without consulting the prescribing physician, where the dispensing of the prescribed drug is changed by another equivalent and interchangeable drug [1, 11].

These issues have been the subject of some controversy, despite the existence of several studies that prove the safety and effectiveness of this practice [46].

So what is the EMA's position on the issue of switching the biosimilar as a reference medicine? Well, the EMA leaves the deliberation to each Member State. In Portugal's case, this decision is taken by INFARMED I.P., which, in collaboration with the National Pharmacy and Therapeutics Commission, provides for the therapeutic switch to take place only after a minimum time to ensure the traceability of the medicine. This information will be available in the National Medicines Formulary, otherwise, it should never be less than six months. On the other hand, automatic substitution is not currently provided for in Portugal [1, 47, 48].

CHAPTER 3

Regulatory Framework for the Development of Biosimilars

The marketing authorisation for biosimilar medicinal products, via EMA, is obtained through a centralised procedure, in which the EMA evaluates the medicinal products for the purpose of authorising their marketing. Comparative characteristics studies evaluate the composition, physical properties, protein structures, purity, isoforms or impurities that derive from the product, as well as biological activity. The production process between the reference biological drug and the biosimilar may, however, present differences. Although biosimilars in the European Union are therapeutic equivalents, their substitution policy and their exchangeability are decisions taken at the national level outside the EMA's remit [6, 49].

3.1. European Medicines Agency

All biotechnologically produced medicinal products are approved in the European Union by the European Medicines Agency through the centralised procedure. There are certainly some biosimilars, such as low molecular weight heparins obtained from the swine intestinal mucosa, which are approved at the national level, however, mostly, and since they resort to biotechnology for production, are approved by the centralized procedure.

First, the entity submits the marketing authorisation application to the EMA. The data are then evaluated by the scientific committees, the Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC), as well as by experts in biological medicinal products and biosimilar specialists. Subsequently, this analysis gives rise to a scientific opinion sent to the European Commission. If applicable, it is for the EC to grant marketing authorisation in the European Union and is valid in all EU Member States [1].

The European Medicines Agency (EMA) was the first organisation to delineate a specific regulatory route for biosimilar medicines - this happened in October 2005. EMA guidelines state that the approval of biosimilars is based on comparability studies, through the characterisation of the protein structure of the biosimilar, as well as its efficacy, safety and immunogenicity. In addition to these aspects, it is considered essential to carry out *in vitro* tests, impurity profile analyses, pharmacokinetic and pharmacodynamic studies, as well as pharmacovigilance monitoring after its approval on the market [50].

There are several important requirements according to the Agency, including the importance of demonstrating robustness and consistency in its manufacturing design, as well as details for additional non-clinical and clinical studies to attest to comparability.

A key point highlighted by EMA is that the clinical benefit has already been proven by the innovative product, so the goal of a biosimilar is to demonstrate similarity to the innovative product, in terms of strength, active substance, route of administration and pharmaceutical form, and not the clinical benefit itself.

In order to compile all legislation concerning biological medicines, the European Medicines Agency has adopted several more individualised guidelines for each type of biosimilar medicine. The general guidelines include the Guideline on Similar Biological Medicinal Products, the Guideline on Similar Biological Medicinal Products containing Biotechnology-derived Proteins as Active Substances: Quality Issues and the Guideline on Similar Biological Medicinal Products containing Biotechnology-derived Proteins as Active Substances: Clinical and Non-clinical Issues [4, 8-10, 33].

In addition, EMA has also developed more specific guidelines: Guideline on biosimilar medicines containing recombinant granulocyte colony-stimulating factor, Guideline on clinical and non-clinical development of similar medicines containing low molecular weight heparins, Guideline on clinical and non-clinical development of similar medicines containing recombinant human insulin and insulin analogue, Guideline on clinical and non-clinical development of similar medicines containing beta interferon, Guideline on clinical and non-clinical development of similar medicines containing monoclonal antibodies: Ethical and non-clinical issues, Guideline on clinical and non-clinical development of similar medicines containing recombinant erythropoietin, Guideline on clinical and non-clinical development of similar medicines containing recombinant follicle - stimulating hormone and Guideline on clinical and non-clinical development of similar medicines containing somatropi. [4, 8-10, 33].

Finally, two other relevant guidelines on Comparability of biotechnology-derived medicinal products after a change in manufacturing process: clinical and non-clinical issues and another one on ICH Q5E biological/biotechnology products subject to changes in their manufacturing processes: comparability of biological/biotechnology products [4, 8-10, 33].

Table 4 - *European Guidelines for the Development and Evaluation of Biosimilar Medicines [51]*

Type of Guideline	*Guideline Title*
General	Guideline on Similar Biological Medicinal Products.
	Guideline on Similar Biological Medicinal Products containing Biotechnology-derived Proteins as Active Substances: Quality Issues.
	Guideline on Similar Biological Medicinal Products containing Biotechnology-derived Proteins as Active Substances: Clinical and Non-clinical Issues.
Specific	Guideline on biosimilar medicines containing recombinant granulocyte colony-stimulating factor.
	Guideline on clinical and non-clinical development of similar medicines containing low molecular weight heparins.
	Guideline on clinical and non-clinical development of similar medicines containing recombinant human insulin and insulin analogue.
	Guideline on clinical and non-clinical development of similar medicines containing beta interferon.
	Guideline on clinical and non-clinical development of similar medicines containing monoclonal antibodies: Ethical and non-clinical issues.
	Guideline on clinical and non-clinical development of similar medicines containing recombinant erythropoietin.
	Guideline on clinical and non-clinical development of similar medicines containing the recombinant follicle-stimulating hormone.
	Guideline on clinical and non-clinical development of similar medicines containing somatropin.
Others	Comparability of biotechnology-derived medicinal products after a change in manufacturing process: clinical and non-clinical issues.
	ICH Q5E biological/biotechnology products subject to changes in their manufacturing processes: comparability of biological/biotechnology products.

3.2. Food and Drug Administration

In the United States, the creation of guidelines for biosimilars did not happen as early as in the European Union. Only more recently has the PGA begun to develop specific guidelines for the approval process for biosimilar drugs. At the level of important factors to consider at the time of the FDA approval process, it is highlighted the need for robustness in the manufacturing process, the similarity of the protein structure, the extent of understanding of the mechanism of action, appropriate pharmacodynamics trials, comparative pharmacokinetic data, immunogenicity data and clinical data regarding the innovative product [50].

In the initial phase, the biosimilar medicinal product entity presents a series of data comparing the candidate medicinal product with the reference medicinal product in order to demonstrate similarity. First, the data is evaluated, starting with detailed analytical characterisation, at the structural and functional level, as well as a comparison, moving to animal studies and, if necessary, comparative clinical studies [22].

The submission of a biosimilar medicinal product shall include some data to demonstrate such similarity with the reference medicinal product, from analytical studies demonstrating that the biosimilar medicinal product is highly similar to the reference medicinal product to toxicity assessment studies. Another aspect refers to a clinical study to demonstrate the safety, purity and potency of the proposed biosimilar product in one or more of the indications for which the reference product is licensed. This typically includes the evaluation of immunogenicity, pharmacokinetics (PK), and, in some cases, pharmacodynamics (PD) and may also include a comparative clinical study [52].

More practically, the application for Marketing Authorisation is made to the FDA and submitted through section 351 (k) of the Public Health Service Act (PHS). This section allows the biosimilar medicinal product to be approved for all therapeutic indications of the reference medicinal product,

This happens several times when discussing the speed of the drug approval process in the United States. This situation is due to the fact that, in 2010, a change was made to the Biologics Price Competition and Innovation Act, enabling the existence of a shortened route for the regulation of biosimilar drugs in the USA. However, it is important to point out that such a change does not diminish the required standards of safety, purity and efficacy.

As with EMA, FDA requires a rigid, sequential approach with rigorous comparability tests, from physical-chemical, analytical, functional, and non-clinical and clinical assessments.

In 2014, the Purple Book was published by FDA, where reference drugs and corresponding biosimilars are found, presenting the medicines authorised for commercialisation in the USA [53, 54].

In 2015, FDA published three guidelines, granting industry guidelines for the development of biosimilar drugs. These include scientific assessments in the demonstration of similarity, considerations about the quality for the demonstration of similarity with the reference medicinal product and a set of questions and answers on the evaluation of the drugs in question [20].

In 2018, the FDA's Biosimilar Action Plan (BAP) was published, providing information regarding actions to stimulate the development of biosimilars. Briefly, the BAP analyses the phases so that development and approval are more effective, clarifying regulation and developing support materials for healthcare professionals and patients to demystify the issue and increase confidence. Nevertheless, the BAP does not address issues related to improvements in pharmacovigilance [53, 55].

Table 5 summarises the key criteria for developing a biosimilar medicine through FDA legislation. FDA's determination of similarity is based on the totality of evidence provided in the marketing application for FDA review. The data set in the marketing application includes extensive analytical comparison to show that the proposed biosimilar and the reference products are extremely similar in structure and function. Animal, human pharmacological, immunological and other data are added as needed to the analytical data in a stepwise manner to provide the necessary information with the ultimate goal of demonstrating similarity.

Table 5 - FDA's development of a biosimilar medicine.

Highly Similar

Analytical Studies	Assess a set of q\uality characteristics, using state-of-the-art technologies and multiple different tests for the same characteristic, to determine whether the proposed biosimilar is highly similar to the reference product. Identify differences in quality characteristics, if any, between the reference product and the proposed biosimilar (examples of quality characteristics include structure and bioactivity. Thoroughly assess the potential impact of any differences observed.
Assessment of Toxicity	
Animal Studies	Support safety decision-making before human exposure to the proposed biosimilar. Provide additional support to demonstrate similarity (but not always necessary).
No Clinically Meaningful Differences	
Human PK and PD studies	Compare the pharmacokinetics (exposure) and, if applicable, the pharmacodynamic (response) profiles of the proposed reference and biosimilar product to support a conclusion of similar efficacy and safety. Consider the most sensitive data element to support a demonstration of no clinically meaningful differences.
Immunogenicity Assessment	Compare the incidence and severity of immune responses generated with the reference product and the proposed biosimilar. Include as part of all clinical studies.
Additional Clinical Studies	Consider only when residual uncertainties remain about demonstrating that there are no clinically meaningful differences after conducting the above-mentioned studies.

FDA advice on the scope and extent of testing during development

The totality of the Evidence

3.3. Other Regulatory Authorities

Besides the European Medicines Agency and the Food Drug Administration, there are other Regulatory Agencies also responsible for the evaluation and monitoring of medicines submitted for marketing authorisation.

