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Research article

Characterization and comparability of biosimilars: A filgrastim case of study and regulatory perspectives for Latin America

Karina Mendoza-Macedo [a], Alexis J. Romero-Díaz [b], Mariana P. Miranda-Hernández [b], Víctor R. Campos-García [b], Nancy D. Ramírez-Ibañez [b], L. Carmina Juárez-Bayardo [b], Karen Moreno-Duran [b], Miriam S. Cedillo-Robles [c], Nestor O. Pérez [b], Helgi Jung-Cook [a], Luis F. Flores-Ortiz [b,*], Emilio Medina-Rivero [b,*]

[a] Departamento de Farmacia, Facultad de Química, Universidad Nacional Autónoma de México, Av. Universidad 3000, Coyoacán, Ciudad de México, C.P. 04510, Mexico
[b] Unidad de Investigación y Desarrollo, Probiomed S.A. de C.V., Cruce de Carreteras Acatzingo-Zumpahuacán s/n, Tenancingo, Estado de México, C. P. 52400, Mexico
[c] Unidad de Calidad, Probiomed S.A. de C.V., San Esteban No. 88, Azcapotzalco, Ciudad de México, C.P. 02020, Mexico

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ABSTRACT

Background: Developing countries have an estimate of ten times more approved biosimilars than developed countries. This disparity demands the need of an objective regulation that incorporates health policies according to the technological and economical capabilities of each country. One of the challenges lies on the establishment of comparability principles based on a physicochemical and biological characterization that should determine the extent of additional non-clinical and clinical studies. This is particularly relevant for licensed biosimilars in developing countries, which have an extensive clinical experience since their approval as generics, in some cases more than a decade. To exemplify the current status of biosimilars in Mexico, a characterization exercise was conducted on licensed filgrastim biosimilars using pharmacopeial and extended characterization methodologies.
Results: Most of the evaluated products complied with the pharmacopeial criteria and showed comparability in their Critical Quality Attributes (CQAs) towards the reference product. These results were expected in accordance with their equivalent performance during their licensing as generics. Accordingly, a rational approval and registration renewal scheme for biosimilars is proposed, that considers the proper identification of CQAs and its thoroughly evaluation using selected techniques.
Conclusions: This approach provides support to diminish uncertainty of exhibiting different pharmacological profiles and narrows or even avoids the necessity of comparative clinical studies. Ultimately, this proposal is intended to improve the accessibility to high quality biosimilars in Latin America and other developing countries.

1. Introduction

Since their introduction, biotherapeutic products have transformed modern medicine by bringing novel and targeted therapies for several life-threatening and chronic diseases, providing healing opportunities and improving the quality of life of patients, while reducing the incidence and severity of side effects. This biotechnology-based field has grown in the last decades, allowing the continuous development and commercialization of similar products in terms of quality, safety and efficacy with respect to a licensed product whose innovation patents had expired.

However, the introduction of these biosimilar products and their increasing worldwide manufacture has been received with controversy, mainly because of the absence of a consensus about the scientific and regulatory requirements needed to confirm their similarity, in spite of the proved quality of biosimilars and their positive impact, intended to increase health coverage and diminish the treatment costs [1].

In 2003 the European Medicines Agency (EMA) became the first regulatory organization that established initial requirements to approve biosimilars, followed by other regulatory and health agencies around the globe [2]. A current concern is the regulatory situation in developing countries, including Latin America, where almost 80% of deaths related to non-communicable diseases occur [3]. Particularly, chronic and degenerative diseases had caused 50% of the disease burden in developing countries along with an estimated loss of $84 USD billions of their income in 2015 [4], becoming practically unaffordable for their patients and health systems.

* Corresponding authors.
E-mail addresses: luis.flores@probiomed.com.mx (L.F. Flores-Ortiz), emilio.medina@probiomed.com.mx (E. Medina-Rivero).
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In this regard, one of the main focuses of the Pan-American Health Organization (PAHO) is to develop a harmonized regulation for biotherapeutic products across Latin America in order to improve equity in health and quality of life. In response, guidelines for biological medicines have been issued in some countries; nevertheless, the requirements for the approval of each type of product (*e.g.*: vaccines, hemoderivatives, allergenic extracts or biotherapeutics) are frequently non-differentiated. Even though the guidance established by the World Health Organization (WHO), the Food and Drug Administration (FDA), the International Conference on Harmonization (ICH) and the EMA were often used as a reference, 12% of Latin American countries have licensed biosimilar products issued as generics without a specific clinical evaluation [5].

Since 2012, Mexico is a leader in Latin America by issuing an updated regulation aimed for biosimilars approval, published by the Mexican Ministry of Health (SALUD) and the Federal Commission for the Protection against Sanitary Risk (COFEPRIS) [6,7,8]. Other regulatory agencies which have issued similar regulations are the Brazilian Health Surveillance Agency (ANVISA) [9], the National Administration of Drugs, Foods and Medical Devices (ANMAT) from Argentina [10], the National Food and Drug Surveillance Institute (INVIMA) from Colombia [11], the National Drug Agency (ANAMED) from Chile [12], the Department for Regulation and Control of Pharmaceutical and Related Products (DRCPFA) from Guatemala [13], the Ministry of Health Directorate-General of Medical Supplies and Drugs (DIGEMID) from Peru [14] and the Ministries of Health from Costa Rica [15] and Ecuador [16].

