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Biossimilares e Intercambialidade: Avaliação do cenário internacional e perspectivas para o contexto brasileiro

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LISTA DE ABREVIATURAS

ANVISA	Agência Nacional de Vigilância Sanitária
ADAs	*Antidrug Antibodies*
EMA	*European Medicines Agency*
EU	*European Union*
FDA	*Food and Drug Administration*
RDC	Resolução da Diretoria Colegiada

RESUMO

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Palavras-chave: biossimilares, intercambialidade, farmacovigilância, extrapolação.

Introdução: A expiração de patentes de medicamentos biológicos referência resultaram no surgimento dos biossimilares, caracterizados por não demonstrarem diferenças clínicas significativas na qualidade, eficácia e segurança, quando comparados com seus inovadores. Enquanto os biossimilares são potenciais alternativas de tratamento para expansão do acesso à saúde, ainda há inúmeras questões em contínuo debate, como a extrapolação de indicações e os riscos envolvidos na intercambialidade entre o medicamento biológico referência e seu biossimilar. Apesar da emergente discussão desde o primeiro biossimilar aprovado em 2015, este tópico permanece pouco explorado pela literatura brasileira e falta posicionamento. ***Objetivo:*** O principal propósito deste estudo é avaliar o cenário internacional dos biossimilares, a extrapolação de indicações e intercambialidade, para identificar perspectivas para o Brasil. ***Métodos:*** Revisão narrativa foi realizada na base de dados virtual PubMed e os endereços eletrônicos das autoridades regulatórias foram consultados para a obtenção de guias, notas e manuais publicados. ***Resultados e Discussão:*** A extrapolação de indicações é um tópico bem estabelecido, no qual tanto a EMA quanto a FDA apoiam a extrapolação de dados com biossimilaridade comprovada e justificativas científicas suficientes. Por outro lado, não há consenso sobre como a intercambiabilidade deve ser tratada. Enquanto a EMA delega as decisões sobre este assunto para cada Estado-membro, a FDA endossa o seu papel na designação de um biossimilar como intercambiável ou não intercambiável. ***Conclusão:*** Tópicos específicos sobre biossimilares ainda precisam de discussões e esclarecimentos adicionais, como consenso sobre a definição de intercambialidade, vias regulatórias de aprovação e nomenclatura. No Brasil, existe a necessidade de regulamentações claras sobre intercambiabilidade, baseadas em informações científicas. Com normatização adequada, educação e endosso do sistema de farmacovigilância, os biossimilares representarão uma oportunidade

importante para tratar doenças complexas com a confiança dos profissionais de saúde e dos pacientes.

ABSTRACT

Key words: biosimilars, interchangeability, pharmacovigilance, extrapolation.

Introduction: The patent expiration of reference biological drugs resulted in the arising of biosimilars, characterized by demonstrating no significant clinical difference in quality, efficacy and safety when compared to their references. While biosimilars are potential treatment alternatives to expand health access, there are still numerous questions in continuous debate, such as extrapolation of indications and the risks involved in interchangeability between the reference biological and the biosimilar drug. Despite the emerging discussion since the first biosimilar approved in 2015, this topic remains underexplored by the Brazilian literature and it lacks positioning. ***Objective:*** The main purpose of this study is to evaluate the international scenario of biosimilar drugs, extrapolation of indications and interchangeability in order to identify perspectives for Brazil. ***Methods:*** Narrative literature review was conducted in the virtual database PubMed and virtual addresses of regulatory authorities were consulted for obtaining published guides, notes and manuals. ***Results and Discussion:*** Extrapolation of indications is a well-stablished topic, in which both EMA and FDA support the extrapolation of data with proven biosimilarity and sufficient scientific justifications. Otherwise, there is no consensus on how interchangeability should be handled. While EMA leaves the decisions on this subject for each member state, the FDA endorses its role in designating a biosimilar as interchangeable or noninterchangeable. ***Conclusion:*** Specific topics around biosimilars still needs further discussion and clarifications, such as consensus on the definition of interchangeability, regulatory pathways of approval and labeling. In Brazil, there is a need for clear and scientific-based governances on interchangeability. With adequate regulations, education and endorsement of pharmacovigilance system, biosimilars will represent an important opportunity for treating complex diseases with the confidence of healthcare providers and patients.