In **Japan**, the Pharmaceuticals and Medical Devices Agency (PMDA), in particular, the 'Office for Cell and Tissue-Based Products', stands out as the organisation responsible for the assessment, regulation and authorisation of biosimilar medicines, dealing with a wide range of activities, from approval reviews to post-authorisation surveillance. The Japanese regulation is based on European legislation and therefore bears a strong resemblance to the binding model of the EMA. The PMDA also highlights the need to conduct clinical trials in order to demonstrate clinical comparability between the biosimilar medicine and the reference medicine. Nevertheless, sometimes conducting comparative studies on pharmacokinetics and pharmacodynamics can be considered sufficient to demonstrate clinical comparability, and no further clinical trials are required. [56, 57] Another debated point from Japan concerns extrapolation, and this can be carried out for all therapeutic indications of the reference medicinal product, provided that equivalent therapeutic effects and clinical comparability are demonstrated [58, 59].

Regarding the **Middle East** market, the emergence of biosimilar medicines has allowed such medicines to reach other countries characterised by a high percentage of poverty, avoiding the poor quality imitations that are so typical of these regions. [39]. The Central Drug Standard Control Organization is the organisation responsible for medicines in India, and its mission is to ensure that all procedures are reliably controlled. Under Indian law, a biosimilar medicine can be approved faster if its reference medicine is approved in the European Union or the United States of America. For example, a biosimilar can be approved with phase III bioequivalence studies with about 100 patients, while EMA requires much more, up to 500. A major peculiarity of the Indian legislation is the lack of market exclusivity for products that are approved for the first time. In these cases, this exclusivity relates only to the patent, plus the fact that the patent is less developed and therefore considered a lower barrier [58, 60].

In **Canada**, the drug approval process is handled by the Biologics and Gene Therapies Directorate (BGTD) of the Health Products and Food Branch (HPFB) of Health Canada. Currently, there are specific guidelines for biosimilar medicines prepared by Health Canada to have more authoritative legislation. The first biosimilar drug approved in Canada was a growth hormone, through Sandoz, called: OMNITROPE, in 2009 [61, 62].

In **South America**, regulatory guidelines follow the EMA and FDA models, with some particularities certainly.

For the registration of biosimilars in Venezuela, the National Institute of Hygiene Rafael Rangel is used, which is based on the generation of information on biosimilarity in terms of quality, safety and efficacy of the reference medicine. It should be noted that extrapolation to use indications is not allowed, so individualised/separate information is generated [49, 63].

The *Instituto Nacional de Vigilancia de Medicamentos y Alimentos* is the Regulatory Authority in Colombia and it is responsible for the inspection and supervision of the marketing and development of health products, as well as the identification and evaluation of sanitary standards and procedures, among others [48].

In Brazil, according to the Brazilian legislation, the National Health Surveillance Agency, the registration of biosimilars is done after the submission of comparative studies between the biosimilar and the reference medicine that confirm the quality, efficacy and safety requirements. When a biosimilar drug is in the approval stage, extensive pre-clinical documentation is required, which should show such points of similarity, ensuring its criteria and attributes [47, 64].

In Chile, the responsible regulatory agency is *El Departamento Agencia Nacional de Medicamentos*, and concerning biosimilars, this is still a developing country in terms of the regulation inherent to them [50].

Argentina's regulatory agency is called *La Administración Nacional de Medicamentos, Alimentos y Tecnología*, and it is governed by the guidelines of the European Union model [65].

The Center for Drug and Food Evaluation of the **China** Drug Administration issued guidelines on "similar biologics" on 28 February 2015. According to the Chinese guidelines, a similar biologic is a "therapeutic biologic" similar to an authorised reference product in terms of quality, safety and efficacy. Regarding clinical trials, the Chinese guidelines suggest that clinical trials for "similar biologics" should start with PK and PD studies based on which clinical efficacy and safety studies should be conducted. Comparability between the similar biological product and the reference product may be done for quality assessment and non-clinical studies based on PK, PD and PK/PD clinical studies. The Chinese guidelines suggest that the assessment of clinical immunogenicity should be based on the results of non-clinical immunogenicity assessment. Where such studies suggest the similarity of the similar biological product to the reference product, then only limited clinical evaluation is required. The approval of "similar biological products" has not been assigned to a separate abbreviated approval route. The approval pathways are subject to the same pathways that apply to innovative biological products. In addition, for the reference product, the Chinese authorities require the product to be approved in China. Reference products approved by foreign regulatory authorities and not approved in China are not acceptable as reference products [52, 53].

The Ministry of Food and Drug Safety (MFDS) of the Government of **South Korea**, through its National Institute for Food and Drug Safety Evaluation, seeks to scientifically evaluate drugs developed by South Korea's pharmaceutical industries. Of note, the national guidelines were based on those of the World Health Organization, the European Union and Japan. [51].

Some countries in **Asia** do not have their own Agency a focus on the evaluation of biosimilar medicines, hence the Association of Southeast Asian Nations (ASEAN) emerged which represents 10 member states in the ASEAN region including Indonesia, Malaysia, Thailand, Philippines, Singapore, Darussalam, Vietnam, Laos, Myanmar and Cambodia. In this sense, it is through this Association, that many decisions of scientific, political, and economic, among others, are taken in order to have an important role in this region [66].

CHAPTER 4

Pharmaceutical Market for Biosimilars

The market for biosimilar medicines is constantly growing, as, over the decades, several biological molecules enter the market, constituting new therapeutic approaches for patients in other therapeutic areas.

4.1. Pharmaceutical Market for Biosimilars: An European Perspective

Sixty-nine biosimilars have already been approved in the European Union, of which 18 belong to the pharmacotherapeutic group of antineoplastic agents, 1 anticoagulant, 17 immunosuppressants, 5 anti-anaemic preparations, 4 calcium homeostasis, 1 pituitary and hypothalamic hormone and analogue, 2 sex hormones and modulators of the genital system, 5 drugs used in diabetes, 1 ophthalmological and 15 immune stimulants.

Antineoplastic agents are used in the treatment of cancer, either alone or in combination with other drugs or treatments. Anticoagulant agents, on the other hand, are used in the prevention or treatment of thrombosis, pulmonary embolism, stroke, heart attack or cardiac arrhythmias, for example, by preventing the formation of blood clots. Anti-anaemic preparations, on the other hand, which, as the name indicates, are effective in preventing or correcting anaemia, since they have particularities that help in this area. Anti-anaemic drugs act on the concentration of red blood cells in the blood, increasing haemoglobin.

Medications associated with calcium homeostasis refer to the maintenance of a constant concentration of calcium ions in the extracellular fluid and this is important for nerve transmission, nerve conduction, muscle contraction, cardiac contractility, blood coagulation, bone formation, excitation-secretion coupling, adhesion, and cell communication. Regarding pituitary and hypothalamic hormones and their analogues, they play a fundamental role in maintaining homeostasis in the human body and are crucial for growth, metabolism and reproduction [67, 68].

Another pharmacotherapeutic class refers to sex hormones that interact as modulators of the onset of autoimmune disease, being generally implicated as enhancers of humoral immunity (with oestrogens) and as natural immunosuppressants (with androgens and progesterone). Thus, it may play an active role in cell proliferation in the context of autoimmunity [69].

With regard to drugs acting in Diabetes, as indicated, such drugs will act in the treatment of Diabetes, and the insulin preparations used are proteins manufactured using recombinant DNA technology and formulated as biological products, helping to regulate blood glucose [70, 71].

Finally, of all the therapeutic indications, immunosuppressants that act on the immune system stand out, as these agents are able to delay or stop the response to attack healthy cells and tissues. In this way, immunosuppressants help prevent cell damage and inflammation. This is the class we will look at in more detail in this chapter [72].

In Table 6 it can be seen that the biosimilar medicines approved in the European Union and their most relevant characteristics, from the active substance, the associated reference medicine, and the pharmacotherapeutic group to which each medicine belongs.

The first biosimilar medicine approved by the European Medicines Agency was Omnitrope, whose active substance is somatropin, which was approved in 2006 and belongs to the group of hypothalamic and pituitary hormones. The most recent biosimilar medicine approved was in March 2022, called Ziextenzo, whose reference medicine is Neulasta, with the active substance pegfilgrastim, belonging to the group of immunostimulants.

Through Table 7 and 8, all the dates of the market authorisations granted to each of the previous biosimilars can be analysed, as well as the company holding the biosimilar.

Table 6 - *Biosimilars approved by EMA and its Pharmacotherapeutic Group (Information taken from EMA).*

Name of the reference medicine	Biosimilar		Pharmacotherapeutic Group
Avastin (bevacizumab)	Mvasi Zirabev Onbevzi Oyavas	Aybintio Alymsys Abevmy	Antineoplastic agents
Clexane (enoxaparin sodium)	Inhixa		Antithrombotic agents
Enbrel (etanercept)	Benepali Erelzi Nepexto		Immunosuppressants
Eprex/Erypo (epoetin alfa)	Epoetin Alfa Hexal Binocrit Abseamed		Antianemic preparations
Eprex/Erypo (epoetin zeta)	Silapo Retacrit		
Forsteo (teriparatide)	Terrosa Movymia Livogiva Sondelbay		Calcium homeostasis
Genotropin (somatropin)	Omnitrope		Pituitary and hypothalamic hormones and analogues
GONAL-f (follitropin alfa)	Ovaleap Bemfola		Sex hormones and modulators of the genital system
Herceptin (trastuzumab)	Ontruzant Herzuma Kanjinti	Trazimera Ogivri Zercepac	Antineoplastic agents
Humanlog (insulin lispo)	Insulin lispro Sanofi		Drugs used in diabetes
Humira (adalimumab)	Imraldi Hefiya Hyrimoz Hulio Idacio	Yuflyma Libmyris Hukyndra Amgevita Amsparity	Immunosuppressants
Lantus (insulin glargine)	Abasaglar (previously Abasria) Semglee		Drugs used in diabetes
Lucentis (ranibizumab)	Byooviz		Ophthalmologicals
MabThera (rituximab)	Truxima Rixathon Riximyo	Blitzima Ruxience	Antineoplastic agents
Neulasta (pegfilgrastim)	Cegfila (previously Pegfilgrastim Mundipharma) Pelgraz Fulphila	Pelmeg Ziextenzo Grasustek Nyvepria Stimufend	Immunostimulants
Neupogen (filgrastim)	Ratiograstim Calcium homeostasis Filgrastim Hexal	Zarzio Nivestim Grastofil Accofil	Immunostimulants
NovoRapid (insulin aspart)	Insulin aspart Sanofi Kirsty (previously Kixelle)		Drugs used in diabetes
Remicade (infliximab)	Inflectra Remsima Flixabi Zessly		Immunosuppressants