According to the updated guidelines, the pathway for biosimilars' approval begins with an exhaustive characterization and a comprehensive comparability study of the Critical Quality Attributes (CQAs), strongly related to the functionality and safety of the biopharmaceutical. These CQAs should comprise the attributes already recognized by the reference product, either found in characterization exercises or during the experience with equivalent molecules. The guidance states that a clinical comparative study should be followed, whose extension is defined by the characterization results and designed to assess meaningful differences, if they exist [17]. In effect, the higher the comparability the less pharmacological studies needed to evidence similarity [6,18,19].

However, one of the major challenges related to the CQA's characterization, between the biosimilar and its reference product, is their proper selection, including the definition of their comparability principles, which, ultimately, allows a rational evaluation of the biosimilar towards their licensing and continuous surveillance. A proper selection is particularly relevant, given that a successful characterization and comparability exercise supports the selection of in-process controls and quality specifications for biosimilars.

1.1. Regulatory challenges in Latin America towards characterization and comparability

For the first-generation biopharmaceuticals (synthesized as analogous of human endogenous proteins), scientific consensuses have allowed the establishment of pharmacopeial monographs stating the minimum attributes to be evaluated. Since licensed products have been safe and effective, the compliance of the control limits specified in these monographs had proved to be useful to ensure quality for human use. The aforementioned, along with an active pharmacovigilance program, set the basis for the comparability studies used for the first biosimilars registration in Europe [20]. This scheme would be adequate for the registration or license renewal of biosimilars in Latin America; nonetheless, pharmacovigilance programs are not fully incorporated or are still in process of being regulated.

Hence, a demonstrated comparability sustained on a comprehensive characterization and the clinical record during the commercialization period of an approved biosimilar, should be considered as the major contributors for their licensing renewal. Whereas, the completion of clinical trials, with narrowed extension as long as CQAs comparability is demonstrated, must be considered for new biosimilar applications in order to diminish the uncertainty of exhibiting an altered pharmacological behavior.

In summary, comparability studies must include pharmacopeial methodologies and selected state-of-the-art-technologies to thoroughly evaluate CQAs, accompanied by the clinical record or narrowed trials as appropriate. The design of the analytical characterization strategy should be planned around this purpose, and the technical capabilities to detect relevant modifications.

1.2. A case of study: filgrastim in Mexico

Filgrastim is a non-glycosylated recombinant human granulocyte colony-stimulating factor (rhG-CSF) indicated for treatment of neutropenia. It was first approved in 1991 by the FDA and belongs to the first generation of biotherapeutic products after the registration of insulin in 1982. Since 2008, nine biosimilars containing filgrastim have been approved by the EMA, one of them recently approved by the FDA. However, over 50 filgrastim biosimilars are available in developing countries, most of them licensed as generic drugs since the early 2000s. For instance, in Mexico eight filgrastim biosimilars are currently commercialized. These latter had demonstrated to be safe and effective, by the absence of adverse events for more than seven years since their licensing, being Filatil® the only product manufactured in this country by Probiomed S.A. de C.V (Mexico City, Mexico) from the drug substance to the drug product. It is important to notice that the other products are commercialized using imported active pharmaceutical ingredients from Korea, Lithuania, India, Cuba, Argentina, Austria, among other countries. Also, Zarzio® (Sandoz International GmbH; Holzkirchen, Germany) obtained its approval in 2014, being in the Mexican market for less than two years.

To illustrate the current status of filgrastim biosimilars in Mexico and propose a rational scheme for their licensing renewal according to the updated regulation, a comparability analysis was performed considering the identified CQAs for this molecule (Table 1). The physicochemical and biological properties were evaluated in comparison to the reference product, Neupogen® (Amgen Inc.; Thousand Oaks, *CA*) [21] using pharmacopeial and extended methodologies which were selected according to their sensitivity, specificity, cost and the need of specialized personnel and infrastructure (Table 2). Extended methodologies were chosen to evaluate each identified CQA, based on the premise that not all the analytical techniques that a manufacturer could afford should be assessed, as their outcomes are not always linked to any functional or pharmacological behavior.

2. Materials and methods

2.1. Chemicals and reagents

All chemicals and reagents used for the analyses were at least ACS grade and were obtained from J.T. Baker (Avantor Performance Materials, Inc.; Center Valley, PA) or Sigma Aldrich (St. Louis, MO). All assays were performed using ultrapure Milli-Q water (Millipore, Billerica, MA).

2.2. Filgrastim samples

Filgrastim biosimilars commercialized in Mexico included: Filatil® from Probiomed S.A. de C.V., Dextrifyl® from Laboratorios Pisa S.A. de C.V., Inmunef® from Lemery S.A. de C.V., Biocilin® from Representaciones e Investigaciones Médicas, S.A. de C.V., Ior LC® from Alvartis Pharma S.A. de C.V., and Biofilgran® from Landsteiner