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1. Introduction

Biologic drugs are large and complex pharmaceuticals whose structure, physicochemical and biochemical characteristics, and manufacturing process have direct influences on their organic activity [1]. Contrary to synthetic molecules, with simpler structures and low molecular weight, which are obtained exclusively by chemical methods, biologics are very heterogeneous, more unstable compounds, with tridimensional structure and high molecular weight (100–1000 times larger than synthetic molecules), obtained through complex methodologies that include the initial production in genetically modified living cell organisms and processing using fermentation and purification methods [2–4].

The development of biologics in the decade of 1980 revolutionized the way physicians treated their patients, especially with diseases for which an effective treatment was not yet available. Notably, biologic medicines have improved the management of disease, ranging from some types of cancer to chronic inflammatory diseases such as rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriasis, and psoriatic arthritis [5]. However, the high cost of biologics also had a direct impact on healthcare budgets around the world and in many countries they are one of the leading costs related to healthcare expenditure [6]. To rein in healthcare expenditure and promote greater population-based access to biological medicines, biosimilars—highly similar, reverse-engineered versions of existing innovator biological medicines and their active ingredients (originator or reference products)—have emerged as less expensive treatment options compared with reference products after their market-exclusivity patents have expired [7, 8].

Of note, other terminologies have also been applied to biosimilars, such as similar biotherapeutic products, biocomparables, and follow-on biologics, among other terms. The latter are no longer used, and the term biosimilars is globally accepted. Regulatory agencies worldwide require a different and more complex processes for the approval of biosimilars compared to generics of synthetic molecules. This is based in a complex set of comparability exercises known as biosimilarity exercise [9].

From a regulatory and clinical point of view, globally, a biosimilar must be as safe, pure, potent, and efficacious as the reference product based on a comprehensive comparability process, such that there are no clinically meaningful differences [10, 11]. Across the United States, Europe, and more universally based on the World Health Organization's standards, establishing biosimilarity follows a stringent yet abbreviated regulatory pathway compared with that for an originator biologic [12, 13]. The regulatory pathways are built to define whether the reference product
Biosimilars and the new similar molecule offer sufficient similarity in terms of structure, purity, pharmacological and clinical characteristics. It is well known that even different batches of the same reference product can exhibit minimal differences through time. These minimal changes could have a direct impact on pharmacokinetics (PK) and pharmacodynamics (PD), as well on efficacy and safety, so the similarity exercise must include a batch-to-batch evaluation of biosimilars in comparison with the reference product [14].

In general, only when all the features in the similarity exercise are matched, the approved product can be defined as a biosimilar [15]. In cases when a product claims to have high similarity to a given innovator but has not provided sufficient evidence, according to all the steps of the regulatory pathway for biosimilars, it might be called an intended copy. Other terms such as “biomimic” and “nonregulated biologic” also have been used for those products [16].

2. Regulatory requirements for approval of biosimilars

Regulatory requirements for approval of biosimilars are generally consistent across the WHO, EMA and Health Canada, and the guidelines issued by the FDA [17, 18]. Although minor differences may exist among these guidelines, sometimes with some small differences in terminology, all these agencies require a stepwise approach to establish biosimilarity of a product. These established regulatory pathways include comparative assessments involving analytical, nonclinical, and clinical studies. The EMA has played a global regulatory lead launching the first regulation to require head-to-head comparative studies for structural characterization, functional in vitro assays, pharmacokinetic and pharmacodynamic evaluations, and safety, efficacy, and immunogenicity assessments. Other agencies have followed the EMA in requiring the same head-to-head studies [19].

Biosimilarity is considered when there is the totality of the evidence from all evaluations, with each step supported by the preceding one:

1. First Step: requirement of analytical studies involving several orthogonal techniques to confirm that the biosimilar has a foundation of quality based on structural and functional similarity to the reference product.

2. Second Step: Nonclinical studies demonstrating that the biosimilar agent acts on the same target or physiologic process and has similar toxicity as the reference product.

3. Third Step: This is the crucial element in the evaluation of a biosimilar product. It is a tailored clinical trial program that compares the pharmacokinetics, clinical efficacy and safety, and immunogenicity of the biosimilar with that of the reference product.

3. Clinical trials for biosimilars

Clinical development of a biosimilar requires a rigorous head-to-head comparison with the reference product and scientific reliable data. The main goal is to demonstrate that any difference in efficacy or safety between the reference product and the biosimilar is less than a prespecified margin of clinical equivalence [20, 21].