Table 7 - *Marketing Authorisation for each Biosimilar (Information taken from EMA).*

Name of the reference medicine	**Biosimilar**	**Marketing-authorisation holder**	**Date of Marketing Authorisation**
Avastin | bevacizumab	Mvasi	Amgen Technology (Ireland) UC	24/08/2017
	Zirabev	Pfizer Europe MA EEIG	26/07/2018
	Onbevzi	Samsung Bioepis NL B.V.	26/07/2018
	Oyavas	STADA Arzneimittel AG	17/09/2018
	Aybintio	Samsung Bioepis NL B.V.	02/04/2019
	Alymsys	Mabxience Research SL	11/02/2021
	Abevmy	Mylan IRE Healthcare Limited	12/11/2021
Clexane | enoxaparin sodium	Inhixa	Techdow Pharma Netherlands B.V.	09/09/2014
Enbrel | etanercept	Benepali	Samsung Bioepis NL B.V.	15/11/2021
	Erelzi	Sandoz GmbH	21/03/2017
	Nepexto	Mylan IRE Healthcare Limited	13/02/2020
Eprex/Erypo | epoetin alfa	Epoetin Alfa Hexal	Hexal AG	15/01/2018
	Binocrit	Sandoz GmbH	14/02/2019
	Abseamed	Medice Arzneimittel Pütter GmbH Co. KG	11/01/2021
Eprex/Erypo | epoetin zeta	Retacrit	Pfizer Europe MA EEIG	26/03/2021
	Silapo	Stada Arzneimittel AG	19/08/2020
Forsteo | teriparatide	Terrosa	Gedeon Richter Plc.	26/03/2021
	Movymia	STADA Arzneimittel AG	21/04/2021
	Livogiva	Theramex Ireland Limited	15/09/2016
	Sondelbay	Accord Healthcare S.L.U.	27/08/2007
Genotropin | somatropin	Omnitrope	Sandoz GmbH	28/08/2006
GONAL-f | follitropin alfa	Ovaleap	Theramex Ireland Limited	27/08/2007
	Bemfola	Gedeon Richter Plc.	18/12/2007
Herceptin | trastuzumab	Ontruzant	Samsung Bioepis NL B.V.	18/12/2007
	Herzuma	Celltrion Healthcare Hungary Kft.	13/01/2016
	Kanjinti	Amgen Europe BV	23/06/2017
	Trazimera	Pfizer Europe MA EEIG	20/05/2020
	Ogivri	Viatris Limited	15/09/2008
	Zercepac	Accord Healthcare S.L.U.	15/09/2008
Humanlog | insulin lispo	Insulin lispro Sanofi	Sanofi-aventis groupe	06/02/2009

Table 8 - *Marketing Authorisation for each Biosimilar (Information taken from EMA - continuation).*

Name of the reference medicine	**Biosimilar**	**Marketing-authorisation holder**	**Date of Marketing Authorisation**
Humira | adalimumab	Imraldi	Samsung Bioepis NL B.V.	06/02/2009
	Hefiya	Sandoz GmbH	07/06/2010
	Hyrimoz	Sandoz GmbH	17/10/2013
	Hulio	Viatris Limited	17/09/2014
	Idacio	Fresenius Kabi Deutschland GmbH	27/09/2013
	Yuflyma	Celltrion Healthcare Hungary Kft.	26/03/2014
	Libmyris	Stada Arzneimittel AG	10/09/2013
	Hukyndra	Stada Arzneimittel AG	10/09/2013
	Amgevita	Amgen Europe B.V.	26/05/2016
	Amsparity	Pfizer Europe MA EEIG	18/05/2018
Lantus | insulin glargine	Abasaglar (previously Abasria)	Eli Lilly Nederland B.V.	25/06/2020
	Semglee	Viatris Limited	05/02/2021
Lucentis | ranibizumab	Byooviz	Samsung Bioepis NL B.V.	23/03/2018
MabThera | rituximab	Truxima	Celltrion Healthcare Hungary Kft.	19/07/2017
	Rixathon	Sandoz GmbH	21/09/2018
	Riximyo	Sandoz GmbH	20/11/2018
	Blitzima	Celltrion Healthcare Hungary Kft.	20/11/2018
	Ruxience	Pfizer Europe MA EEIG	22/11/2018
Neulasta | pegfilgrastim	Pelgraz	Accord Healthcare S.L.U.	20/06/2019
	Fulphila	Mylan S.A.S | Viatris Limited	19/12/2019
	Pelmeg	Mundipharma Corporation (Ireland) Limited	18/11/2020
	Ziextenzo	Sandoz GmbH	28/03/2022
	Grasustek	Juta Pharma GmbH	18/08/2021
	Cegfila (previously Pegfilgrastim Mundipharma)	Mundipharma Corporation (Ireland) Limited	17/02/2017
	Nyvepria	Pfizer Europe MA EEIG	15/06/2017
	Stimufend	Fresenius Kabi Deutschland GmbH	15/06/2017
Neupogen | filgrastim	Ratiograstim	Ratiopharm GmbH	13/07/2017
	Calcium homeostasis	Teva GmbH	01/04/2020
	Filgrastim Hexal	Hexal AG	12/04/2006
	Zarzio	Sandoz GmbH	04/01/2017
	Nivestim	Pfizer Europe MA EEIG	11/01/2017
	Grastofil	Accord Healthcare S.L.U.	27/08/2020
	Accofil	Accord Healthcare S.L.U.	24/03/2022
NovoRapid | insulin aspart	Insulin aspart Sanofi	Sanofi-aventis groupe	15/11/2017
	Kirsty (previously Kixelle)	Mylan Ireland Limited	09/02/2018
Remicade | infliximab	Inflectra	Pfizer Europe MA EEIG	16/05/2018
	Remsima	Celltrion Healthcare Hungary Kft.	26/07/2018
	Flixabi	Samsung Bioepis NL B.V.	12/12/2018
	Zessly	Sandoz GmbH	27/07/2020

4.2. Pharmaceutical Market for Biosimilars: An American Perspective

Regarding what happens in the United States of America, the American Agency has so far approved 36 biosimilars, of which 11 belong to the pharmacotherapeutic group of antineoplastic agents, 13 immunosuppressants, 1 anti-anaemic preparation, 2 drugs used in Diabetes, 1 ophthalmologic, 8 immune stimulants.

In the case of the Food Drug Administration, the first approved drug was more recently in 2015 - Zarxio, whose active substance is filgrastim and belongs to the group of immunostimulants and has "Neupogen" as a reference drug.

The following Table 9 illustrates the American market, presenting those biosimilar medicines approved in the market, including the associated reference medicine, the active substance and also the pharmacotherapeutic group to which they belong. In Table 10, all the information about the marketing authorisation data of each biosimilar is referenced.

Table 9 - Biosimilars approved by FDA and its Pharmacotherapeutic Group (information taken from FDA).

Name of the reference medicine	Biosimilar	Pharmacotherapeutic Group
Avastin | bevacizumab	Alymsys Mvasi Zirabev	Antineoplastic agents
Enbrel | etanercept	Erelzi Eticovo	Immunosuppressants
Procrit | epoetin alfa	Retacrit	Antianemic preparations
Herceptin | trastuzumab	Herzuma Kanjinti Ogivri Ontruzant Trazimera	Antineoplastic agents
Humira | adalimumab	Abrilada Amjevita Cyltezo Hadlima Hulio Hyrimoz Yusimry	Immunosuppressants
Lantus | insulin glargine	Rezvoglar Semglee	Drugs used in diabetes
Lucentis | ranibizumab	Byooviz	Ophthalmologicals
Rituxan | rituximab	Riabni Ruxience Truxima	Antineoplastic agents
Neulasta | pegfilgrastim	Fulphila Fylnetra Nyvepria Udencya Ziextenzo	Immunostimulants
Neupogen | filgrastim	Nivestym Releuko Zarxio	
Remicade | infliximab	Avsola Inflectra Ixifi Renflexis	**Immunosuppressants**

Table 80 - *Marketing Authorisation for each Biosimilar (Information taken from FDA).*

Name of the reference medicine	Biosimilar	Marketing-authorisation holder	Date of Marketing Authorisation
Avastin | bevacizumab	Alymsys	Amneal Pharmaceuticals LLC	13/04/2022
	Mvasi	Amgen	14/09/2017
	Zirabev	Pfizer	27/06/2019
Enbrel | etanercept	Erelzi	Sandoz	30/08/2016
	Eticovo	Samsung Bioepis	25/04/2019
Procrit | epoetin alfa	Retacrit	Pfizer (Hospira)	15/05/2018
Herceptin | trastuzumab	Herzuma	CELLTRION	14/12/2018
	Kanjinti	Amgen	13/06/2019
	Ogivri	Mylan	01/12/2017
	Ontruzant	Samsung Bioepis	08/01/2019
	Trazimera	Pfizer	11/03/2019
Humira | adalimumab	Abrilada	Pfizer	15/11/2019
	Amjevita	Amgen	23/09/2016
	Cyltezo	Boehringer Ingelheim	25/08/2017
	Hadlima	Samsung Bioepis	23/07/2019
	Hulio	Mylan	06/07/2020
	Hyrimoz	Sandoz	30/10/2018
	Yusimry	Coherus BioSciences, Inc.	17/12/2021
Lantus | insulin glargine	Rezvoglar	Eli Lilly and Company	17/12/2021
	Semglee	Mylan Pharmaceuticals Inc.	28/07/2021
Lucentis | ranibizumab	Byooviz	Samsung Bioepis Co., Ltd.	17/09/2021
Rituxan | rituximab	Riabni	Amgen	17/12/2020
	Ruxience	Pfizer	23/07/2019
	Truxima	CELLTRION	28/11/2018
Neulasta | pegfilgrastim	Fulphila	Mylan Pharmaceuticals	04/06/2018
	Fylnetra	Kashiv BioSciences, LLC	26/05/2022
	Nyvepria	Pfizer (Hospira)	10/06/2020
	Udencya	Coherus BioSciences, Inc.	02/11/2018
	Ziextenzo	Sandoz	04/11/2019
Neupogen | filgrastim	Nivestym	Pfizer (Hospira)	20/07/2018
	Releuko	Kashiv BioSciences, LLC	25/02/2022
	Zarxio	Sandoz	06/03/2015
Remicade | infliximab	**Avsola**	**Amgen**	**06/12/2019**
	Inflectra	**Pfizer (Hospira)**	**05/04/2016**
	Ixifi	**Pfizer**	**13/12/2017**
	Renflexis	**Samsung Bioepis**	**21/04/2017**

4.3. Remicade®

In order to understand the regulatory framework of a biosimilar medicine, a more practical study of Remicade® and its biosimilars was undertaken. The approval process described was centralised by the European Medicines Agency.

