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Potential Regulatory and Commercial Environment for Biosimilars in Latin America

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ABSTRACT

Objectives: Biosimilars are increasingly attractive to payers around the globe because of mounting financial pressure. Many Latin American governments are developing abbreviated regulatory pathways for biosimilars. There are limited data regarding how certain regulatory agencies in the region plan to address biosimilar access. This study explores potential opportunities and challenges for biosimilar drugs in Brazil, Mexico, Argentina, Chile, and Venezuela. **Methods:** We conducted targeted literature reviews, followed by key informant interviews, to understand the expected regulatory environment for biosimilars. We also asked questions about the economic, political, and historical factors that could play a role in the extent to which biosimilar-specific pathways have been developed across countries to date, and will continue to evolve in the future. **Results:** Brazil has led the development of biosimilar regulation in Latin America, with two distinct pathways, one for more complex molecules such as monoclonal antibodies and a less rigorous path for simpler molecules such as pegylated interferon and low molecular weight heparin. Other countries have been slower to respond, in part because of the degree of emphasis within each country for the advancement of biosimilar regulatory standards. Signs of relaxed standards akin to those seen in Brazil's "individual development" pathway were found in other countries. **Conclusions:** The example of the two-pathway system coupled with governmental prioritization of local manufacturing capabilities in Brazil should promote increased biosimilar utilization within the country. Assuming that the two-pathway system demonstrates success in Brazil, we hypothesize that other Latin American countries may adapt aspects of this "local" model for developing a regulatory pathway for biosimilars.

Keywords: biosimilar pharmaceuticals, drug industry, drug legislation, Latin America.

Introduction

The use of biosimilars is increasingly attractive to payers around the globe because of mounting financial pressure from high expenditures on expensive biologics. For example, in Brazil, biotherapeutic products represented 2% of medicines prescribed, yet accounted for 41% of the annual Ministry of Health pharmaceutical budget in 2010 [1]. Health agencies view the use of biosimilars as a cost-saving measure that could help alleviate pharmaceutical budgetary concerns. Although biosimilars can potentially have safety, efficacy, or quality concerns, many governments are trying to boost the utilization of biosimilars by developing regulatory channels in hopes of expanding market access.

In Latin America, many governments have developed or are developing abbreviated regulatory pathways for biosimilars to increase access while enacting sufficient quality standards to ensure safety and efficacy [2]. The World Health Organization (WHO) guidelines for biosimilars, which were finalized in 2009, have been used as a template for many of these countries. These guidelines confirm key principles of biosimilarity, including stand-alone manufacturing process development and demonstrated comparability [3]. There are limited data regarding how national agencies in Latin America plan to address biosimilar access in their respective countries. This study explores potential opportunities and challenges for biosimilar drugs in light of the regulatory environments that exist in Brazil, Mexico, Argentina, Chile, and Venezuela.

Methods

For this exploratory study we first conducted online searches, using Google and PubMed, in English, Spanish, and Portuguese to gain an in-depth understanding of the evolution of regulations in each of the five target countries: Argentina, Brazil, Chile, Mexico, and Venezuela. These countries were chosen as representing the leading pharmaceutical markets in Latin America because of their populations and purchasing power (in gross domestic product per capita). We also explored economic, political, and

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Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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historical factors that could contribute to a higher emphasis on the development of policies to regulate biosimilar products within the respective markets ("Biosimilar Emphasis").

We then conducted interviews with an expert informant in each country. Expert informants ranged from officials at federal regulatory agencies responsible for enacting regulation to policy experts and advisors at leading industry organizations within the countries. For each interview, we asked a structured set of questions designed to refine our understanding of what policies currently exist for regulating biosimilar products in each country, and what specific requirements are expected to be enacted in the future to regulate the review and approval of biosimilars. Interviews were conducted in Spanish and Portuguese.

Findings were analyzed relative to a framework adapted from the work by Dr. Valdair Pinto on biosimilar regulatory pathways in Brazil [4]. This approach was chosen because it defines a range of potential pathways for regulating biologic drugs ranging from the highest burden of proof for new biological agents to two alternative pathways for follow-on biological products. In the case of the "comparability" alternative pathway, certain categories of information may be substituted with comparative data, while for certain less-complex biosimilars that meet the criteria of the "individual development" pathway (referred to by Pinto as the "desevolvimento individual" pathway), the requirement for certain clinical data may be waived entirely. This spectrum creates a broad framework against which other countries' potential regulatory requirements for biosimilars can be compared. Our adapted framework is described in Table 1.