INTRODUCTION

The American agency Food and Drug Administration (FDA) defines biological drugs as products obtained by biotechnological processes in living systems. Therefore, the resulting molecules are larger compared to the traditional synthetic molecules and involves higher complexity. This biological category includes hormones (e.g. insulin), cytokines (e.g. interferons) and monoclonal antibodies (e.g. trastuzumab and bevacizumab), the latter highlighted by the meaningful application in oncological and autoimmune diseases (Pinto, 2012).

In consequence of the patent expiration of reference biologics, the biosimilars emerged as a new category of drugs, characterized by demonstrating no significant clinical divergence compared to the reference product in terms of quality, efficacy and safety (Reinisch, Smolen, 2015). Different from synthetic drugs, the biological products are not liable to identical replications considering that minimal variations in any aspects involved in their complex manufacturing process can affect the safety and efficacy of the final product.

The manufacturing process of biological medicines are complex and involve steps that require high accuracy and sensitivity, such as genetic manipulation, fermentation and purification. Moreover, production is affected by impurities arising from the process itself and post-translational modifications, including glycosylation, oxidation and deamination. These factors have significant influence on the final pharmaceutical product profile (Grozdanova *et al.*, 2016). For this reason, the biosimilarity of a drug must be validated by a comparability test, which is the direct comparison of a biosimilar candidate with its reference biological (Pinto, 2012).

In Brazil, the National Health Surveillance Agency (ANVISA) disclosed in 2015 the first biological drug approved by comparability study, Remsima® (infliximab), the Remicade® biosimilar. Further in 2015, ANVISA approved the first biosimilar manufactured in Brazilian territory, filgrastim. These approvals represent the contribution of biosimilars to the delivery of additional treatment options to patients and the increased opportunities of treatments with more economically viable alternatives (Fernandes *et al.*, 2018).

Despite the achievement in health access, the rise of biosimilars brought numerous questions that remain in continuous debate among pharmaceutical companies,

healthcare professionals and regulatory agencies. Relevant issues include: presence of impurities or undetectable chemical changes in comparability tests; extrapolation of biosimilar approvals from one tested clinical indication to all indications already approved in the reference drug insert and, finally, the risks involved in the interchangeability and/or automatic substitution between the reference biological and the biosimilar drug (McKinnon *et al.*, 2018).

Synthetic generic drugs are considered interchangeable when their efficacy and safety have been proved equivalent to the reference drug (Fernandes *et al.*, 2018). In contrast, biosimilars are not identical copies of their reference biodrugs due to the molecule complexity and the immunogenic potential. For this reason, the application of interchangeability remains subjective in this circumstance (Grozdanova *et al.*, 2016). Whereas, in the United States, the FDA designates a biosimilar as interchangeable under certain conditions, in the European Union (EU), the European Medicines Agency (EMA) delegates this decision to national regulatory agencies (Blandizzi, Meroni, Lapadula, 2017).

The first biosimilar was approved in Brazil in 2015, and despite the emerging movements around biosimilars since then, the discussion on this topic remains underexplored by the Brazilian literature. In addition, ANVISA has not demonstrated a concrete and leading position on interchangeability. In fact, ANVISA declared in 2017, that this matter was not in its regulatory scope and appointed the judgment for establishing interchangeability of biosimilars to prescribing physicians and the Ministry of Health (ANVISA, 2017).

Therefore, the main objective of this study is to evaluate the reality of biosimilar drugs and the positioning and application of extrapolation of indications and interchangeability in the international scenario, by collecting the main information and positions of international regulatory authorities, in order to identify perspectives for Brazil. Additionally, the study aims to recognize the approaches used for the traceability of adverse events and their relevance to patient safety.