Remicade® is an anti-inflammatory drug, usually used when other medicines or treatments have failed in adults with the following diseases: Rheumatoid Arthritis, Crohn's Disease, Ulcerative Colitis, Ankylosing Spondylitis, Psoriatic Arthritis and Psoriasis [73].

In the case of Rheumatoid Arthritis, it is an immune system disease that causes inflammation of the joints, and Remicade® is given together with another medicine, Methodrex. Crohn's disease is already going through a disease of inflammation of the digestive tract, which can lead to the formation of fistulas. Ulcerative colitis and ankylosing spondylitis are diseases that cause inflammation, under the effect of ulcers in the lining of the intestine and pain in the joints of the spine, respectively. Finally, psoriatic arthritis and psoriasis cause the appearance of desquamative red plaques on the skin, the first of which simultaneously causes inflammation of the joints.

Regarding how Remicade® is used, this is the preparation of a solution for infusion in the form of powder. At the time of treatment, all patients are monitored for possible reactions, and it is therefore strictly crucial that it be administered with the supervision of a specialist doctor.

Remicade® may also be used in younger patients aged 6 to 17 years who have Crohn's disease or severe ulcerative colitis and who have not been responsive to other medicinal products/treatments or even are unable to receive such therapeutic strategies [73, 74]. Nevertheless, there are few biosimilars with therapeutic indications approved for paediatrics. This is because we are talking about biological medicines with larger and more complex molecules than chemically synthesised medicine. However, the administration processes are more invasive, using the parenteral route, which means an added difficulty for children. In this sense, this point is still considered a delicate issue, and the Regulatory Agencies themselves do not always agree in this area [75, 76].

The active substance in Remicade® is INFLIXIMAB, which is a monoclonal antibody, a type of protein that is designed to recognize and bind to a specific structure - antigen [73].

In practical terms, Infliximab binds to a chemical messenger - tumour necrosis factor-alpha and, once it is involved in the inflammation process, acts directly in this direction. Thus, it will promote TNF-α blockade, reducing inflammation and other symptoms associated with the disease in question, as represented in Figure 5 [77, 78].

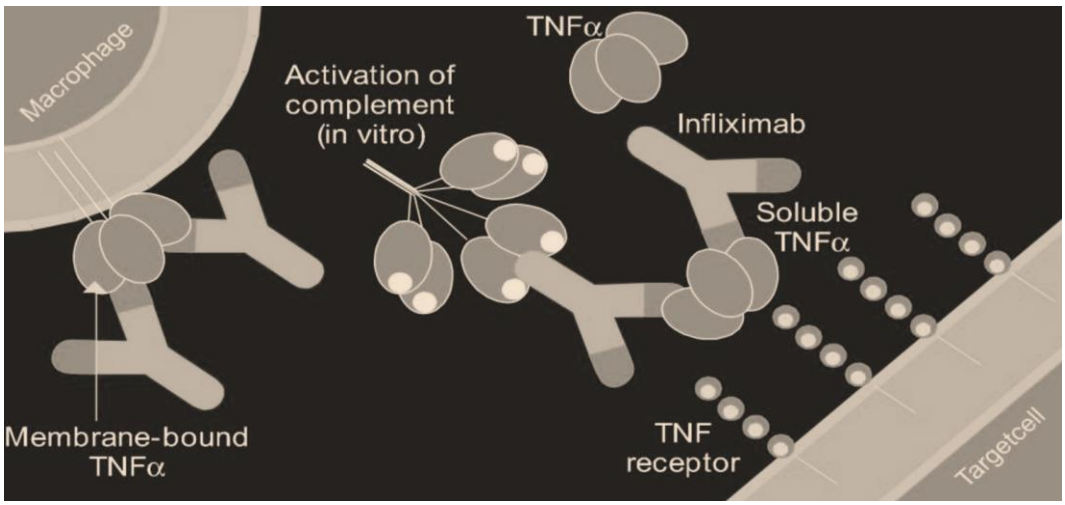


Figure 5 – *Mechanism of action for Infliximab.*

Remicade® is a reference medicine with the following characteristics: 100 mg concentrate powder for infusion solution. Each vial contains 100 mg of Infliximab. Your mode of administration is intravenously over 2 hours. Remicade® belongs to the pharmacotherapeutic group: immunosuppressants, as inhibitors of tumour necrosis factor-alpha (TNF-α) [79].

Regarding its mechanism of action, the active substance (Infliximab) is a man-murine chiming monoclonal antibody that binds with a high affinity to both soluble and transmembrane forms of TNF-α, but not a lymphotoxin (TNF-β). When administered at the recommended doses and concentrations, it is an effective, safe and generally well-tolerated drug. Its mechanism of action involves neutralization of the biological activity of TNF-α through the binding with high affinity to the soluble and transmembrane forms of TNF-α and inhibits the binding of TNF-α with its receptors. This neutralization leads to an overall reduction in inflammation [78].

4.3.1. Remicade® Approval Process

The REMICADE®'s approval process began on March 27, 1998, and the first evaluation report was released to all members of the Committee for Medicinal Products for Human Use (CHMP) on June 8, 1998. Subsequently, some questions were raised, and a consolidated list of questions was transmitted to the company on 30 November 1998. The evaluation report with the answers to these questions was then released by the Rapporteur within the CHMP on 25 January 1999.

On February 24, 1999, the CHMP discussed this same report and convened a group of experts to reflect on some specific clinical points, including safety, post-marketing and efficacy studies. In this context, a list of quality aspects to be taken into account in this medicinal product has also been recommended.

Finally, on 19 May 1999 the CHMP, based on the data submitted, as well as the scientific discussion within the Commission, issued a positive opinion for the granting of a Marketing Authorisation to Remicade®. It should also be reported that such opinions have also been forwarded to the European Commission to follow up on this decision [80].

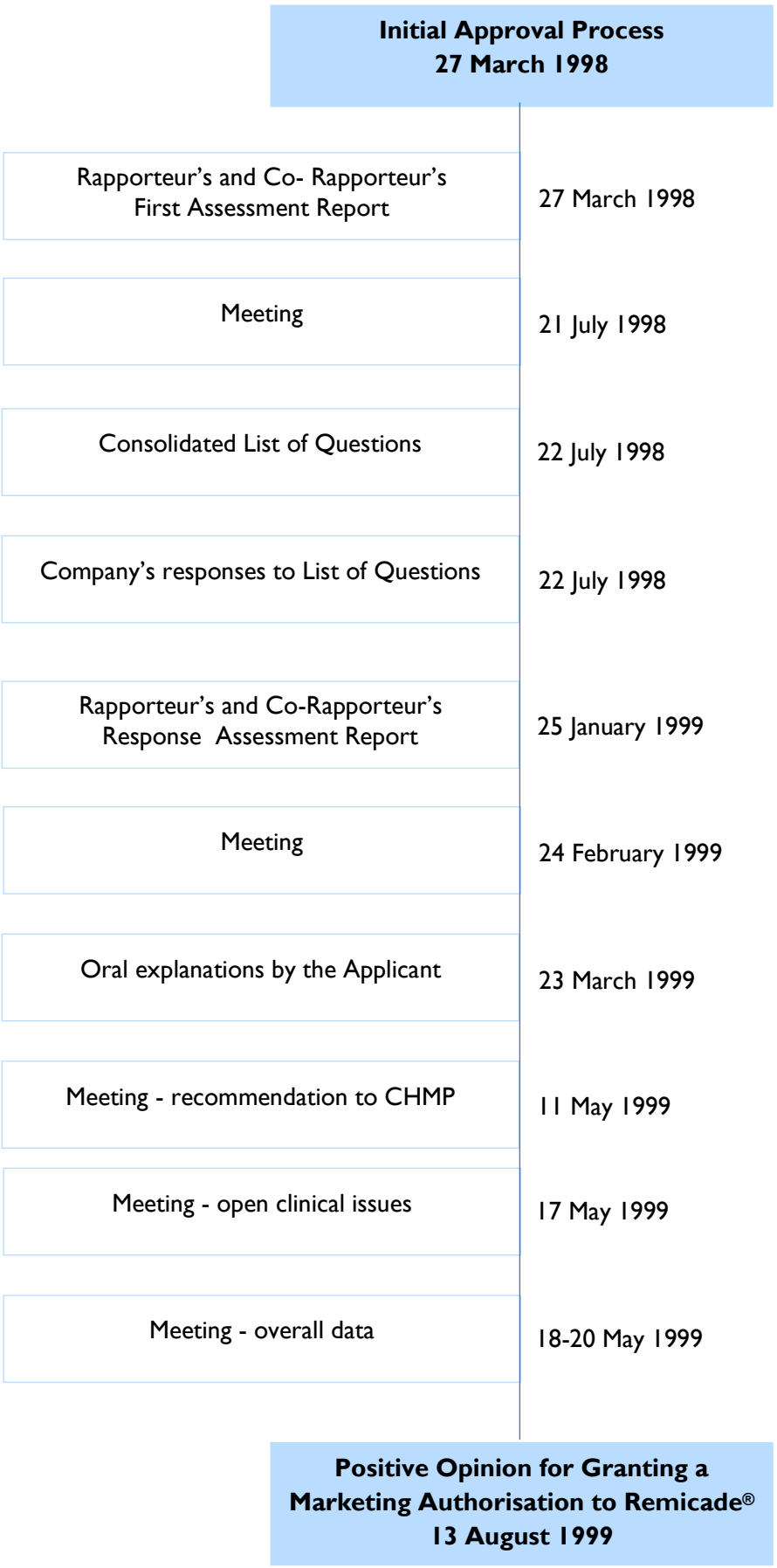


Figure 6 - *Approval Process of Remicade®, via centralised EMA's pathway (Information taken from EMA).*

4.3.2. Remicade® Biosimilars

Concerning the reference medicine - Remicade® - four biosimilar medicinal products were approved for use in the European Area. The four biosimilar drugs (Inflectra, Remsima, Flixabi, Zessly) are anti-inflammatory drugs, whose active substance is Infliximab. In this sense, the four medicinal products are similar to a biological medicine, called a reference medicine, already authorised in the European Union - Remicade®.

Such medications are used in the treatment of adults with the following diseases: Rheumatoid Arthritis, Crohn's Disease, Ulcerative Colitis, Ankylosing Spondylitis, Psoriatic Arthritis and Psoriasis. Furthermore, they can be used in children between 5 and 17 years of age who have Crohn's Disease or Severe Ulcerative Colitis and have been first submitted to other treatments or medications without success. Its mode of administration is via infusion form, into a vein for 2 hours. With regard to the approval process, it has already differed among the four medicinal products, although similar [81-84].