The choice of a clinical trial design depends on several factors, and the specific design selected for a particular trial should be explicitly justified in the clinical
protocol [21]. The selection of the primary endpoints in terms of efficacy and safety is a multistep process that includes the statistical design of the main study, as well as the calculation of the appropriate sample size to ensure statistical power. The process requires clear understanding of the comparability prespecified margins. According to the WHO, the selected margin should represent the largest difference in efficacy/safety that matters to the clinical practice. By definition, any difference in result contained within the range would have no clinical relevance. The comparability margins for a certain endpoint result from clinical reasoning, being frequently neither well established nor universally accepted. Thus, the choice of the sample size should be well justified by the sponsors of the study, being usually a combination of the opinion of experts and previously published analyses. In general, phase II trials are not required to biosimilars once the dose of the reference product has been previously established. Comparative clinical (phase I and phase III) trial designs for biosimilars are similar to those for any biologic with respect to most-sensitive patient population, sample size, endpoints, and study duration. The trials should be randomized, double-blinded, and adequately powered [20].

Because the goal of a comparative clinical trial is to demonstrate that the proposed biosimilar is equivalent to the reference product, superiority trials are not appropriate. Instead, nonsuperiority trials, including equivalence and noninferiority designs, are most suitable [22]. Although sometimes noninferiority trials can be used, an equivalence study design is preferred to demonstrate that the biosimilar is equivalent to the reference product. The goal in an equivalence trial is to reject the null hypothesis of nonequivalence and accept the alternative that the biosimilar and reference products are equivalent. The trial should determine whether the biosimilar is no worse and not better than the reference product. This accomplishment is achieved using a two-sided test that requires a superior and an inferior margin limit, the prespecified equivalent margins is selected to detect clinically meaningful differences in effectiveness between the biosimilar and reference product at 95% confidence interval [20]. There are cases that a one-sided noninferiority design may be appropriate, although only if justified (for instance, if the reference product has a wide safety margin). Noteworthy a one-sided test does not demonstrate equivalence, just demonstrates that the biosimilar is not inferior to reference product.

Sample size, study duration and different endpoints are other important considerations in the design of a comparative clinical trial. Sample size is the most important factor of the power of a study and may be affected by the equivalence margins and treatment effects. As long as the equivalence margins narrow, the minimum sample size increases at the same time. On the contrary, the larger the equivalent margins, the lower the number of patients required. The disease for which the biosimilar is being studied will influence the duration of the study. In rheumatic autoimmune conditions, because most of them are chronic, the comparative clinical trial should be of sufficient duration so that both beneficial clinical effects and potential adverse effects may be observed and well documented. Commonly the endpoints selection is based on the endpoints used in the clinical trials of the reference product [20, 22].

4. Regulatory scenario in the underdeveloped world

In Latin America, a heterogeneous regulatory landscape, and nonconsistent approval practices for biosimilars creates decision-making challenges for practicing clinicians. Most Latin American countries have adopted guidelines for the approval of biosimilars. However, among several marketed biologics in the region, there are currently a couple of molecules that could be considered true biosimilars, based
Biosimilars on the WHO criteria. On the other hand, there are products called intended copies approved before the update of the regulations and not following the requirements of a specific biosimilarity pathway. Unlike biosimilars, which have proved efficacy and safety by rigorous head-to-head comparative studies and received approval from international regulatory agencies, none of the intended copies underwent head-to-head clinical trials compared with reference product and received approval from the global agencies such as EMA, FDA, or Health Canada. So safety and efficacy of those biomimics are not fully established. There is a considerable effort in the region to harmonize the regulation on biosimilars [23].

A growing number of countries in Asia have established or are establishing regulatory pathways for evaluation and approval of biosimilars. Japan and South Korea released guidelines in 2009 [24], and Singapore and Malaysia have generally followed EMA guidelines. India released official biosimilar guidelines in 2012 [25].

5. Other regulatory and clinical questions on biosimilars: extrapolation of indications and nomenclature

Omnitrope, a growth hormone biosimilar, was the first biosimilar approved in the world, and CT-P13 was the first biosimilar Mab approved. Since the C-P13 approval in South Korea and Europe, a great deal of experience has been accumulated, which has helped to answer important questions, especially regarding the importance of preclinical essays, extrapolation of indications, and establishing the clinical trial (CT) models and the most sensitive populations [26].