METHODS

Narrative literature review was conducted in the virtual database of scientific data PubMed for identification of English publications, published from 2008 to 2018, that

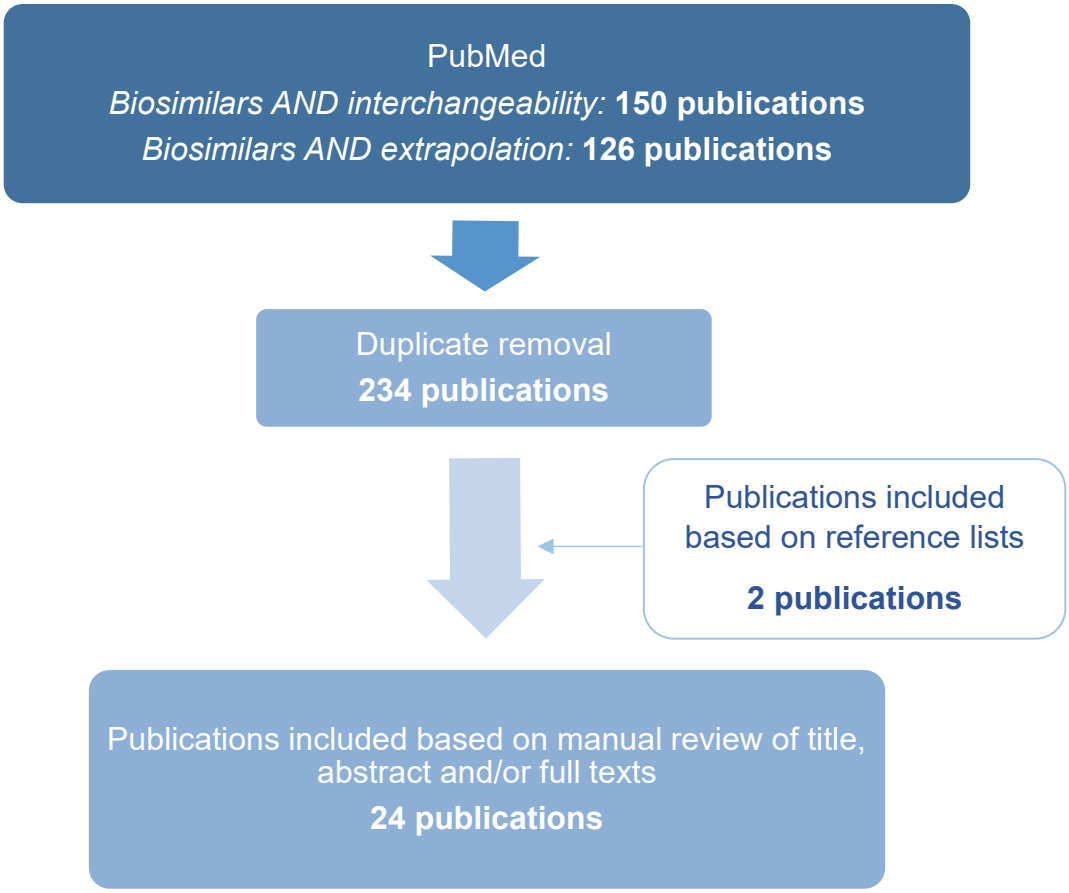
discussed interchangeability and extrapolation in the scenario of biosimilars (Rother, 2007). The search was strategically performed with the following combination of keywords: “biosimilars and interchangeability” OR “biosimilars and extrapolation”. Titles, abstracts and/or full texts were manually assessed to determine whether the discussion of the resulting publications was strictly related to the purpose of this study.

In addition, specific virtual addresses of regulatory authorities of interest (e.g. ANVISA, FDA and EMA) were consulted for obtaining published guides, notes and manuals. Therefore, the totality of the information was obtained from reliable and responsible sources among the scientific class.

RESULTS AND DISCUSSION

The research resulted in 234 publications and a manual filter selected 22 articles covering the topics of interchangeability and/or extrapolation. Subsequently, 2 articles were manually included based on the reference lists of the formerly chosen publications, as shown in the flowchart in Figure 1.

Figure 1. Flowchart of search results.