4.3.2.1. Inflectra

Regarding the approval process of INFLECTRA, through EMA, this was through a centralized procedure, as well as the others mentioned previously.

The procedure began on 14 July 2012, followed by a meeting between 16 and 19 July 2012, in which the CHMP drew up a Consolidated List of Questions to send to the Applicant, which was sent the following day to the Applicant.

On 16 November the Applicant submitted the answers to the Consolidated List of Questions. Following this, the rapporteurs released the Joint Evaluation Report on such responses to all CHMP members on 9 January 2013.

During the meeting from 7 to 10 January 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Council on the Risk Management Plan.

Still, within the CHMP, a list of outstanding issues has been issued in writing or orally. On 29 April 2013, the Applicant then submitted the answers to outstanding questions. To this end, the PRAC again adopted the Council on the RMP, and the rapporteurs released the Joint Evaluation Report on such responses to all CHMP members on 24 May 2013.

The Applicant then orally stated the outstanding issues raised, between 27 and 30 May, the CHMP agreed to a second list of outstanding issues to be addressed in writing by the Applicant. After the Applicant submitted the replies to the second list and the PRAC had gathered, the rapporteurs reissued the Joint Evaluation Report and on 27 June 2013 the CHMP, taking into account all the data collected and the scientific discussion generated, issued a positive opinion to be granted a marketing authorisation.

It is also important to mention that Inflectra was the second biosimilar approved by the FDA and the first Remicade® biosimilar also approved for marketing in the United States. According to the FDA, the approval of Inflectra was based on a review of evidence including structural and functional characterisation, animal study data, pharmacokinetic and pharmacodynamic data, clinical immunogenicity data and other clinical safety and efficacy data that demonstrated that Inflectra is biosimilar to Remicade® [81].

Figure 7 - *Approval Process of Inflectra, via centralised EMA's pathway (Information taken from EMA)*

4.3.2.2. Remsima

As for the drug Remsima, its approval process began on 21 March 2012, and the application was submitted to the EMA on 1 March 2012.

On 8 June 2012, the first Evaluation Report of the Rapporteur and the Co-Rapporteur was released to all CHMP members. Like previous procedures, during the meeting from 16 to 19 July 2012, the CHMP agreed to the Consolidated List of Questions to be sent to the Applicant, and that list was sent on 20 July. Later, on 16 November 2012, the Applicant submitted his answers to the questions asked and the rapporteurs released the Joint Evaluation Report to the CHMP on 28 December 2012.

During the meeting from 7 to 10 January 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC advice and shortly thereafter, between 14 and 17 January, the CHMP agreed to a list of outstanding issues to be put to the Applicant.

On 29 April 2013, the Applicant submitted the replies to the CHMP's List of Outstanding Issues and during the meeting of 13 to 16 May, the PRAC again adopted the PRAC Council.

The rapporteurs then released the Rapporteurs released the Updated Joint Evaluation Report to CHMP members on 14 May 2013, also sending 10 days later (on 24 May 2013), the Updated Joint Evaluation Report on The Answers to the List of Outstanding Issues.

From 27 to 30 May 2013, the CHMP reconvened to hear orally the Applicant's clarifications on some questions raised in the 2nd Consolidated List of Questions, and the Applicant agreed to answer the remaining questions in writing.

On June 5, 2013, the Applicant submitted the missing responses at the meeting with the PRAC, between 10-13 June, the PRAC Council was again adopted for discussion of the Risk Management Plan submitted.

Finally, the Joint Evaluation Report was released to all CHMP members on 19 June 2013 and, after analysis of the data collected and subsequent scientific discussion, the Committee issued a positive opinion for Remsima to be introduced to the market on 27 June 2013 [82].

Figure 8 - *Approval Process of Remsima, via centralised EMA's pathway (Information taken from EMA).*

4.3.2.3. Flixabi

The Flixabi approval process began on March 25, 2015, and the EMA had already received the application for submission on March 3 of this year.

The first Evaluation Report was released to the CHMP on 12 June 2015 and the PRAC also issued its first report on 22 June 2015.

It was then the PRAC's responsibility to adopt a general assessment and advice on this submission, during the meeting from 6 to 9 July 2015. At another meeting (23 July 2015), the CHMP confirmed the consolidated list of questions to be sent to the applicant. In the same context, Good Clinical Practice (GCP) inspections were requested to confirm the quality, safety and efficacy of the product, and the final report resulting from the inspections was issued on 8 October 2015.

The Final Report on the applicant's responses to the consolidated list of questions to CHMP members was released on 24 November 2015.

During this period, some outstanding issues were also raised, to which the CHMP allowed them to be clarified in writing and/or orally. Following, on 24 February 2016, the applicant presented orally the answers to the outstanding questions, as well as in writing in the second list of outstanding questions.

On 16 March 2016, the Joint Evaluation Report on replies to the list of outstanding questions was released to the CHMP and, subsequently between 29 March and 1 April 2016, the Committee issued a positive opinion to grant a Marketing Authorisation to Flixabi [83].

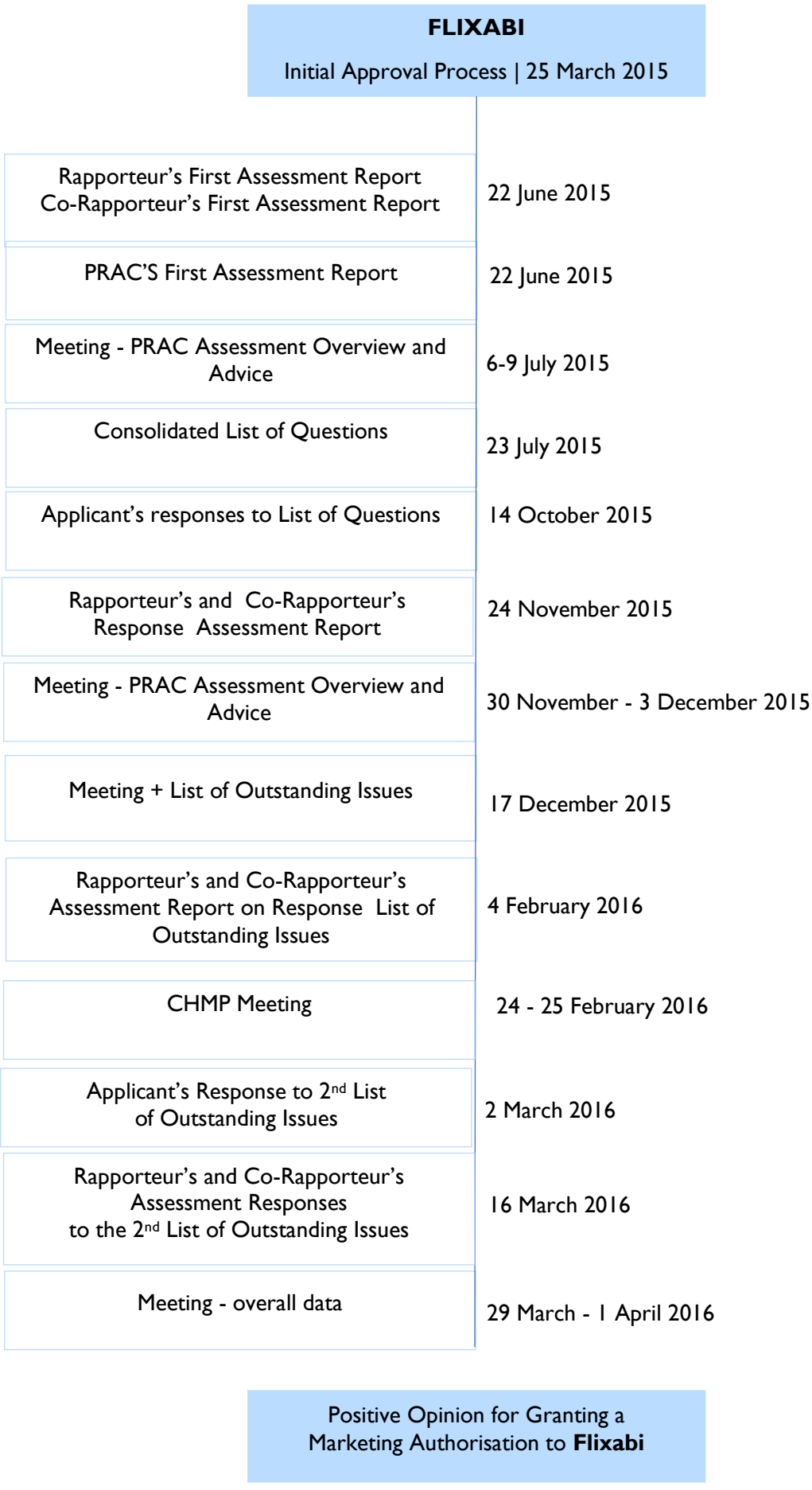


Figure 9 - *Approval Process of Flixabi, via centralised EMA's pathway (Information taken from EMA).*

4.3.2.4. Zessly

The process of approving the biosimilar drug ZESSLY began with its submission to the EMA on 21 April 2017, however, only on 18 May 2017, did the EMA begin its official procedure.

On August (4, 7 and 16) the Rapporteur, Co-Rapporteur and the PRAC made the first Evaluation Report reach all members of the Committee for Medicinal Products for Human Use.

Later, during the meeting on 14 September, the CHMP agreed to send a Consolidated Question list to the Applicant and its replies were submitted on 19 December 2017.

The Rapporteurs then released the Joint Evaluation Report on the Applicant's responses on 29 January 2018. On 8 February, the PRAC convened the Council to seek advice from the CHMP and on 22 February, the CHMP issued an issue of outstanding issues.

After these replies were clarified by the Applicant (on 26 February 2018), and the same replies were examined within the CHMP on 7 March, the Committee finally issued the marketing authorisation on 22 March 2018 [84].

