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Review

Strengths and weaknesses of the Brazilian regulation on biosimilars: A critical view of the regulatory requirements for biosimilars in Brazil

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Marcos Renato de Assis and Valdair Pinto

Abstract: Biological products or biopharmaceuticals are medicinal products derived from living systems and manufactured by modern biotechnological methods that differ widely from the traditional synthetic drugs. Monoclonal antibodies are the most rapidly growing type of biologic. They are much larger and more complex molecules with inherent diversity; therefore, different manufacturers cannot produce identical biological products, even with the same type of host expression system and equivalent technologies. Thus, legal follow-on biologics manufactured and marketed after patent expiration are usually referred to as biosimilars. Biosimilarity is based on a comparability exercise whereby unavoidable clinical differences are evaluated and must meet equivalence or non-inferiority criteria. Biosimilars need to comply with different regulatory requirements for market authorization in different sites. There are several other related issues that need to be defined by the national authorities, such as interchangeability, labeling and prescribing information. The Brazilian health surveillance agency follows the key principles established by the World Health Organization for the assessment of biosimilarity, although does not adopt the name `biosimilar'. However, the agency also made a compromise on a standalone application pathway that does not require the usual comparability exercise with the reference product, originating nonbiosimilar copies. Interchangeability and the use of nonproprietary names are not regulated, giving rise to pressures on physicians and conflicts of interest in the decision making on biosimilar use. The scope of this article is to present the Brazilian regulation on biosimilars, its strengths and weaknesses, and to discuss it in the face of regulations in the USA and Europe.

Keywords: Biosimilar Pharmaceuticals; Antibodies, Monoclonal; Government Regulation

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Introduction

Biological products or biopharmaceuticals are medicinal products derived from living systems and manufactured by modern biotechnological methods. They are typically proteins produced by deoxyribonucleic acid (DNA) recombinant technology but they can also be complex sugars, nucleic acids or tissue extracts that differ from the traditional synthetic and small-molecule drugs in many aspects.[1] Monoclonal antibodies are the most rapidly growing type of biologic, as they are extremely targeted therapies. They are much larger and more complex molecules, generally unstable, not completely characterized in view of their complex structure and, most importantly, due to inherent diversity and microheterogeneity, the source and manufacturing process mostly define their identity.[2] It is impossible for different manufacturers to produce identical biological products, even with the same type of host expression system and equivalent technologies. Thus, legal follow-on biologics manufactured and

Correspondence to:
Marcos Renato de Assis
Famema – Marília Medical School, R. Monte Carmelo, 800 – Fragata, Marília SP 17519-030, Brazil
a.assismr@gmail.com

Valdair Pinto
Okrafields Medicina Farmacêutica Ltda., São Paulo, SP, Brazil

marketed after patent expiration are referred to as biosimilars to indicate they are not identical, but similar products.[1,3]

While generics only require a demonstration of pharmaceutical equivalence by means of a pharmacokinetic comparison in healthy volunteers, biosimilars demand a set of studies on comparative biochemical and analytical characterizations, preclinical and clinical data to assure the differences related to the original product lie within an acceptable range with no clinical implications. Therefore, biosimilarity is based on a comparability exercise whereby unavoidable clinical differences are evaluated and must meet equivalence or non-inferiority criteria.[1,3] Biosimilars need to comply with different regulatory requirements for market authorization in different sites, which will be discussed here.

International regulatory outlook

Biosimilars are defined as copy versions of an already authorized biological 'innovator' product (or reference product) with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise. According to the World Health Organization (WHO), head-to-head comparisons of a biosimilar candidate against the reference product are mandatory for establishing biosimilarity in biological products.[3] If a copy version of a biological product is developed without the comparability exercise, it should not be labeled as biosimilar, even if it is eventually approved in a country with a less stringent national regulatory authority.[2] These products (which disregarded the comparability exercise) cannot rely on data generated with the reference product and should be licensed through the ordinary processes used in a full licensing application.[3]

Many countries have developed specific regulations for market approval of biosimilars. The European Medicine Agency (EMA) is the most advanced regulatory authority in this area, having developed a comprehensive number of legal documents and guidelines, which are often considered a model for other countries.[4] Regulated countries such Japan, Canada and Australia follow a similar approach to EMA and have published their requirements. In 2009, WHO has also issued guidelines to provide globally acceptable principles for licensing biological products that claim to be similar to approved reference products.[3] WHO has established the following points as key principles for the assessment of biosimilarity:

(1) Biosimilars (or 'similar biotherapeutic products,' as termed by WHO) are not generics and many characteristics associated with the approval process generally do not apply.
(2) Demonstration of biosimilarity involves a stepwise comparability exercise starting with the comparison of quality data (i.e. manufacture and analytical data), which will be a prerequisite for the reduction of nonclinical and clinical data required for approval.
(3) The basis for licensing of a biosimilar depends on its demonstrated similarity to a suitable reference product in quality, nonclinical and clinical parameters.
(4) Any relevant difference found in the quality, nonclinical or clinical studies will likely preclude its qualification as a biosimilar.
(5) If the comparability exercise with the reference product is not accomplished throughout its development process as described in the guidelines, biosimilarity cannot be attributed to the final product.
(6) Effective regulatory oversight of biosimilars, as well as other biotherapeutic products, is critical to managing their potential risks and maximizing their benefits.

WHO guidelines also highlighted that several important issues associated with biosimilars need to be defined by the national authorities, including intellectual property issues, interchangeability, labeling and prescribing information.[3]

In the US, a piece of legislation referred to as the Biologics Price Competition and Innovation Act (BPCI Act), also called the Biosimilar Act, was passed in 2010.[5] This legislation has provided the US Food and Drug Administration (FDA) the legal framework to develop its guidelines on the subject that started to be released in 2012.[6] Despite the differences between regulations and guidelines in different countries, there is a solid convergence on some requirements for approval of biosimilars, which is interesting to highlight:

(1) A complete dossier on manufacturing and quality;
(2) Comparative non-clinical and clinical studies;

Table 1. Summary of the ANVISA RDC 55/2010 requirements for each drug approval pathway.

	New biologic products	Biologic products (follow on)	
		Comparability (biosimilar)	Standalone (nonbiosimilar)
CMC documentation	Required	Comparative	According to standards*
Preclinical studies	Required	Comparative	Requirements may be reduced
Phase I and II clinical studies	Required	Comparative	Requirements can be waived and may not be comparative
Phase III clinical studies	Required	Comparative	Comparative with exceptions$
Immunogenicity studies	Required	Required	Required
Same reference as comparator	NA	Yes	Not specified
Risk management plan	Required	Required	Required
Extrapolation of indications	NA	Possible	Not possible

*As per specifications of (Chemical manufacture and Control).
$Blood derivatives, vaccines and oncological drugs.
ANVISA, National Health Surveillance Agency in Brazil; RDC, resolution of the board of directors; CMC, Chemical manufacture and Control; NA, not applicable.

(3) Studies designed with sensitivity to detect differences, and planned as non-inferiority or equivalence with predefined margins;
(4) Nonclinical and clinical immunogenicity studies;
(5) Postmarketing risk management plan and risk minimization strategies.

The Brazilian regulation

In December 2010, the National Health Surveillance Agency (ANVISA), responsible for drug regulation in Brazil, has issued a revised directive for biologic products ('Resolution of the board of directors' RDC 55/2010), specifying the minimum requirements to submit an application for registration of new and follow-on (copies) biologic products.[7] Considered within the scope of the document are therapeutic proteins, monoclonal antibodies, vaccines, therapeutic serum, blood derivatives, tissue extracts and some living organisms. It contains the basic principles enumerated above, but also includes some provisions viewed with some concerns since they are not completely aligned with international trend.

In the ANVISA terminology, two terms are used: 'new biologic product,' which is a new biologic entity not yet registered; and 'biologic product,' which refers to copies or follow-on products containing an active substance already registered by the agency. The obvious intention with this nomenclature is to make clear that biosimilarity is not necessarily a precondition for the approval of copy biologic products. Notwithstanding using the denomination of 'biologic products' for copies, whether they are similar or not, is confusing and therefore is considered inappropriate.

According to Brazilian regulation, the applicant may submit a 'biologic product' (copy) *via* two possible pathways: (a) by comparability with the reference product, resulting in a true biosimilar; or (b) *via* standalone application (*via de desenvolvimento individual*), with a reduced dossier and resulting in a nonbiosimilar copy. This individual development pathway introduces a more permissive approach in which the copy product does not require a full comparison with the original one. Therefore, this alternative pathway might approve products with an unknown degree of dissimilarity (Table 1).

In the Brazilian regulations, there is no minimum period of time between the authorization of the biological innovator and the request for a biosimilar license, that is, there is no relation to the patent issue.[8]

Similar to other international regulations, when ANVISA approves a product, the holding company is committed to present and execute a continuous monitoring plan for safety and efficacy by a pharmacovigilance system. Unfortunately, in Brazil, the results of these observational studies are usually not made available to the medical community.

A biosimilar and its reference comparator should be registered and licensed in their country of manufacture; exceptions can eventually be accepted by ANVISA after considering documentation on epidemiological impact of its use in Brazil.

