



Practical Issues Concerning the Approval and Use of Biosimilar Drugs for the Treatment of Multiple Sclerosis in Latin America

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Abstract: The use of biosimilar drugs for multiple sclerosis (MS) has become widespread in Latin America, with the goal of reducing costs of treatments, promoting the sustainability of healthcare systems, and improving patient access to these therapies. There is currently a need to define and comply with requirements to guarantee the efficacy, safety, and quality of these drugs. Thus, the objective of the present study was to compile up-to-date information from each Latin American country assessed on

(a) approval of biosimilar drugs by regulatory agencies; (b) use of biosimilar drugs, pharmacovigilance plans, risk management; and (c) update in the knowledge on different molecules. To do so, a group of experts from Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, Mexico, Panama, Peru, Uruguay, and Venezuela met to discuss the current situation regarding good practices and risks associated with the use of biosimilar drugs in their respective countries. Regulation, risk management plans, and pharmacovigilance in the whole continent must guide the strategies on the commercialization and access of biosimilar drugs and copies of complex molecules. Current

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regulations must be implemented for the registration of biosimilar drug products and complex molecules. It is paramount to ensure that new products follow the best quality standards at all stages beyond being safe and efficient. Uncontrolled interchangeability between original biological and biosimilar should be avoided. Latin America requires the implementation and full use of strong pharmacovigilance programs. National and multinational clinical studies are required to demonstrate the similarity in safety, efficacy, and immunogenicity profiles of complex molecules, as well as biological and biosimilar products.

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PLAIN LANGUAGE SUMMARY

Biosimilars, which are also known as biopharmaceuticals, are drugs designed to be as efficient and as safe as original drugs and developed using biological products, such as bacteria, yeast, and cells. These biosimilar drugs tend to be cheaper and, for this reason, have gained much attention for the treatment of diseases such as multiple sclerosis (MS). However, the regulation of biosimilars is still a matter of discussion. This study brings a list of recommendations from the Latin American Forum of Experts in Multiple Sclerosis regarding this subject. Forum members

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agree that current regulations should be strictly applied; biosimilar products should be traceable; substitutions between biosimilar and original biological drugs should be controlled; programs must be implemented to detect any safety problems associated with the use of original and biosimilar drugs; national studies should be conducted in Latin America to identify possible differences in the use of these medications for MS; the well-being and safety of patients must be prioritized over economic aspects; and healthcare professionals should be trained and educated regarding the use of original biological or biosimilar products for the treatment of MS.

INTRODUCTION

Biosimilar drugs are biological products with an active ingredient that is highly similar, but not identical, to a reference biological product that has been authorized for use by a regulatory agency. These are new versions of reference products that have been developed independently after the patent of the original product has expired, driven by the high costs of reference biological drugs, which affect patients and the whole healthcare system [1]. Biologic therapies were introduced over a decade ago for the management and treatment of chronic inflammatory diseases [2] and their regulation remains a worldwide discussion.

Biosimilars differ from synthetic chemical generic products because they originate from a living organism, such as bacteria, yeast, and mammalian cells [3]. This implies the occurrence of posttranslational modifications, such as glycosylation, which lead to heterogeneity and intrinsic variability [2]. Moreover, biological products have high molecular weight and a complex, heterogeneous, and only partially characterized structure. They also present higher risk of immunogenicity, with variable composition, quality, pharmacokinetics, and pharmacodynamics, demanding robust characterizations of these molecules [4].

Biosimilar drugs rely on an extremely complex manufacturing process that is impossible to reproduce without adequate information. Small changes to the manufacturing process can cause

important alterations in pharmacokinetics, pharmacodynamics, quality, efficacy, and product safety. However, most of the information regarding the manufacturing process of biological products (e.g., cell line, cultures, fermentation temperature, pH, growth media, filtration, and purification) is not fully accessible because of proprietary status, which poses an important challenge to biosimilar developers [3]. Although biosimilars and complex molecules (such as glatiramoids) cannot be expected to be identical to reference products with the current technology available, developers of biopharmaceuticals should seek to manufacture drugs of compatible quality levels [1]. Beyond production, the whole scheme of packing, distributing, and storing the product may affect its final efficacy and/or safety.

The principles applied to generic drugs are not compatible to define equivalence between the original and biosimilar biological compound. A detailed evaluation is needed to compare, among other aspects, efficacy and safety to establish biosimilarity between two molecules. This distinction also affects the nomenclature used for biological products, with some stakeholders preferring that biosimilars have the same International Nonproprietary Name (INN) of their reference product—a clear misconception [5].