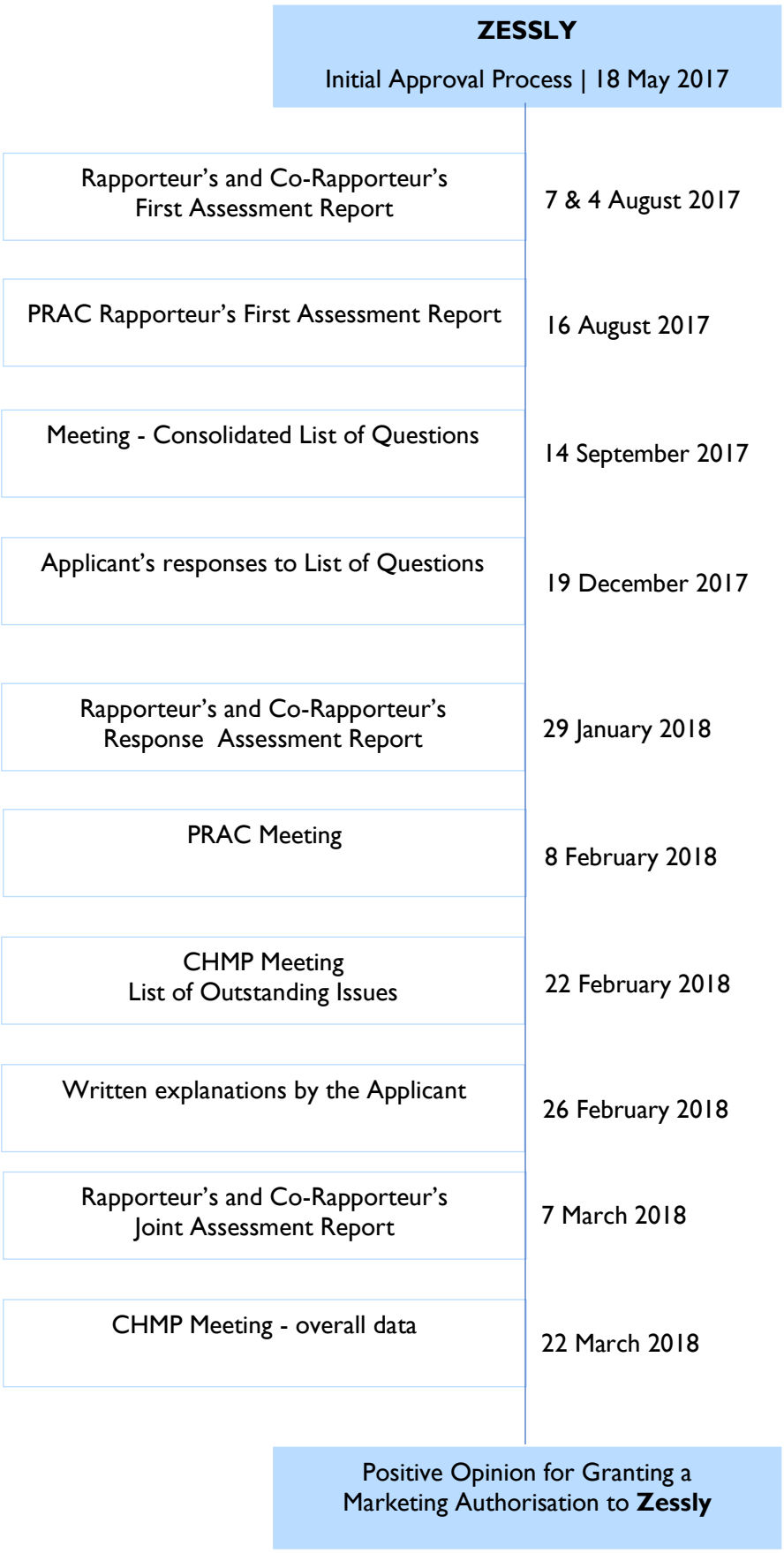


Figure 10 - *Approval Process of Zessly, via centralised EMA's pathway (Information taken from EMA).*

CHAPTER 5

Challenges and Future Prospects

CHALLENGES AND FUTURE PROSPECTS

Reflection on biosimilar medicines becomes fundamental to bringing together ideas, discussing issues and, essentially, reflecting on their benefits, risks, regulatory particularities and future perspectives.

Currently, at the scientific level, 'one of the great challenges of efficacy and safety of biosimilar medicines lies in the difficulty of demystifying the concepts of biosimilar, generic and *biobetter*. The research of these medicines nowadays allows the clarification of society about them, so that it is receptive to this evolution of science. Therefore, it is essential to transmit, inform and clarify, both to patients and health professionals, that different therapeutic strategies exist and are available to us. In a basic way, we can say that a generic medicine, unlike a biosimilar, has simpler chemical structures and is developed to be equivalent to another reference medicine that has a small chemical molecule. As with biosimilar medicine, the greatest difficulty lies with the researcher himself, as he has to move as far away from it as possible. Such a situation can bring some concern, leading to the associated costs being considerably increased when the initial procedures have to be performed again from scratch. The great challenge of the relevance of biosimilars medicine will always be to prove similarity and not to prove a non-inferiority situation about the reference medicine.

Another challenge is the misinformation on the fundamentals, studies and efficacy of these medicines, which promotes ignorance and naturally generates distrust regarding the quality, safety and efficacy of biosimilar medicines. Well, nowadays, in the field of research it is possible to state that during the whole process of development and production of a biosimilar, the profiles are proven, through clinical trials that assess the pharmacokinetics, efficacy, safety and immunogenicity of the biosimilar compared to the reference one. In this way, it is proven, through tests that demonstrate that the properties of the product, which may affect its immunogenicity, have not been altered.

Bearing in mind that the market for biosimilar medicines is very complex, specific and large, it also entails high costs. The cost required to develop a biosimilar medicine, in itself, is a challenge, taking into account the high-tech equipment and manufacturing material needed, making it very expensive throughout the process, including all the clinical trials needed to prove its efficacy, also highlighting the importance of investment in human resources, since it is essential to involve specialized personnel in different fields of science to ensure the proper development of this type of medicine.

One of the most referred to and extremely important challenges in the use of biosimilars refers to regulation, which allows professionals to have safety and trust in their administration. In general, the existing legislation can still be considered quite recent, causing a certain instability, and insecurity in its implementation in some countries. Nevertheless, the marketing of biosimilar medicines has more than ten years of experience in the European Union and during this time, biosimilars have maintained safety, efficacy and quality proven throughout the process.

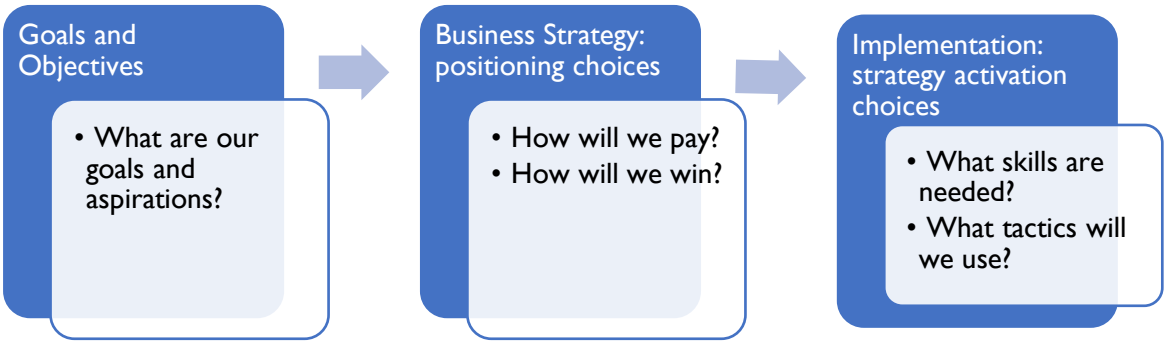
The truth is that the regulatory authority responsible for the approval of biosimilar medicines is the same as for reference biological medicines, and it is governed by the rigour and compliance with the criteria of safety, efficacy and quality required.

Regarding pharmacovigilance, biosimilar medicines, as well as reference biological medicines, are identified as a group of medicines that require additional monitoring. The Risk Management Plan presents the identified risks, minimisation measures and strategies to collect immunogenicity data.

A much-discussed aspect among scientists refers to the interchangeability and substitution, which must be analysed case by case, and it is the obligation of health professionals to be informed about the benefits and risks that such a change may bring to the patient. To this end, the study of the patient and the clinical analysis are essential for adequate and effective medical advice, in order to consider the best therapeutic option for the patient in question, according to the stage of the disease.

Yet another challenge in this area is to prove that the extrapolation of data is preserved, which is easily corroborated with all the justification submitted to the EMA and additional clinical trials requested, as well as the inclusion of additional safety measures for monitoring these medicines to ensure their safety.

Information and the implications of the dissemination of biosimilars are central to investment in them. To address the opportunities for pharmaceutical companies to invest in the development of biosimilar medicines, Deloitte has presented a study on Market Entry Strategies for Biosimilar Medicines, as depicted in the figure below.



Regarding the goals and objectives defined, one should reflect on the real value of the business, keeping in mind the global vision of biosimilars, including the financial and non-financial goals. Next, it is crucial to understand which countries and regions can be considered and the potentials for this market segment, and also substantiate which are the most attractive therapeutic areas, specifying what the missing needs in this area are. Bearing in mind the possibility of the existence or emergence of competing biosimilars and new commercial partners, it is important to reflect on their influence on the competitive market and, consequently, the prices charged, which would influence the cost and profit ratio.

The use of biosimilars in therapeutics in the socio-economic context we are living in can be considered as a solution for many therapeutic strategies, as the reduction in costs of such medicines with reference biologicals allows such action, meeting the current needs of the population and the studies that allow the medium and short term needs of the population to be scientifically confirmed.

In the case of treatments reserved for the last therapeutic stages, in a more advanced phase of the disease or for more serious patients, we can state that through the administration of biosimilars, a greater number of patients would be able to access the medicines and more quickly. In addition, through cost reduction with biosimilars, the additional budget could be directed to areas of innovative and/or underserved therapies, thus contributing to the very high expenses or the inadequacy of the budget.

Biosimilar medicines today are a reality! Biosimilar medicines are a complex and innovative world, but with great potential to acquire a promising and prominent role in society. It is expected that investment will be made in the improvement of legislation regarding biosimilars, so that the desirable and necessary harmonisation/harmonisation of guidelines becomes a practical and not just a theoretical reality.

Until now, biosimilar medicines have demonstrated their importance and efficacy in the fight against diseases and mainly for the well-being of the Person, who for various reasons has developed a disease, will be a great contribution to the quality of life of people all over the world. As patents on biological medicines expire, the potential for biosimilar medicines to become a more equitable and sustainable state-of-the-art treatment will become increasingly evident and achievable.

CHAPTER 6

Final Considerations

FINAL CONSIDERATIONS

This Dissertation entitled 'A regulatory perspective on biosimilar medicines' aims to reflect on and understand the procedures regarding the regulatory framework for biosimilar medicines in the world, bearing in mind the definition in the Portuguese legislation, which defines medicine as 'any substance or combination of substances presented as having properties for treating or preventing disease in human beings or its symptoms or which may be used in or administered to human beings to establish a medical diagnosis or, by exerting a pharmacological, immunological or metabolic action, to restoring, correcting or modifying physiological functions. As there are scientifically proven biosimilar medicines within this definition, it is important to reiterate that when the patient benefits from their administration, clinical practice should be patient-focused.

