PERSPECTIVE

Biosimilarity and Interchangeability

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Biosimilarity in Latin America

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The introduction of new legislation in Latin America for the approval of biosimilar products follows implementation of EU legislation in 2005 for biosimilars approval. The establishment of regulatory processes for these complex drugs will ensure that evidence of safety and efficacy is obtained before approval. Biosimilars are high on the health-policy agenda because they are less costly and potentially more accessible, and also because of the imminent expiration of a number of patents on biological products. Within individual Latin American countries, the regulatory processes and stages of implementation vary.

Keywords: Biosimilarity, complex drugs, Latin America

Introduction

Many people in Latin American countries still have difficulty accessing medicines to improve their health and quality of life, despite an increasing number of pharmaceutical products on the market. The World Health Organization (WHO) has recommended the use of the essential drug lists to guide the selection, registration and procurement of drugs by governments, to ensure access to medicines at an affordable price. For small-molecule drug products, generic formulations are considered an important health-policy issue in most Latin American countries, mainly because of reduced costs and social benefits provided by the government. The demonstration of interchangeability of generic formulations with the reference formulation has been a requirement in some Latin American countries since 1970 [1, 2].

Biotherapeutic products account for a large percentage of the government health budget, because of the number of expiring patents on biological products due in the next few years. An important issue for discussion is the use of biosimilar products because of their accessibility and economic relevance. Most governments in Latin America are interested in improving access to more affordable biotherapeutic products; however, quality, safety and efficacy of these products are always a concern. Unlike small molecule generics, copies of biological products can be similar, but not identical, to innovator biologicals. Thus, the generic versions of biological products are referred to as 'similar biological drug products'. These products are usually referred to as biosimilar products by the European Medicines Agency (EMA), follow-on biologics by the US Food and Drug Administration (FDA), or subsequently entered biologics by the Public Health Agency of Canada [3]. In Brazil, the new biotherapeutic products are called new biological products, and the copies are called biological products that can be licensed by the comparative pathway or the individual development pathway [4].

The biosimilar concept can often be misinterpreted and used inconsistently, and the potential implication of this is a concern. These include negative perception and impaired acceptance of biosimilars among prescribing physicians and patients [5, 6]. Biosimilar products may be defined as

a copy version of previously authorized biological medicinal products that demonstrate similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise. On the other hand, biologicals or biocopies are biological medicinal products that are developed on their own and not directly compared and analyzed against a licensed new biological. It is unknown whether, and which, physicochemical differences exist compared with other biological of the same class [5].

The development of biologicals is complex and has high associated costs. Only a few pharmaceutical companies in Latin American countries are able to provide biosimilar products [7]. A regulatory policy for biosimilars is being developed in several Latin American countries and, in general, follows guidelines that were established either by WHO or EMA [8]. In addition, the appropriate use of generic and biosimilar medications is important for maintaining financial equilibrium within the health system [9].

In this paper, we aim to review the current issues on biosimilarity of pharmaceutical formulations in Latin American countries. In addition, we refer to legislation in different countries and present future perspectives.

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Biosimilars development in Latin American countries

Biosimilar products aim to mimic the innovator product in molecular size and complexity during the manufacturing process; however, minor changes in production can have serious implications on safety and efficacy. Like all biologicals, the main problem related to the safety of a biosimilar is its immunogenicity [8, 10]. Therefore, the approval of biosimilar products requires the performance of pharmacokinetic, preclinical and clinical analytical studies, such as physicochemical assays, biological and immunological tests. These issues have been established by WHO, and have been incorporated into the main drug registry entities worldwide [11]. In addition, it is essential to implement a pharmacovigilance system after product commercialization, so that safety and efficacy of biosimilar products can be evaluated [10].

The establishment of regulatory processes for structurally complex drugs such as biosimilars is a long-standing challenge, and has become increasingly urgent owing to rapid technological advances and the expiration of innovator patents in this class [12]. Legislation for biosimilars approval in the EU was implemented by the Committee for Medicinal Products for Human Use of EMA in 2005. Both preclinical *in vitro* assays and *in vivo* animal and clinical studies in patients are required to compare the biosimilar product with the reference product. In the US, several natural source products and recombinant proteins have already been approved as similar drugs under Section 505(b)(2) of the Food, Drug, and Cosmetic Act [13].