We also asked questions to supplement our understanding of the level of Biosimilar Emphasis in each country as a result of economic, political, and historical factors that may exist (e.g., governmental programs to develop local industry and/or cut costs, past safety issues with biosimilars). These factors could have played a role in the extent to which biosimilar-specific pathways have been developed across countries to date, and will continue to evolve in the future.

Market size, degree of interaction with international thought leaders, and local production capabilities were chosen as factors that could contribute to the degree of Biosimilar Emphasis within a country. Market size, for instance, is likely to bring opportunities of scale to capture economic savings through discounted prices that presumably would come with competition from biosimilar products. Countries were categorized into small (<20 million), midsized (20–50 million), or large (>50 million) population. Similarly, interaction with international thought leaders was assumed to be positively correlated with market size, as leading clinicians and academics in larger countries are more likely to be engaged by thought leaders in other countries because of the economic and research opportunities that exist within their market. Finally, local production capabilities was inferred to indicate a greater policy emphasis on biosimilars, because countries that have chosen to develop local production capabilities are more likely to have prioritized the development of a regulatory pathway for the review and approval of locally produced biosimilar products. Of note, market size and interaction with international thought leader categories were defined and assigned subjectively, while the local production categories were assigned on the basis of comments from primary research.

Throughout, we have used the term "biosimilars" as the most common usage in the English-language literature. However, other terms were noted during our research. For example, biosimilars are frequently referred to as "biologics" in Brazil, as differentiated from "new biologics" to refer to a new branded agent, "biocomparables" in Mexico, or "medicamento biológico similar" in Argentina.

Results

The financial pressure to adopt biosimilars in each country is high because biologics consume a sizeable portion of national pharmacy budgets. Nevertheless, each country varies in its propensity to increase access to biosimilars. Findings for each country are detailed below and summarized at the end of the section in two tables. Table 2 contains the current expectations for biosimilar regulation in each country in the context of WHO guidelines. Table 3 lists attributes that could affect a country's policy development pertaining to the regulation of biosimilars.

Brazil

Current situation

In Brazil, *the Agência Nacional de Vigilância Sanitária* is in charge of regulating biologics and biosimilars. Historically, Brazil had the same regulatory pathway for new biologic products and for copies. However, in 2010, *the Agência Nacional de Vigilância Sanitária* passed resolution RDC 55/2010, creating new regulatory pathways for new biologic products and biosimilars [1]. For biosimilars, two pathways emerged: a "comparability" pathway and an "individual development" pathway. The individual development pathway originated in response to the high government expenditure on pegylated interferon to treat hepatitis C. The Brazilian government sought a lower-cost, high-quality option to relieve budgetary pressure, with the Brazilian government partnering with a Cuban manufacturer (CIGB) to produce pegylated interferon in Brazil. The regulatory requirements were reduced for the new interferon molecule, which was similar to the previously licensed molecule but pegylated using a new technology [1]. The success of this project led Brazil to incorporate the individual development pathway into the RDC 55/2010 guidelines, by which clinical requirements can be reduced "depending on the amount of knowledge of pharmacological properties, safety and efficacy of the originator product" [1]. This pathway is suitable for certain types of less complex biotherapeutics such as pegylated interferon and low molecular weight heparin [1]. In the individual development pathway, the dossier, quality issues,

Table 1 – Potential data requirements/policies for biosimilars.

Data requirement/policy	New biological products	Comparability (biosimilar) pathway	Individual development (nonbiosimilar) pathway
Chemistry, manufacturing and controls documentation	Required as for new drug	Comparative data only	According to developing standards
Preclinical studies			Comparative data with exceptions
Phase I clinical studies			Can be waived/may not be comparative
Phase II clinical studies			Can be waived/may not be comparative
Phase III clinical studies			Comparative data with exceptions
Extrapolation of indications	Yes	Possible (with conditions)	Not possible