Considering the 24 selected publications, the subject of interchangeability was addressed in 18 articles. Extrapolation of indications was discussed in 14 articles. Nine publications assured extrapolation of approved indications of the reference product for biosimilars against five positions that were inconclusive or concluded the opposite. Regarding interchangeability, there is not unanimity on the definition for interchangeability within regulatory authorities and even less consensus on how interchangeability should be handled. Eleven publications were uncertain or against the exchange between biosimilars and their references while only seven publications defended the possibility of switching.

Biological products and Biosimilars

Compared to synthetic drugs, biological products have a greater complexity due to their manufacturing aspects that depend on living organisms and include sophisticated processes, such as recombinant DNA technology, controlled gene expression and antibodies technologies (Blandizzi, Meroni, Lapadula, 2017). These processes in cell systems generate an impurity profile, consisting of host cell proteins, DNA and endotoxins, which have an impact on the final pharmaceutical product (Grozdanova *et al*., 2016).

Other complexity of biological molecules includes the presence of glycoproteins in their structure. In order to build these proteins, the molecule undergoes post-translational glycosylation, which is responsible for defining the glycosylation profile of the molecule's Fc portion (McKinnon *et al.*, 2018). This glycosylation profile's outcome suffers influence by the manufacturing processes and the resulting terminal sugar in the heavy chain can alter the safety or efficacy of a biologic drug. Variation in the glycosylation profile, such as the removal of fucose in the terminal position, may result in higher affinity to natural killer cells, which induces antibody-dependent cellular cytotoxicity and lead to the lysis of the target cell (Chang, Hanauer, 2017).

Due to this profile of biological drugs, one significant concern is their natural potential to induce human immune responses, such as hypersensitivity and infusion reactions, which compromises their safety and tolerability. Immunogenicity also includes the possibility of immune complexes formation, which may lead to the biological activity

neutralization and changes in its clearance, affecting both efficacy and pharmacokinetic properties (Reinisch, Smolen, 2015).

A phenomenon that can trigger immunogenicity is the recognition by the immune system of biological drugs as non-self-antigens, leading to the generation of antidrug antibodies (ADAs). ADAs are capable of intercepting biological drugs binding with the target domain, which can nullify their action and decrease their efficacy. A second cause of decreased efficacy is the attachment of ADAs to biological drugs in other domains that may accelerate their clearance and affect their pharmacokinetic standards. Lastly, the combination formed by ADAs and biodrugs binding is associated to the manifestation of local and systemic adverse immune events (Blandizzi, Meroni, Lapadula, 2017).

Although the biosimilars have equal complexity, an advantage of biosimilars in contrast to the biological reference products is the less demanding requirements for its approval as a new medicine. Nevertheless, the licensing pathway for biosimilars have more prerequisites than for generic drugs. The general distinctions of each regulatory pathway are shown in Table 1.

Table 1. Required data for approval of each drug category.

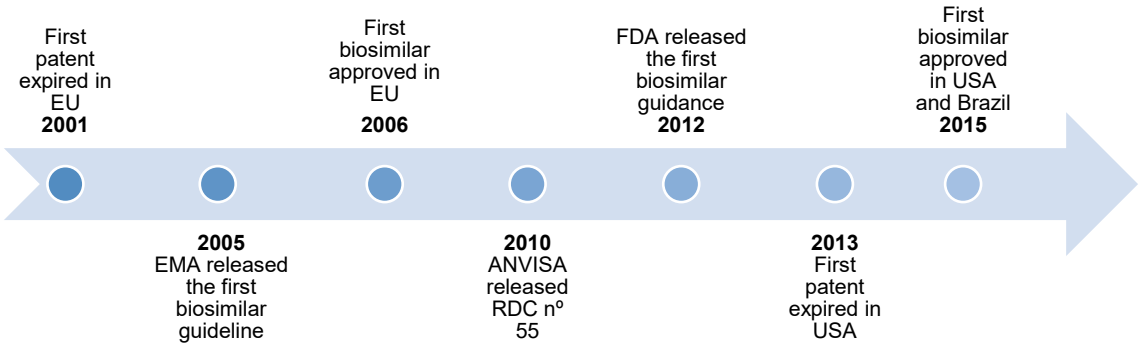
Generics	**Biologics**	**Biosimilars**
1. Quality	1. Quality	1. Quality
2. Purity	2. Purity	2. Purity
3. Stability	3. Stability	3. Stability
	4. Potency	4. Potency
	5. Immunogenicity	5. Immunogenicity
	6. Full non-clinical and clinical studies	6. Abbreviated preclinical and clinical studies
		7. Comparability studies
		8. Post-marketing monitoring

Source: Adapted from Grozdanova *et al*., 2016.