Internationally, standalone applications are justified or even desirable when biosimilarity is not the objective or cannot be anticipated (e.g. biobetters). Biobetters are copies of existing biologic products intentionally made different to explore pharmacokinetic or pharmacodynamic advantages; for example: darbepoetin is a biobetter of erythropoietin in which hyperglycosylation increases half-life. However, in these cases it is expected that submissions are robustly supported by a complete dossier, as suggested in the WHO guideline and contrary to what ANVISA has indicated in the RDC55/2010.[3,7]

Discussion on nonproprietary names, interchangeability and extrapolation

Two major issues up until now (September 2018) have not been regulated by the Brazilian agency: a system to designate nonproprietary names of active principle, and the condition of interchangeability.

After recommendation of WHO, the FDA recently published its final guideline regarding the nonproprietary names for biological products.[9] Essentially, due to the fact that the reference product and its biosimilars are not identical, they need receive different common names (International Nonproprietary Names [INN] for WHO, United States Adopted Name [USAN] in the US and Denominações Comuns Brasileiras (Common Brazilian Denominations [DCB]) in Brazil). As per WHO and FDA, the disambiguation is resolved by adopting a composite name for biologicals with a core (same for reference and biosimilars) and a four-letter suffix different for each pharmaceutical product. ANVISA has not adopted the WHO recommendation nor the FDA rule on naming and, as indicated in Table 2, there is no discrimination on nonproprietary names for biosimilars and reference. This differentiation is needed to provide the prescribing physician the option to designate the product to be dispensed and, perhaps more importantly, to ensure the necessary traceability for safety assessments. As emphasized by the FDA, the consequences of immunogenicity of these large biotherapeutical proteins in patients with autoimmune disease may vary widely and calls for an effective pharmacovigilance, even with the initial expectation of low risk.[10]

Interchangeability is the condition whereby two or more pharmaceutical products can be changed or even alternated during the treatment, without any compromise to the efficacy and safety. Interchangeability usually authorizes automatic substitution, meaning that the medical prescription can be changed to any interchangeable product without the participation of the treating physician. Basically, it is a regulatory definition.[11] The notion of interchangeability is accepted with few exceptions for synthetic drugs and small peptides coined as generics because active substances are identical. Nonetheless, biosimilars, nonbiosimilar copies, and the reference products do not have identical active substance and in principle should not be considered interchangeable. FDA has established clear rules on this issue, demanding efficacy and safety data showing that no additional risks are incurred by the patient when comparing the exchange between two products with the exclusive use of the innovative product.[5] EMA, on the other hand, does not have the authority to designate a biosimilar as interchangeable and the decisions rest with each member state in the EU. The concept of interchangeability in Europe is 'the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber.' Many of the European countries, such as the UK, Finland, Denmark, and Norway, have supported physician-led switching.[12] Unfortunately, in many countries, Brazil among those, interchangeability had not been defined by a regulatory agency and thus left a perilous gap in this matter. A recent ANVISA clarification note states that interchangeability is more directly related to clinical practice than to regulatory status.[13] In addition, it emphasizes medical evaluation as essential in the case of substitution and interchangeability of biosimilar products and their comparators, but in the same paragraph, states that multiple exchanges between these products is not acceptable, as traceability

Table 2. Comparison of main features of Brazilian regulation on biosimilars in relation to the European Medicines Agency, US Food and Drug Administration and World Health Organization.

	Brazil	Europe	USA	WHO
Denomination	*Produto biológico**	Biosimilar	Biosimilar	Similar biotherapeutic product
Regulatory pathways	Two pathways: comparability and individual (standalone)	Only by comparability		
Primary source of regulation	Resolution of board of directors of ANVISA	EMA guidelines were developed after directives approved by European parliament	FDA guidelines were developed after the BPCI Act passed by American Congress	Approved by expert committee
Biosimilarity	Not defined and not required in the individual pathway	Defined and required as precondition for approval		
Reference Product	Not required in the individual pathway	Defined and required in all cases		
Nonclinical and clinical studies	In the individual pathway, a unique comparator is not required	Detailed guidance Same reference product is required in all comparisons		
Interchangeability	Not regulated	Regulated by member states	Defined by law (BPCI Act) based on scientific criteria	Not regulated
Extrapolation among indications	Possible with defined criteria			
Nonproprietary names	No rule; same names for reference and all biosimilars	Possible disambiguation through manufacturer identification	Final rules in place with core name and suffix	Biologic Qualifier with suffix