Extrapolation of Indications: This topic had been an important regulatory advantage for biosimilars and had a direct impact on costs to the health systems. It involves considering the potential to extrapolate the efficacy and safety data from one already studied condition to the other indications of the reference product, for which the biosimilar was not directly tested [14].

A cost reduction for biosimilars is implied in the possibility of extrapolation of indications, as a result of transitioning from conducting several phase III trials, as is the norm, to only conducting one comparative pivotal trial. The extrapolation of indications has been supported by the WHO under the following conditions:

1. A sensitive clinical test model is used to detect potential differences between both products;
2. The mechanisms of action and/or the involved receptor in the studied pathology and the extrapolated one are the same;
3. Sufficient characterization of safety and immunogenicity of the biosimilar, and there are no unique/additional safety issues expected for the extrapolated indication;
4. Rational and convincing arguments that the efficacy findings from the clinical trial can be extrapolated to the other indications [27].

The case of the extrapolation of CT-P13 was initially controversial. As the first mAb biosimilar to receive approval worldwide, this monoclonal antibody opened the doors to further discussions about extrapolation. At first, the Canadian agency did not approve the extrapolation of indications for inflammatory bowel disease (IBD). The rationale behind this decision was based on differences in the fucosylation profile between CT-P13 and the RP, which was related to a diminished binding capacity with FcγRIIIa. This receptor is related to the antibody-dependent cell-mediated cytotoxicity (ADCC), which is an immune response important in IBD pathophysiology. When analyzed through very sensitive in vitro models using isolated natural killer cells from the patients with Crohn's disease, this biosimilar showed a reduced ADCC. However, in less-sensitive models with mononuclear cells from peripheral blood or total blood, this difference was no longer significant. The decision of the Canadian agency for the extrapolation of the indication for IBD
was reverted based on postmarketing results showing no additional efficacy/safety problems in Crohn's disease and results of additional physicochemical analysis [28].

In general, to establish the extrapolation of indications, the manufacturer must use the most sensitive population in randomized clinical trials to detect clinically meaningful differences in not only efficacy but also safety and immunogenicity. The most sensitive population must be well defined and is a population with the clinical condition in which the difference of the effect between the reference product and placebo is the highest (the placebo-adjusted efficacy) [29].

The extrapolation of indications has been authorized by regulatory agencies based on the totality of evidence and also evidence gathered through real-life data showing good outcomes in terms of safety and efficacy for all indications approved [29–31].

The nomenclature of biosimilars has a direct influence on the physician's ability to prescribe an intended biologic medicine. Mostly the naming system has a great impact on the pharmacovigilance, traceability, and interchangeability of biosimilars [32]. If a "biosimilar" is not identical to the reference product, it is reasonable to question whether both drugs should be equally named.

The WHO proposes the use of a unique identification code, called the biological qualifier (BQ), to differentiate drugs under the same International Nonproprietary Name (INN). The BQ complements the INN with the addition of four random consonants to identify the manufacturer of the active substance that would be applied to all drug substances of biological medicines, including biosimilars, innovator products, nonglycosylated and glycosylated proteins, and impure mixtures, and complex biologically extracted products, such as heparin or pancreatin, with the exception of vaccines [33]. The FDA followed the recommendations of the WHO using the same suffix strategy [34].

The proposed suffix should be unique; devoid of meaning; composed of four lowercase letters, of which at least three are distinct; nonproprietary; attached to the core name with a hyphen; and free of legal barriers that would restrict its usage. However, in Asia and Latin America, naming policies are heterogeneous so far.

6. Interchangeability of biosimilars

A number of real-world scenarios, of a medical and nonmedical nature, may lead to cross-switching between biosimilars of the same reference product.

At first we must recognize medical switching occurs when one medication is exchanged for another at the physician's discretion [15]. The objective of a medical switch is always to optimize the patient's treatment benefit. This is not the case for a medical cross-switch involving biosimilars.

In specific instances, cross-switching may be medically necessary to address intolerance issues, such as the avoidance of an irritating excipient (citrate-free vs. citrate-containing biosimilars of adalimumab) or a prefilled delivery device for one biosimilar to which a patient exhibits a hypersensitivity (a needle cover containing a derivative of latex versus a latex-free needle shield) [35, 36].