The approval pathway for biosimilars includes different steps for demonstrating biosimilarity. For approval by the FDA, a proposed biosimilar must be compared to the reference product in terms of structure, function, animal toxicity, human pharmacokinetics and pharmacodynamics, clinical immunogenicity and clinical safety and effectiveness (FDA, 2015). While for EMA approval, the data requirements include comparative clinical and non-clinical studies, comparative quality studies and pharmaceutical quality studies (EMA, 2017).

Requirements for biosimilars approval are well stablished mainly in EU and the United States, with their regulatory authorities EMA and FDA, respectively. Since these regions retain the largest and most competitive biological markets globally, their necessity for releasing guidances on biosimilars is even larger and their pathways became a model for other countries' legislations.

Figure 2. Biosimilar timeline in EU, USA and Brazil.



Source: Adapted from Rovira, Lindner, Giménez, 2013 and Lucio, Stevenson, Hoffman, 2017.

In Brazil, ANVISA published in 2010 the Collegiate Board Resolution (RDC) No. 55, which details the conditions for approving biosimilars. The requester industry can choose two different pathways for regulatory registration, the individual development pathway or the development by comparability (ANVISA, 2010), detailed in Table 2.

Table 2. Requirements for biosimilar approval in Brazil.

Individual development	Development by comparability
Total evidence regarding development, production, quality control and non-clinical and clinical data. No requirement of comparative clinical studies for phases I and II. Phase III clinical studies are always required. Extrapolation of safety and efficacy data for other therapeutic indications is not applicable for drugs approved through this pathway.	Analytical and biological comparison between the comparator and the biosimilar candidate, necessary to determine the degree of comparability. Comparative studies of safety and efficacy, pharmacodynamics and pharmacokinetics, cumulative toxicity, phase III clinical studies and, when available, phase IV studies.

Source: Adapted from ANVISA, 2010.

Extrapolation of indications

Extrapolation of clinical data across indications is the expansion of the efficacy and safety evidences from a therapeutic indication that was clinically tested for the biosimilar to other therapeutic indications that has been already approved for the reference biologic (EMA, 2017). Once the biosimilarity is proven by comparability studies, both EMA and FDA support the extrapolation of data for non-tested indications with appropriate and sufficient scientific justifications, summarized in Table 3.

Table 3. Extrapolation guidelines for EMA and FDA.

EMA	FDA
Safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated by the totality of tests in one therapeutic indication. Additional data may be required if the active substance of the reference product interacts with several receptors; the active substance itself has more than one active site; the studied therapeutic indication is not sensitive for differences in all relevant aspects of efficacy and safety.	If the product meets the requirements as a biosimilar based on sufficient data demonstrating safety, purity and potency in an appropriate condition of use, it may be licensed for one or more additional conditions. However, FDA recommends tests in the most sensitive condition and demands scientific justification for each solicited condition of use, which may include the mechanism of action for each indication; immunogenicity in different patient populations; description of differences in toxicities in each indication and patient population.

Source: Adapted from Curigliano *et al*.,2016.

Brazilian legislation has determined that, once the proposed product meets the licensing requirements as a biosimilar through comparability development pathway, the extrapolation for one or more additional indications for which the reference product already is licensed may be claimed. In order to justify extrapolation, the clinical test used must demonstrate ability to detect potential differences between the products, the mechanisms of action and receptors involved for the intended indications must be the same and both safety and immunogenicity of the product must be sufficiently defined (ANVISA, 2010).

In EU, biosimilars of different complexities earned grant for extrapolation for all indications approved for the reference biologic, from filgrastim to infliximab (Weise *et al.*, 2014). Infliximab was the first monoclonal antibody biosimilar approved in the EU and it obtained license for all previously approved indications by both EMA and FDA.