*In the Brazilian regulation the expression *produto biológico* refers to the whole class or only to the copies, depending on the context.
ANVISA, National Health Surveillance Agency in Brazil; BPCI Act, Biologics Price Competition and Innovation Act, EMA, European Medicines Agency; FDA, US Food and Drug Administration; WHO, World Health Organization.

and monitoring of use are very difficult in these cases. Therefore, the current regulation delegates this complicated decision to payers or physicians. This situation can increase the risk of physicians' conflicts of interest and pressure by large-profit health insurance providers including medical cooperatives and private health management organizations. Physicians who are part of a medical cooperative are often pressured by the directory board to prescribe the cheapest medicine and procedure on the grounds that they could be undermining the profit of all coworkers. Physicians who provide services to health insurance companies can lose their accreditation if they are considered big spenders when advocating against a cheaper biosimilar. Physicians linked to public health services have job stability and can easily prescribe all the approved drugs in the country according to the regulation of each condition. However, the pharmaceutical companies have varied the price of biologics in order to receive the label of first-choice medication in the clinical protocols and therapeutic guidelines of the government. Thus, the difference of values between original drugs and biosimilars is not at all clear. There are obvious risks if the payers' decision is only based on the product's approval by the regulatory authorities. As the editorial from Minghetti and colleagues points out, 'When the prescription of a biosimilar arises from a payer's policy, it is not substitution in the proper sense, and if it constitutes an administrative limit to the prescriber's freedom, it should have a different name, such as a "constrained prescription".'[14]

In the private sector, the pressure on the physician to use biosimilars was felt early, especially within medical cooperatives. In the public sector, we have recently seen a government move to create a cost-based hierarchy of biologic prescriptions. A technical note by the Ministry of Health [15] was published at the beginning of this year proposing two lower-cost products as the first-line prescription for rheumatoid arthritis. This initiative did not address the biosimilar product and was received under a great discussion. Only 2 months later, another note[16] preserved the prescription order of the biologics but now with the necessary flexibility to use any approved drug since justification is presented. In addition, when indicating what product should be used without studies to support this decision, physicians expose themselves to be held accountable for any treatment-related failures or complications.

The first biosimilar approved by the comparative development pathway in the country, and at present the only monoclonal antibody in the field of rheumatology, is the biosimilar infliximab, Remsima® (Pfizer), which was approved for all eight indications of the original licensed biologic product. ANVISA RDC 55/2010 addresses criteria for extrapolation, which cannot be granted *via* standalone application, but it does not solve all the controversies involved among different indications. There is still a need for more detailed regulation on this issue. Another concern is when the prescribing physician is usually not notified on what drug was delivered for the patients in the public sector, except when the patients receive their drug administration at an assisted (immunobiological) therapy center where the prescribing physician works or when this center shares information with the physician.

It is necessary to pay attention to the increasing knowledge on technical and regulatory aspects of biosimilars, especially in Brazil, where there is either a huge private market for the use of biological products, or a great cost to the government that subsidizes these medications free of charge within the public health system for several diseases.

The Brazilian Society of Rheumatology is developing the official positioning regarding biosimilars, in order to motivate more definite positioning from ANVISA.

Currently, biologics consume 43% of the Ministry of Health's resources with medicines, about US$1.2 billion per year.[17] Cost reduction is the major motivator of biosimilar development, but the proportion of savings is not comparable to the magnitude seen with generics.[18] Moreover, there are no clear estimates of what will be the decrease in the value of these medicines in Brazil.

Conclusion

The directive for licensing biosimilars published by the Brazilian Regulatory Agency in 2010 is very much aligned with the principles seen on the WHO norms and standards for the evaluation of similar biotherapeutic products. However, it includes some controversial changes such as nomenclature (naming the copies as *produto biológico*, avoiding the use of the term biosimilar), and the addition of an alternative pathway of approval not based on the comparability exercise.

Designating approved copies of biologic products as biosimilars after the comparability exercise has been well received by most regulatory authorities and the academic world. ANVISA may find an opportunity to revise its regulation and also adopt this expression. It has been generally recognized that many important issues associated with biosimilars need to be defined by the national authorities; we therefore emphasize the need for regulation on the topics of labeling, extrapolation and interchangeability. We believe the absence of a governmental position on these issues threatens the good practice of physicians and the health of patients, and is worsened by the concerns of traceability. The development of biosimilars backed by proper regulation can provide cost savings while also preserving clinical effectiveness and safety for the patients.

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Conflict of interest statement

In the last 12 months, MRdA has given lectures and/or consultancy to Novartis, UCB and Janssen. In the last 12 months, VP has given lectures and/or consultancy to AbbVie, Allergan, Janssen and Roche.

ORCID iD

Marcos Renato de Assis https://orcid.org/0000-0002-6567-4570

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