The use of biosimilar drugs has become widespread in Latin America partially with the interest in reducing the costs of biological therapies. In some countries, biosimilar prices may be up to 40% lower than the branded product [6]. This favors the sustainability of health systems and improves patients' access to these therapies. Moreover, by reducing costs, one can redirect resources to other healthcare priorities [7]. However, this precept may not always be respected and some countries may opt for drugs exclusively on the basis of the cost of the product.

With patents for some molecules used in the treatment of multiple sclerosis (MS) expiring, biosimilar options have emerged in Latin America. Original immunomodulatory drugs used for MS treatment have already lost their patent and newer drugs will lose their patents within the next decade [8]. Biosimilars have become a reality for countries such as Argentina, Colombia, Ecuador, Mexico, and Peru, but these drugs are expected to also enter markets in

other countries in the region. Regulations and decision-making processes regarding the approval and use of biopharmaceuticals vary in Latin America according to each country's reality and public policies [4].

The generalized use of biosimilar drugs entails the definition and fulfillment of requirements that can guarantee the efficacy, safety, and quality of these drugs during their commercialization, thus protecting the well-being and health of patients. In fact, the introduction of new treatment options in the market should be driven by the interest of patients, not the interest of governments regarding expenditure [8]. Regarding the safety of these drugs, pharmacovigilance programs should encompass reports of adverse effects in the post-marketing phase. However, this is not always fulfilled, especially considering that few Latin American countries have adequate post-marketing monitoring systems actively in place [5]. Recent new European legislation on pharmacovigilance has been implemented to guarantee adequate risk management through reports on adverse reactions and compilation of data from all patients [9].

The Latin American Forum of Experts in Multiple Sclerosis has been active for nearly a decade and is completely independent from the pharmaceutical industry. It is a space for learning, discussion, and consensus on MS. The last couple of meetings of the forum have allowed us to address this new period of global changes observed in therapeutic indications.

The objective of the present study was to obtain current information from each Latin American country represented in the forum regarding (a) approval of biosimilar drugs by regulatory agencies; (b) use of biosimilars, pharmacovigilance plans, and risk management; and (c) updates in the knowledge of different molecules.

METHOD

The Latin American Forum of Experts in Multiple Sclerosis published a scientific article in 2015 [8] stating the position of forum members from nine countries in the region and their recommendations on the use of biosimilars for the treatment of MS. Three years later, a group of experts from

Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, Mexico, Panama, Peru, Uruguay, and Venezuela that are a part of the forum met face-to-face and virtually to review together the situation of each country regarding good practices and risks associated with the use of biosimilar drugs and to make recommendations concerning this subject. Issues related to the use of biosimilar products for MS therapy in Latin America were discussed in a meeting of specialists that occurred in Bogota, in April 2018. The discussion did not include systematic and non-systematic reviews since there are no publications on biosimilars for MS.

RESULTS AND RECOMMENDATIONS

Biopharmaceuticals for the Treatment of Multiple Sclerosis in Latin America

The availability of biological drugs used in MS in each country is presented in Table 1. In

Argentina and Mexico, there are biosimilar interferons and glatiramer acetate or glatiramoids. Costa Rica, Ecuador, and Peru only present glatiramer acetate and biosimilar drugs, and Bolivia only has a biosimilar drug for interferon beta 1a. Brazil, Chile, Colombia, Panama, Uruguay, and Venezuela do not have biosimilar drugs for MS therapy.

Good Practices in the Report and Use of Biosimilars in Latin America

The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have widely regulated in Europe and the USA, respectively, the registration of biosimilar products, applying shorter and less complex approval procedures than those of the original products. However, both agencies require demonstrations of comparability between products assessed regarding quality, efficacy, and safety. The guidelines of the EMA and the FDA regarding biosimilars adopt a stepwise

Table 1 Availability of biological and complex non-biological drugs in each country for the treatment of multiple sclerosis

Country/drug	Interferon	GA	Natalizumab	Alemtuzumab	Ocrelizumab
Argentina	XY	XY	X	X	
Bolivia	Y				
Brazil	X	X	X	X	X
Chile	X	X	X	X	X
Colombia	X	X	X	X	X
Costa Rica	Y	Y	X	X	X
Ecuador	Y	Y	X	X	
Mexico	XY	XY	X	X	X
Panama	X		X	X	X
Peru	Y	Y	X	X	X
Uruguay	X	X			
Venezuela					