Clinical evidences showed efficacy in treating conditions of rheumatoid arthritis and ankylosing spondylitis and the biosimilar was also approved for the use in psoriasis and inflammatory bowel diseases. Additionally, FDA has approved adalimumab biosimilar for all indications of its originator, which included not only the tested conditions of rheumatoid arthritis and psoriasis, but also ulcerative colitis and Crohn's disease (Chang, Hanauer, 2017).

Extrapolation of indications might result in price reductions in drug development and shorter time for market availability (Chang, Hanauer, 2017). While some defend that once the comparability is assured, the extrapolation avoids unneeded and even unethical studies in the population to prove a point already proven (Curigliano *et al.*,2016), on the other hand, the discussion whether extrapolation involving completely different conditions (e.g. from a nononcological to an oncological indication) should be authorized remains inconclusive (Weise *et al.*, 2014).

Interchangeability

Interchangeability for generic drugs regards an automatic substitution of a reference synthetic drug to its generic at the dispensing by a pharmacist (ANVISA, 2007). However, for biosimilars, this definition is not unanimous among all regulatory authorities. Depending on the definition adopted by each regulatory authority, interchangeability of biosimilars is a form of switch, which may differ between medical and non-medical decisions, as indicated in Table 4.

Table 4. Definition of switching between a biological reference product and its biosimilar for FDA and EMA.

Regulatory Authority	Definition of switching
EMA	**Interchangeability** refers to the possibility of replacing a reference biological product with a biosimilar that is expected to have the same clinical effect. This replacement can be performed as: **Switching**, a clinical decision by the prescriber of exchanging one medicine for another. **Automatic substitution**, which is the practice of a pharmacist of dispensing one medicine instead of another equivalent and interchangeable medicine without consulting the prescriber.
FDA	**Interchangeability** refers to a biosimilar that can substitute a reference biological product without the intervention of the health care provider who prescribed the reference product.

Source: Adapted from EMA, 2017 and FDA, 2017.

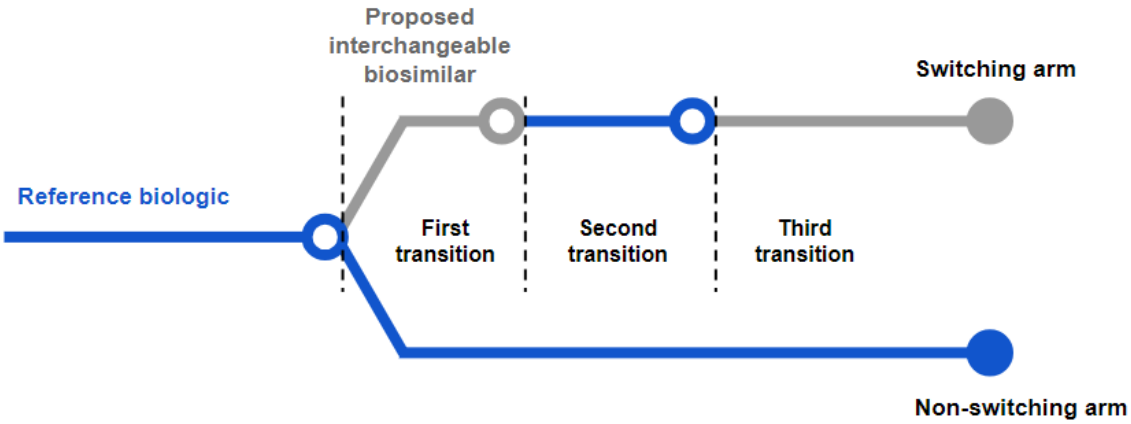
In EU, EMA declares that interchangeability of biosimilars is not in their scope and leaves the decisions on this subject for each member state (McKinnon *et al.*, 2018). Regulatory authorities from Finland, Netherlands, Scotland, Ireland and Germany supports interchangeability under the prescriber physician monitoring (Kurki *et al.*, 2017). Nonetheless, the Italian agency suggests the use of biosimilars only for the treatment of naïve patients and 15 EU countries had limited or prohibited substitution or/and automatic substitution of reference biologics with biosimilars (Niederwieser, Schmitz, 2011).