In Latin America, the regulation of biosimilars varies considerably between different countries, and some of the so-called biosimilars were approved before an adequate clinical test was carried out [8]. In some countries, the lack of interchangeability for some biosimilar products becomes a serious concern in the health system, when a reference medicine is substituted by a multisource product. Hence, some guidelines and legislative purposes on biosimilar medicines began to be introduced in Latin America [7]. Currently, clinical issues have been defined and have continually been revised. These issues include indications of differences in the amino acid chain and in the glycosylation patterns on biochemical quality side and the kind of clinical trial to be carried out [8].

Brazil

In Brazil, the *Agência Nacional de Vigilancia Sanitária* is in charge of regulating biologicals and biosimilars. The resolution RDC 55/2010 was published in 2010. This regulation has different and specific regulatory pathways for new biological products and for copies. This resolution establishes the minimum requirements for the approval of biological products in Brazil, aiming to assure the quality, safety and efficacy of these medicines [14]. For the similar biotherapeutic products, two regulatory pathways, a comparative pathway and an individual development pathway, are in place. The comparability pathway is more rigorous and requires comparative phase I, II, and III trials to the originator biological product, and will allow extrapolation into other indications. At least one comparative phase III study (equivalence or non-inferiority) with the originator (new) biological product is mandatory. In the individual development pathway, a reduced dossier can be presented. The applicant needs to present complete data on quality issues, but it does not have to be comparative. Non-clinical and clinical studies can be reduced, depending on the amount of knowledge of pharmacological properties, safety and efficacy of the originator product. Extrapolation of indications will not be accepted in the individual development pathway [4].

In 2011, a recent guideline was published to elucidate the regulatory requirements for the comparability exercise regarding the quality criteria of the biological products. The evaluation criteria for the quality of biological products involve available analytical techniques, biochemical characterization, physicochemical and immunochemical properties, biological activity, and impurities. Besides the use of quality data, the registration of a biological product requires non-clinical and clinical studies. The extent of these non-clinical and clinical data depends directly on the product class, level of characterization for modern analytical methods, differences observed on the reference product, and clinical experience with the product class [15].

Chile

Until 2011, no specific regulatory pathway was in place for biosimilars in Chile.

All products were required to provide the full complement of clinical studies to gain registration, as they considered that the similar drugs available had a different chemical composition because they were manufactured through different processes [11]. In 2011, Chile's *Agencia Nacional de Medicamentos* (ANAMED) released draft guidance for the evaluation of biosimilars. Chile has referenced the EMA and WHO guidelines in developing a regulatory pathway for biosimilars. This future regulatory law will ask manufacturers to provide comparative studies with the reference drug to characterize the product adequately and to demonstrate biosimilarity. This will most likely include phase I, II, and III comparative studies, and may allow for extrapolation of indications [16].

Other Latin American countries

In Argentina, legislation numbers 7075 and 7729 were published in 2011. These legislations stated the requirements for biosimilar products, as well as non-clinical and clinical studies, to have these products approved. In Mexico, the *Ley Orgánica de la Administracion Pública Federal* is the legislation on biosimilars registration; however, the requirements are vague, and regulatory authorities need to conduct the kind of clinical studies that will be required for approving individual drugs. The Decree No. 37006 was published in 2012 in Costa Rica. It states the biosimilar regulations on the basis of international guidelines. Currently, no other countries are in the process of creating their regulations. Some of these countries have decided to open discussions with the academic community, such as Colombia [8].

Conclusion

Although the introduction of biosimilars

to the market has its advantages, some medical professionals are still not familiar with the definition of biosimilars. In addition, it is important to assure total transparency from all the parties involved with the regulation and approval processes of those treatments [10, 13].

Biosimilar products are gradually being introduced into clinical practice. In the near future, the agents with increased complexity will be introduced into the global markets. These products may potentially reduce healthcare costs. Some uncertainties are related to its safety and efficacy, particularly when reference biological drugs have multiple indications. Therefore, assuring the safety and efficacy of biosimilars by means of non-clinical and clinical studies is crucially required, as patients' welfare is much more relevant than any economic interest involved [17, 18].

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