Drugs available in each country are marked "X". Letter "Y" refers to biosimilar interferon beta or glatiramoid. Empty spaces mean that the drug is not available. Availability does not necessarily mean that the treatment is covered by the public health system with reimbursement. All prescriptions in all countries require extensive reports from the prescribing physician. Reimbursement may start and stop according to government negotiations with the pharmaceutical industries

GA glatiramer acetate

Table 2 Regulatory agencies of the Latin American countries assessed in the present study

Country	Institution	Type	Since
Argentina	Administración Nacional de Medicamentos y tecnología médica—ANMAT	Agency	1992
Bolivia	Agencia Estatal de Medicamentos y Tecnologías en Salud—AGEMED	Agency	2017
Brazil	Agência Nacional de Vigilância Sanitária—ANVISA	Agency	1999
Chile	Instituto de Salud Pública de Chile—Agencia Nacional de Medicamentos	Agency	1979
Colombia	Instituto Nacional de Vigilancia de Medicamentos y Alimentos—INVIMA	Agency	1993
Costa Rica	Dirección de Regulación de Productos de Interés Sanitario del Ministerio de Salud	Specialized unit	1927
Ecuador	Agencia Nacional de Regulación, Control y Vigilancia Sanitaria—ARCSA	Agency	2012
Mexico	Comisión Federal para la Protección contra Riesgos Sanitarios	Agency	2001
Panama	Dirección Nacional de Farmacia y Drogas—Ministerio de Salud	Specialized unit	1963

Table 2 continued

Country	Institution	Type	Since
Peru	Dirección General de Medicamentos, Insumos y Drogas—DIGEMID	Specialized unit	1990
Uruguay	División Evaluación Sanitaria—Ministerio Salud Pública	Specialized unit	2010
Venezuela	Ministerio del Poder Popular para la Salud—Instituto Nacional de Higiene Rafael Rangel	Specialized unit	1938

Specialized units are those within the Ministry of Health; agencies are separate agencies. Partial data available at https://www.redeami.net/web/eami/seccion/contenedor_secciones/eami_conten_directorio_de_autoridades.htm

approach for the development of these drugs, applying a comprehensive physicochemical and biological characterization [2]. Moreover, statistical assessments of quality attributes have gained the attention of both organizations, considering that current statistical approaches have serious weaknesses within a range-based hypothesis of comparison [10]. MS is currently not listed as a therapeutic area with approved biosimilar drugs by the EMA [3], although glatiramoids are in use.

Regulation to register biosimilar drugs in most Latin American countries has become stronger, frequently based on the regulations of the EMA and FDA. All countries in Latin America have an established and regulated pharmacovigilance program from a local regulatory agency (Table 2). Unfortunately, interchangeability among different products takes place often, as negotiations for better prices continue between the government and pharmaceutical companies. It seems more reasonable to avoid the inclusion of products with unproven efficacy and safety into the reimbursement system than to remove them from it if deemed necessary. Cost-benefit studies are

more productive than better prices per vial with uncertain outcomes for the patient.

The report by healthcare professionals of adverse effects associated with the use of these drugs is mandatory. In fact, knowledge on adverse effects of the monoclonal antibodies alemtuzumab and daclizumab for MS treatment was a concern to most neurologists evaluated in a recent survey in Latin America [11]. However, most countries in Latin America have multiple agencies to which adverse effects can be reported, which should be integrated for a better outcome [5].

Brazil has been considered to have one of the most advanced regulations regarding biosimilars, leading the development of this field in Latin America [4, 6]. Argentina is also advanced in the regulation of biosimilar products and is a major manufacturer in Latin America [6]. Other countries, such as Bolivia, are still in the development phase of draft regulations [4]. The biosimilar markets in countries such as Chile, Mexico, and even Venezuela, where foreign exchange controls pose important challenges for pharmaceuticals, are expected to expand [6]. Should a biosimilar interferon beta or a glatiramer be approved and used in a particular country, interchangeability among products must be avoided.

Risks in Registration and Use of Biosimilars in Latin America

As a result of the prioritization of economic aspects and matters of access to biological drugs, some Latin American countries have implemented flexible requirements for the registry of biosimilars. This allows a reduction in the quantity, extension, or complexity of comparative clinical and non-clinical trials designed to demonstrate efficacy, safety, and immunogenicity prior to obtaining authorization for commercialization. Occasionally, similar criteria as those applied for the approval of generic drugs are applied. Some Latin American countries have implemented a “third approval pathway,” where a biosimilar may be granted approval based only on information published in the literature regarding reference or innovative medications, a

decision which has been considered highly risky to the population’s health [4]. Moreover, most Latin American countries do not require clinical trials prior to the approval of biosimilars; these trials are very resource-consuming but in an ideal situation should be conducted after equivalence studies [8]. Nevertheless, a significant number of biosimilar products are available in the market without approval as such by either the EMA or FDA.