Moreover, the European Society for Medical Oncology reinforced that interchangeability and switching should be allowed particularly if the physician has necessary knowledge about the medicines, the patient is aware of the situation and a nurse is carefully supervising possible changes and adverse events that may occur (Tabernero *et al.*, 2017).

In contrast to EMA, the FDA endorses its role in designating a biosimilar as interchangeable and it may give approval for two different designations: noninterchangeable and interchangeable biosimilars (Declerck *et al.*, 2018). The FDA draft guidance regarding interchangeability describes as interchangeable a biosimilar that alternates or switches with the reference biological and evidences no increased risk of safety or reduced efficacy compared to the exclusive use of the reference product (FDA, 2017). Up to the present, there are no biosimilars designated as interchangeable approved by FDA (NCSL, 2018).

In order to be assigned by FDA as an interchangeable biosimilar, the sponsor must successfully conduct a switching study, which requires a specific study design. The demands include a lead-in period of treatment with the originator biologic followed by a period of randomized treatments in two different arms, the switching and non-switching arm. The non-switching arm should continue with the reference product, while the switching arm incorporates the interchangeable candidate, with at least three transitions between the originator and the product under investigation, as illustrated in Figure 3.

Figure 3. Switching study design recommended by FDA.



Source: Adapted from FDA, 2017.

However, the decision of allowing the replacement of reference products for their biosimilars at the pharmacy level depends on individual state laws (Reinisch, Smolen, 2015). Thus far, 45 states enacted biosimilars substitution laws and each state

regulated the requirements differently. Even with this variation, state legislation provisions mostly contemplate common topics, such as the demand for FDA's approval as an interchangeable biosimilar, the compliance with the prescriber's decision and proper notification to patients and prescribers (NCSL, 2018).

Evidences of clinical experiences on interchangeability of biosimilars have been shown controversial and inconclusive. A study with nine subjects who switched from the originator infliximab to the biosimilar CT-P13 showed that, even with the exchange, a similar clinical outcome was maintained by the biosimilar CT-P13. Among these patients, one had experienced an adverse event post-switching and other experienced loss of efficacy (Kang *et al.*, 2015).

A Finnish study observed that exchange of infliximab to the biosimilar resulted in a corresponding clinical efficacy and no safety concerns when compared to the reference product's response during the first year for 39 patients. Similarly, a Danish registry included 768 subjects who had experienced nonmedical switch from reference infliximab to CT-P13 and it indicated that, for majority of patients, the substitution did not affect their disease activity (Becciolini *et al.*, 2017). Nonetheless, none of the studies mentioned were adequate to the requirements for demonstrating interchangeability proposed by FDA, seeing that there were only single switches, the comparator arm was not existing or appropriate and the long-term response remains unclear.

Furthermore, negative aspects of switching were detected across several studies in which subjects who underwent substitution from the originator to the biosimilar experienced adverse events (e.g. acute hypersensitivity reactions, rash and infusion reactions) after switching (McKinnon *et al.*, 2018) and higher loss of efficacy and discontinuation rates (Declerck *et al.*, 2018). Lastly, a reference center for rare rheumatic diseases observed patients with long-term and stable remission who suffered relapse soon after changing from infliximab to CT-P13 (Cantini *et al.*, 2017).

Currently in Brazil, the interchangeability of biosimilars in under wide discussion in forums and audiences, however, this subject has still not reached a consensus and it remains uncertain. In 2017, ANVISA published the Clarification Note No. 3, which declared that interchangeability should not be assessed at the moment of sanitary registration, once there is no requirement of interchangeability demonstration tests for

the biosimilar approval. Thus, ANVISA assigned the decision of assessing the interchangeability to prescribing physicians and the Ministry of Health (ANVISA, 2017).