As biosimilar medicines are a clinical alternative to biological medicines, we can state that their emergence follows the fact that biological medicines are associated with very high costs, preventing many patients with different chronic diseases from seeing their therapeutic strategy as something merely unaffordable. Now, biosimilar medicines, as biological medicines highly similar to other biological medicines of reference, being a very significant cost process, biosimilars have come to make access to them possible.

In this line of research, the European Union, through the quality of the European Medicines Agency, has been standing out in this area for its intervention in the field of biosimilars, having already more than ten years of proven clinical experience. In this sense, we can see that it has been a pioneer in the approval of biosimilar medicines, through the drafting of specific quality, safety and efficacy guidelines for biosimilars. As an example, there are currently sixty-nine biosimilars approved for use in Europe, compared to thirty-six biosimilars approved for marketing in the United States. Both Regulatory Agencies seek to excel in the quality, safety and efficacy of their medicines, by requiring several tests, in particular, comparative studies between the biosimilar medicine and its reference medicine, in order to demonstrate the comparability between the medicines and ensure their similarity.

As an example, the European Medicines Agency has approved four biosimilars of Remicade® - Inflectra, Remsima, Flixabi and Zessly - since 2018. Throughout the approval process of these biosimilars, each critical step is listed so that the parameters requested by the Agency are met. To ensure compliance with such requirements, the actions of the Committee for Medicinal Products for Human Use, as well as the presence of the advisory body of the Pharmacovigilance Risk Assessment Committee, are essential for the EMA to give its positive opinion regarding the introduction of a new medicine on the market. Throughout scientific research, issues such as demonstrating biosimilarity, extrapolation, safety monitoring, interchangeability, switching and substitution have become strategies/measures/actions/ inherent in the world of biosimilars that must be studied continuously. Despite the evolution and proof of their efficacy, there is still much to be done, as ignorance of them is still very prevalent.

The key to the success of biosimilar medicines lies in even more rigorous, demanding and universal regulation, as well as greater knowledge and acceptance and awareness of health professionals, since they are the ones who play the role of credible informants both for patients, through recommendation and prescription, and for potential investors in their production, in order to ensure the safety and efficacy of cheaper medicines. When biosimilar medicines are used, they bring benefits to the National Health System, companies and patients. Thus, biosimilar medicines can enable more patients to be treated with biological strategies at an earlier stage of the disease, which is more affordable. During this research, it was possible to conclude that, even though the topic is only a few decades old, it is already well grounded and documented, with credible and proven studies on the topic.

Chapter 7

References

REFERENCES

[1] AGENCY, EUROPEAN MEDICINES - **Biosimilar Medicines - An Informative Guide for Health Professionals**. 2019.

[2] LONGSTAFF, COLIN, et al. - **How do we assure the quality of biological medicines?** *Drug Discovery Today*. Vol. 14. n.º 1 (2009). p. 50-55. Available at: https://www.sciencedirect.com/science/article/pii/S1359644608003383. 1359-6446

[3] PORTELA, M. C., et al. - **[Biologicals and Biosimilars: Gaps in the Pharmacovigilance System in Portugal]**. *Acta Med Port*. Vol. 30. n.º 3 (2017). p. 205-212. 0870-399x

[4] **Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues**. European Medicines Agency, 2014.

[5] PRINJA, SHANKAR; PANDAV, CHANDRAKANT - **Economics of COVID-19: challenges and the way forward for health policy during and after the pandemic**. *Indian Journal of Public Health*. Vol. 64. n.º 6 (2020). p. 231-233. Available at: https://www.ijph.in/article.asp?issn=0019-557X;year=2020;volume=64;issue=6;spage=231;epage=233;aulast=Prinja>. 0019-557X

[6] **O sistema regulador europeu de medicamentos - Uma abordagem coerente à regulação de medicamentos na União Europeia**. European Medicines Agency, 2016.

[7] GONÇALVES, JOÃO, et al. - **Biosimilar monoclonal antibodies: preclinical and clinical development aspects**. *Clin Exp Rheumatol*. Vol. 34. n.º 4 (2016). p. 698-705.

[8] AGENCY, EUROPEAN MEDICINES - **Guideline on Similar Biological Medicinal Products**. 2014.

[9] USE, COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN - **Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues**. *London: European Medicines Agency*. (2006).

[10] AGENCY, EUROPEAN MEDICINES - **Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues**. 2014.

[11] ASSOCIATION, EUROPEAN GENERIC MEDICINES - **Biosimilars - handbook.**

[12] SCHIESTL, M., et al. - **The role of the quality assessment in the determination of overall biosimilarity: a simulated case study exercise**. *Biologicals*. Vol. 42. n.º 2 (2014). p. 128-32. 1045-1056

[13] ZALAI, DÉNES; DIETZSCH, CHRISTIAN; HERWIG, CHRISTOPH - **Risk-based Process Development of Biosimilars as Part of the Quality by Design Paradigm**. *PDA journal of pharmaceutical science and technology / PDA*. Vol. 67. (2013). p. 569-580.

[14] GONÇALVES, J. - **Medicamentos biossimilares: o estado da arte**. Lidel - Edicoẽs Técnicas, Lda., 2018. Available at: https://books.google.pt/books?id=YZ3lvgEACAAJ. 9789897522604

[15] GRANDE, ENRIQUE; CARRATO, ALFREDO - **Biosimilars: What they are and their use in oncology**. *Cancer and Chemotherapy Reviews*. Vol. 6. (2011). p. 141-148.

[16] GONCALVES, JOAO, et al. - **Biosimilar monoclonal antibodies: Preclinical and clinical development aspects**. *Clinical and experimental rheumatology*. Vol. 34. (2016).

[17] **Biosimilar Development Process**. FDA. Available at: https://www.fda.gov/files/drugs/published/Biosimilar-Development-Process.pdf,

[18] DESANVICENTE-CELIS, ZAYRHO; GOMEZ-LOPEZ, ARLEY; ANAYA, JUAN-MANUEL - **Similar biotherapeutic products: overview and reflections**. *Immunotherapy*. Vol. 4. n.º 12 (2012). p. 1841-1857. 1750-743X

[19] DRANITSARIS, GEORGE; AMIR, EITAN; DORWARD, KRISTINE - **Biosimilars of biological drug therapies**. *Drugs*. Vol. 71. n.º 12 (2011). p. 1527-1536. 1179-1950

[20] FDA, US - **Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product**. *Maryland: FDA*. (2015).

[21] LIU, HUI F, et al. - **Recovery and purification process development for monoclonal antibody production**. Taylor & Francis, 2010. 1942-0862

[22] KOZLOWSKI, STEVEN - **US FDA Perspectives on Biosimilar Biological Products**. IBBR University of Maryland: 2014.

[23] GENAZZANI, A. A., et al. - **Biosimilar drugs : concerns and opportunities**. *BioDrugs*. Vol. 21. n.° 6 (2007). p. 351-6. 1173-8804

[24] AL-SABBAGH, AHMAD, et al. - **Development of Biosimilars**. *Seminars in Arthritis and Rheumatism*. Vol. 45. (2016).

[25] BIOSIMILARS, AMGEN - **Developing Biosimilars: The process and quality standards**. 2017.

[26] MELLSTEDT, H.; NIEDERWIESER, D.; LUDWIG, H. - **The challenge of biosimilars**. *Ann Oncol*. Vol. 19. n.° 3 (2008). p. 411-9. 0923-7534

[27] ROGER, SIMON D - **Biosimilars: How similar or dissimilar are they?** *Nephrology*. Vol. 11. n.° 4 (2006). p. 341-346. 1320-5358

[28] VULTO, A. G.; JAQUEZ, O. A. - **The process defines the product: what really matters in biosimilar design and production?** *Rheumatology (Oxford)*. Vol. 56. n.° suppl_4 (2017). p. iv14-iv29. 1462-0324

[29] LOWE, D., et al. - **Advances in Protein Chemistry and Structural Biology**. Academic Press, 2011. Available at: https://www.sciencedirect.com/science/article/pii/B9780123864833000045.Cap. - Aggregation, stability, and formulation of human antibody therapeutics. 1876-1623

[30] WARNE, NICHOLAS W. - **Development of high concentration protein biopharmaceuticals: The use of platform approaches in formulation development**. *European Journal of Pharmaceutics and Biopharmaceutics*. Vol. 78. n.° 2 (2011). p. 208-212. Available at: https://www.sciencedirect.com/science/ article/pii/S0939 6411111000889. 0939-6411

[31] AL-SABBAGH, AHMAD, et al. - **Development of biosimilars**. *Seminars in Arthritis and Rheumatism*. Vol. 45. n.° 5, Supplement (2016). p. S11-S18. Available at: https://www. sciencedirect.com/science/article/pii/S0049017216000287. 0049-0172

[32] KURKI, P., et al. - **Interchangeability of Biosimilars: A European Perspective**. *BioDrugs*. Vol. 31. n.° 2 (2017). p. 83-91. 1173-8804

[33] AGENCY, EUROPEAN MEDICINES - **Guideline on Immunogenicity Assessment of Therapeutic Proteins** 2017.

[34] AAPRO, M., et al. - **Comparative cost efficiency across the European G5 countries of originators and a biosimilar erythropoiesis-stimulating agent to manage chemotherapy-induced anemia in patients with cancer**. *Ther Adv Med Oncol*. Vol. 4. n.º 3 (2012). p. 95-105. 1758-8340

[35] PRADITPORNSILPA, KEARKIAT, et al. - **Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies**. *Kidney International*. Vol. 80. n.º 1 (2011). p. 88-92. Available at: https://www.sciencedirect.com/science/article/pii/S0085253815549405. 0085-2538

[36] WEISE, M., et al. - **Biosimilars: what clinicians should know**. *Blood*. Vol. 120. n.º 26 (2012). p. 5111-7. 0006-4971

[37] PERPOIL, A., et al. - **Public Health Impact of Using Biosimilars, Is Automated Follow up Relevant?** *Int J Environ Res Public Health*. Vol. 18. n.º 1 (2020). 1661-7827

[38] VAZ, ANTÓNIO FARIA, et al. - **Medicamentos biossimilares**. *Revista Portuguesa De Farmacoterapia*. Vol. 5. n.º 3 (2013). p. 44-51. 2183-7341

[39] SHARMA, ATUL, et al. - **Regulatory Perspective of International Agencies for Development of Biosimilar Products (Monoclonal Antibodies): An Overview**. *Therapeutic Innovation & Regulatory Science*. Vol. 54. n.º 5 (2020). p. 965-977. Available at: https://doi.org/10.1007/s43441-020-00112-8. 2168-4804

[40] GUIDELINE, ICH HARMONISED TRIPARTITE - **Comparability of biotechnological/ biological products subject to changes in their manufacturing process Q5E**. 2013.