On the contrary, nonmedical switching occurs when a clinically stable patient, whose current therapy is effective and well tolerated, is switched to another therapeutic alternative [37]. This switching or cross-switching is not related to improving efficacy, safety, and/or convenience, but rather it is moved for the purpose of reducing costs or to ensure that the patient has continued access to the same type of drug [38]. Nonmedical cross-switching is, in general, governed by a third party (e.g., a payer who insists that patients align with the particular biosimilar covered by the health-plan drug formulary or based on an employer-plan offering), initiated by a
hospital pharmacist to avert supply-chain issues due to an unreliable manufacturer, or it may be necessary for a traveling or relocating patient whose current biosimilar might not be geographically available [31, 39, 40]. Out-of-pocket expenses, incentives promoted by the payer, copayment, rebates, or fixed reimbursement hospital fees to inpatient day despite the medication used may also influence a decision to cross-switch to another biosimilar version, or alternatively reverse-switch to the reference product when the economic incentives disappear.

Interchangeability is a characteristic between two or more products that indicates that switching these products back and forth represents no additional risk in terms of efficacy or safety to patients when compared with the products alone [41]. It is not clear so far whether the interchangeability of biologics may impact on immunogenicity safety and efficacy. The FDA, for instance, has recently published a draft requiring clinical data supporting interchangeability [41]. This draft includes evidence from at least one prospective clinically controlled study with a sufficient lead-in-period of treatment with the RP, followed by a randomized two-arm period (switching versus nonswitching). The switching arm should have a minimum of three switches with each one crossing over to the alternative product.

On the contrary, the European guidelines do not provide recommendations on interchangeability, which leaves decisions concerning access to the European national regulatory authorities.

In the United States and many European countries, there is already more than one approved biosimilar from the same reference product and the assessment of efficacy and safety equivalence, and the switching data were obtained from comparison studies. Despite growing evidence, additional data are still needed in order to investigate whether interchangeability is a viable process. A couple of consensuses regarding use of biosimilars have been published for some patient groups [42–45].

These recommendations or consensuses recognize biosimilars as an opportunity to increase access to expensive therapies and would accept receiving biosimilar treatment once it was prescribed, respecting a shared decision between the physician and the patient. Medical societies in general agree that the decision to switch products should be based on a shared decision between patient and physician [43, 45].

7. Biosimilars in rare diseases: an opportunity

Rare diseases represent a challenge for the modern medicine. The orphan drugs used in the treatment of rare diseases are often associated with high treatment costs. For many health systems, the costs to treat patients with rare diseases are not affordable. For the development of biosimilars to rare diseases, which should reduce costs, there are a number of associated challenges, such as the high costs of obtaining the reference product for manufacturing purposes; the small of batches in order to determine batch-to-batch variability; difficulties in obtaining a large enough population size for phase I and III trials; and in some cases a heterogeneous population with the condition. However, we expect to update this chapter in the next few years as new biosimilars are approved to treat rare diseases, given this is such an important topic to health systems, patients, and the pharma industry [46, 47].

8. Pharmacovigilance

According to the World Health Organization (WHO), pharmacovigilance is defined as the science and activities relating to the detection, evaluation, understanding, and prevention of adverse drug reactions (ADRs) or any other
drug-related problems. A good pharmacovigilance practice requires reporting of all types of suspected reactions, suspected drug–drug or drug–food interactions, ADRs associated with drug withdrawal, medication errors or overdose, and lack of efficacy to regulatory authorities. Moreover, pharmacovigilance also requires aggregate reports, such as periodic safety update reports (PSURs) and risk management plans (RMPs) [48].

Theoretically, the biological effects of biosimilars in terms of efficacy and safety may differ from those of innovator compounds because of the differences in their manufacturing process, which could cause structural variations and impact on their stability. Moreover, the parenteral nature of the biosimilar agents could also affect their immunogenicity. These clinically important differences highlight that pharmacovigilance of biosimilar compounds is equally necessary as for innovator compounds.

As discussed previously, biosimilar compounds do not have to undergo the same clinical development processes as biooriginators and usually omit the phase II trials. This shortened clinical development process may require greater post-marketing vigilance [49]. Other implications for pharmacovigilance as immunogenicity for the same compound differ in patients with different diseases for various reasons such as route of administration of the drug, concomitant medicine use, and disease indication. Therefore, pharmacovigilance strategies for biosimilars need to be as robust as those for the reference products. Additionally, healthcare professionals play a key part in improving pharmacovigilance through accurate reporting and recording of ADRs [50].

In developing countries, healthcare is often fragmented, with limited financial resources for pharmacovigilance systems. There is also a lack of awareness among physicians about accurate reporting, which may contribute to under-reporting of ADRs [32].
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Biosimilars