In addition, when defining the regulation for biosimilars, any given country must consider its capability to implement what is agreed upon. In Latin America, a proposed solution to this issue is continuing education programs for the technical teams of regulatory agencies [4]. Other studies have emphasized the importance of educational materials from the EMA and the FDA [7] and training for healthcare professionals of various fields and levels [5, 8]. Ultimately, the prescribing physicians assume the efficacy and safety risks of drugs they have not been properly informed about. This form of “existence-based medicine” is not good for the patient or the physician in charge.

Critical Considerations Regarding Therapeutic Equivalence

Demonstrations of biosimilarity differ significantly from approvals of generic drugs, in which only equivalence needs to be demonstrated. Determining critical quality attributes is an essential step in evaluating biosimilarity [1]. Thus, the process for a biosimilar drug is likely to be more complex and detailed than that of the reference product. The process requires comparable data that are almost superimposable over the reference through “fingerprinting” to detect differences among highly complex molecules. Therefore, an extensive characterization regarding physicochemistry, biology, and immunogenicity is needed before planning trials for efficacy and safety. Regarding MS, few researchers in Latin America have so far been involved in phase III clinical trials, though this number has increased over the past years [11].

The requirements concerning the need for clinical trials differ among EMA, FDA, and Latin

American regulatory agencies. Clinical trials that are needed to determine effectiveness are not clear, because although “head-to-head” studies meet the criteria for evaluating relative efficacy, they are not always requested as a result of the complexity that is necessary for their design, especially with drugs that have already been approved. On the other hand, agencies agree that equivalence, safety, and efficacy of the novel biosimilar should be equal to or higher than the novel drug. The main outcome is the non-inferiority of the new drug. However, the margin for non-inferiority or equivalence is determined case-by-case, since there are no general criteria for all countries [12].

RECOMMENDATIONS FROM THE GROUP OF EXPERTS

On the basis of the discussions and current literature on the subject, the group of experts defined the following list of recommendations, which are summarized in Fig. 1:

RECOMMENDATIONS FROM THE GROUP OF EXPERTS

Based on the discussions and current literature on the subject, the group of experts defined the following list of recommendations, which are summarized in Figure 1:

- Strictly apply current regulations for biosimilar products and complex non-biological molecules, thus guaranteeing the quality, efficacy and safety of drugs used for the treatment of MS.
- Develop mechanisms that allow the traceability of products prescribed for the treatment of MS.
- Avoid uncontrolled interchangeability regarding biological, original or similar drugs.
- Implement a strong pharmacovigilance program that allows the detection of safety problems associated with the use of original and biosimilar drugs.
- Conduct national and Latin American studies that can demonstrate the differences, if there are any, in the safety and efficacy profiles of original and biosimilar drugs for the treatment of MS.
- Prioritize protecting the well-being and safety of the patient regarding economic aspects associated with the availability of pharmaceutical products.
- Educate healthcare professionals on issues that allow them to conduct an adequate and evidence-based selection and prescription of original biological and biosimilar products to patients with MS.

Fig. 1 Summarized recommendations regarding the use of biosimilars for the treatment of multiple sclerosis

- Strictly apply current regulations for biosimilar products and complex non-biological molecules, thus guaranteeing the quality, efficacy, and safety of drugs used for the treatment of MS.
- Develop mechanisms that allow the traceability of products prescribed for the treatment of MS.
- Avoid uncontrolled interchangeability regarding biological, original, or similar drugs.
- Implement a strong pharmacovigilance program that allows the detection of safety problems associated with the use of original and biosimilar drugs.
- Conduct national and Latin American studies that can demonstrate the differences, if there are any, in the safety and efficacy profiles of original and biosimilar drugs for the treatment of MS.
- Prioritize protecting the well-being and safety of the patient regarding economic aspects associated with the availability of pharmaceutical products.
- Educate healthcare professionals on issues that allow them to conduct an adequate and evidence-based selection and prescription of original biological and biosimilar products to patients with MS.

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Compliance with Ethics Guidelines. This article does not contain any studies with human participants or animals performed by any of the authors.

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