[41] BLANK, TOBIAS, et al. - **Safety and toxicity of biosimilars - EU versus US regulation**. *GaBI J*. Vol. 2. n.º 3 (2013). p. 144-150.

[42] SCHELLEKENS, HUUB; MOORS, ELLEN - **Clinical comparability and European biosimilar regulations**. *Nature biotechnology*. Vol. 28. n.º 1 (2010). p. 28-31. 1546-1696.

[43] LEE, JAYMI F; LITTEN, JASON B; GRAMPP, GUSTAVO - **Comparability and biosimilarity: considerations for the healthcare provider**. *Current medical research and opinion*. Vol. 28. n.º 6 (2012). p. 1053-1058. 0300-7995

[44] MCCAMISH, M.; WOOLLETT, G. - **The continuum of comparability extends to biosimilarity: how much is enough and what clinical data are necessary?** *Clin Pharmacol Ther*. Vol. 93. n.º 4 (2013). p. 315-7. 0009-9236

[45] FERNANDES, JOÃO PEDRO PEIXOTO; GONÇALVES, JOÃO PAULO - **Segurança e Eficácia Clínica na Substituição de Medicamentos Biossimilares.**. 2015.

[46] BRAUN, JÜRGEN; KUDRIN, ALEX - **Switching to biosimilar infliximab (CT-P13): Evidence of clinical safety, effectiveness and impact on public health**. *Biologicals*. Vol. 44. n.º 4 (2016). p. 257-266. Available at: https://www.sciencedirect.com/science/article/pii/S104510561630001X. 1045-1056

[47] OLIVEIRA, RITA; AIRES, TERESA - **Biossimilares: Velhas Questões, Novos Desafios**. *Gazeta Médica*. (2018).

[48] - **Market Review - European Biosimilar Medicine Markets 2020**. Brussels, Belgium: Medicines for Europe, 2020. Available at: https://www.medicinesforeurope.com/wp-content/uploads/2021/03/Biosimilar%20Market%20Review-Final.pdf.

[49] TSIFTSOGLOU, ASTERIOS S.; RUIZ, SOL; SCHNEIDER, CHRISTIAN K. - **Development and Regulation of Biosimilars: Current Status and Future Challenges**. *BioDrugs*. Vol. 27. n.º 3 (2013). p. 203-211. Available at: https://doi.org/10.1007/s40259-013-0020-y. 1179-190X

[50] DALLER, JUSTIN R. - **Biosimilars: A consideration of the regulations in the United States and European union**. *Regulatory toxicology and pharmacology RTP*. Vol. 76. (2016). p. 199-208.

[51] KURKI, PEKKA; EKMAN, NIKLAS - **Biosimilar regulation in the EU**. *Expert Review of Clinical Pharmacology*. Vol. 8. n.º 5 (2015). p. 649-659. Available at: https://doi.org/10.1586/17512433.2015.1071188. 1751-2433

[52] GHERGHESCU, IOANA; DELGADO-CHARRO, M BEGOÑA - **The biosimilar landscape: an overview of regulatory approvals by the EMA and FDA**. *Pharmaceutics*. Vol. 13. n.º 1 (2020). p. 48. 1999-4923

[53] JORDAN, JOHN B.; CHRISTL, LEAH - **FDA Biosimilar Action Plan: could improving pharmacovigilance of biologics improve patient and physician confidence in biosimilars?** *Expert Opinion on Drug Safety*. Vol. 19. n.º 3 (2020). p. 229-232. Available at: https://doi.org/10.1080/14740338.2020.1733966. 1474-0338

[54] - **Purple Book - Database of Licensed Biological Products**. Food and Drug Administration. Available at: https://purplebooksearch.fda.gov/

[55] CHRISTL, LEAH A; WOODCOCK, JANET; KOZLOWSKI, STEVEN - **Biosimilars: the US regulatory framework**. *Annu Rev Med*. Vol. 68. n.º 1 (2017). p. 243-254.

[56] YAMAGUCHI, TERUHIDE; ARATO, TERUYO - **Quality, safety and efficacy of follow-on biologics in Japan**. *Biologicals*. Vol. 39. n.º 5 (2011). p. 328-332. 1045-1056.

[57] GENERICS; INITIATIVE, BIOSIMILARS - **Biosimilars approved in Japan**. Posted 07/03/2014 at http://gabionline. net/Biosimilars/General/Biosimilars. 2015.

[58] KALAISELVAN, V., et al. - **Pharmacovigilance in India: Present Scenario and Future Challenges**. *Drug Safety*. Vol. 42. n.º 3 (2019). p. 339-346. Available at: https://doi.org/10. 1007/s40264-018-0730-7. 1179-1942

[59] ARATO, TERUYO - **Japanese regulation of biosimilar products: past experience and current challenges**. *British journal of clinical pharmacology*. Vol. 82. n.º 1 (2016). p. 30-40. 0306-5251

[60] MEHER, BIKASH R, et al. - **Biosimilars in India; current status and future perspectives**. *Journal of pharmacy & bioallied sciences*. Vol. 11. n.º 1 (2019). p. 12.

[61] CANADA, HEALTH - **Guidance for sponsors: information and submission requirements for subsequent entry biologics (SEBs)**. Health Canada Ottawa, Canada, 2010.

[62] DECLERCK, PAUL, et al. - **The language of biosimilars: clarification, definitions, and regulatory aspects**. *Drugs*. Vol. 77. n.º 6 (2017). p. 671-677. 1179-1950

[63] AZEVEDO, VALDERILIO FEIJÓ, et al. - **Potential regulatory and commercial environment for biosimilars in Latin America**. *Value in health regional issues*. Vol. 1. n.º 2 (2012). p. 228-234. 2212-1099

[64] DE ASSIS, MARCOS RENATO; PINTO, VALDAIR - **Strengths and weaknesses of the Brazilian regulation on biosimilars: a critical view of the regulatory requirements for biosimilars in Brazil**. *Therapeutic Advances in Musculoskeletal Disease*. Vol. 10. n.º 12 (2018). p. 253-259. 1759-720X

[65] GONZÁLEZ-RAMÍREZ, RODRIGO; CASTAÑEDA-HERNÁNDEZ, GILBERTO - **The challenges of developing and commercializing biosimilars in Latin America**. Future Science, 2019. 2046-8954

[66] - **Association of Southeast Asian Nations - Bureau of East Asian and Pacific Affairs**. U.S. Department of State, 2019. Available at: https://www.state.gov/association-of-southeast-asian-nations-asean/

[67] RIZZOLI, RENÉ; BONJOUR, JEAN-PHILIPPE - **Dynamics of Bone and Cartilage Metabolism (Second Edition)**. Burlington: Academic Press, 2006. Available at: https://www.sciencedirect.com/science/article/pii/B9780120885626500212.Cap.-Chapter 20 - Physiology of Calcium and Phosphate Homeostases. 978-0-12-088562-6

[68] SUBRAMANIAN, UMAMAHESWARI - **Introduction to Basics of Pharmacology and Toxicology: Volume 2 : Essentials of Systemic Pharmacology : From Principles to Practice**. Singapore: Springer Singapore, 2021. Available at: https://doi.org/10.1007/978-981-33-6009-9_42.Cap. - Hypothalamic and Pituitary Hormones. 978-981-33-6009-9

[69] CUTOLO, M., et al. - **Sex hormones influence on the immune system: basic and clinical aspects in autoimmunity**. *Lupus*. Vol. 13. n.º 9 (2004). p. 635-8. 0961-2033

[70] DAVIES, M., et al. - **Introduction of biosimilar insulins in Europe**. *Diabet Med*. Vol. 34. n.º 10 (2017). p. 1340-1353. 0742-3071

[71] PUNTHAKEE, ZUBIN; GOLDENBERG, RONALD; KATZ, PAMELA - **Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome**. *Canadian Journal of Diabetes*. Vol. 42. (2018). p. S10-S15. Available at: https://www.sciencedirect.com/science/article/pii/S1499267117308134. 1499-2671

[72] CUADRADO, MARIA-JOSE, et al. - **Is it time for biosimilars in autoimmune diseases?** *Autoimmunity Reviews*. Vol. 12. n.º 10 (2013). p. 954-957. Available at: https://www.sciencedirect.com/science/article/pii/S1568997213000414. 1568-9972

[73] - **Remicade** European Medicines 2022. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/Remicade#:~:text=Remicade%20is%20an%20anti%E2%80%91inflammatory%20medicine.%20It%20is%20usually,%28a%20medicine%20that%20acts%20on%20the%20immune%20system%29%3B,

[74] - **Remicade - INFLIXIMAB**. Jassen Biotecnh Available at: https://www.Remicade.com/,

[75] VIEIRA, I.; SOUSA, J. J.; VITORINO, C. - **Paediatric Medicines - Regulatory Drivers, Restraints, Opportunities and Challenges**. *J Pharm Sci*. Vol. 110. n.º 4 (2021). p. 1545-1556. 0022-3549

[76] - **Needs for paediatric medicines**. EMA: European Medicines Agency, 2020. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/needs-paediatric-medicines,

[77] NARULA, NEERAJ, et al. - **Comparative efficacy and rapidity of action for infliximab vs ustekinumab in biologic naive Crohn's disease**. *Clinical Gastroenterology and Hepatology*. Vol. 20. n.º 7 (2022). p. 1579-1587. e2. 1542-3565

[78] BALDASSANO, ROBERT, et al. - **Infliximab (REMICADE) therapy in the treatment of pediatric Crohn's disease**. *The American journal of gastroenterology*. Vol. 98. n.º 4 (2003). p. 833-838. 0002-9270

[79] HERMOSILLA, JESÚS, et al. - **Comparative stability studies of different infliximab and biosimilar CT-P13 clinical solutions by combined use of physicochemical analytical techniques and enzyme-linked immunosorbent assay (ELISA)**. *BioDrugs*. Vol. 33. n.º 2 (2019). p. 193-205. 1179-190X

[80] - **Remicade: EPAR - Procedural steps taken before authorisation**. European Medicines Agency: 2005.

[81] - **Inflectra: EPAR - Public Assessment Report**. European Medicines Agency, 2013.

[82] - **Remsima: EPAR- Public Assessment Report**. European Medicines Agency: 2013.

[83] - **Flixabi: EPAR - Public Assessment Report**. European Medicines Agency: 2016.

[84] - **Zessly: EPAR - Public Assessment Report**. European Medicines Agency: 2018.