Seventy five percent of the Brazilian population depends exclusively on the Unified Health System, which cannot bear the demand (WHO, 2010). Consequently, majority of patients are unable to follow up with the same physician and, as a result, treatment decisions rarely rely on the patient's clinical history. In addition, the Ministry of Health, through the Unified Health System, provide for population the acquisition of drugs free of costs and, since biologic medicines are expensive, patients mostly depend on the availability in the public system. However, the high cost of these medicines may directly influence not only the physician's decision on behalf of patients' financial conditions but also the government's decision on which drug to buy for the population. In these scenarios, treatment decisions based on scientific evidences and the patient's individual response or clinical history may not become a priority.

Pharmacovigilance, Traceability and Nomenclature

In consideration of the shorter development duration for biosimilars in comparison with the reference biologics, the studies are insufficient for properly detection of possible risks. For this reason, biosimilars should apply a robust pharmacovigilance program for a solid surveillance during post marketing phase (Blandizzi, Meroni, Lapadula, 2017), such as the implementation of active surveillance to capture adverse events reports. The main purpose of pharmacovigilance is to identify and comprehend adverse events and evaluate whether a risk is related to the use of a certain medicine. From the recognition of potential or confirmed risks, pharmacovigilance is also responsible for the execution of activities or actions to promote risk awareness and minimization, as applicable (Reinisch, Smolen, 2015).

In order to evaluate accurately the relation of adverse events to the correct pharmaceutical product, the traceability of risks must be achievable. One feasible facilitator would be the notification of the batch number or the obligation of a distinct nomenclature for a simple discernment between originators and biosimilars (Blandizzi, Meroni, Lapadula, 2017). Hence, International Nonproprietary Name (INN) system established by WHO should not be used in the prescription, taking into consideration that this nomenclature system nominates the original biologic and its biosimilars with

the same INN (Rak Tkaczuk, Jacobs, 2014). To distinguish them, the most appropriate alternative would be the use of the brand name or the INN plus an unique identifier, such as an exclusive number according to approval order or a 4-letter suffix code, as proposed by WHO (Grozdanova *et al.*, 2016).

Between trade name and batch number, the first has been proved more effective for traceability of biosimilar products, since physicians neglect the batch number when reporting adverse events. Specific labeling would not only permit traceability, but also certify precise prescription and assure the correct dispensing and administration for each patient (Blandizzi, Meroni, Lapadula, 2017).

Awareness of Biosimilars

Healthcare professionals and patients are determinant parts for the effective consolidation of biosimilars in clinical practice. An online research conducted by an advocacy group with 738 users of biological products showed that 19% of the patients would accept the exchange of the biological drug by the biosimilar. In case of automatic substitution, it is unanimous among the patients that this decision should be decided and authorized only by the physician.

These results show not only a lack of knowledge of patients but also a lack of awareness and proper guidance practiced by the healthcare professionals. This might be a result of a gap of knowledge regarding biosimilars by these professionals, which require urgent education and training on this subject to better instruct the population and build a confidence relationship. Moreover, there is a need for pharmacovigilance training for multidisciplinary professionals, in order to raise the awareness and contribution to the pharmacovigilance system with proper reporting of adverse events. In the long-term, the resulting awareness will build a more assertive and reliable scientific-based evidences.

CONCLUSION

Biosimilars are potential treatment alternatives to expand health access, especially considering the extrapolation of indications, which is a well-stablished topic. However, this new drug classification still needs further discussion and clarification in other significant topics among regulatory authorities, such as consensus on the definition of interchangeability, regulatory pathways of approval and labeling. In the current Brazilian scenario of absent regulation on interchangeability and lack of awareness, the patient may undergo a switch without knowledge or orientation, which can affect the traceability of adverse events or even cause treatment failure. Considering the inequalities and difficulties of the Brazilian health system, there is a need for clear and scientific-based governances on interchangeability, as exemplified by the FDA, which classifies the biosimilars as interchangeable or noninterchangeable after the conduction of solid studies. With adequate regulations for interchangeability and labeling, education of professionals and patients and endorsement of pharmacovigilance system for risk-benefit monitoring, biosimilars will remain as an important opportunity for treating complex diseases with the confidence of healthcare providers and patients.

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