Review of regulation of biological and biotechnological products in Latin American and Caribbean countries

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Abstract

The regulation of the biological and biotechnological products constitutes a significant challenge, since they are part of a sector of the pharmaceutical industry that is currently experiencing rapid growth. Unlike conventional medicines, the manufacture of these products involves the use of living organisms and processes that impede manufacturing consistency. Even though there are numerous international reference documents related to biotechnological product regulation, there is no consensus by official entities that are considered reference institutions, with regard to the most important definitions used and the mechanisms for product regulation.

The Pan-American Health Organization (PAHO), through the Technology, Health Care and Research Area, has developed a series of activities that are described in this document. The objective of this publication is to present the current picture of biotechnological and biological product regulation in the Latin American and Caribbean Region, in order to offer guidance that will facilitate the regulation of these products in a harmonized manner among the countries of the Member States, as well as responding to the request from some regulatory agencies to address the growing demand for licensing applications of these products.

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1. Overview

Biological products, as defined by the World Health Organization (WHO [1]), are medicines obtained from microorganisms, blood or other living tissues whose manufacturing procedures may include one or more of the following elements: growth of microorganism, strains in different types of substrate, use of eukaryotic cells, biological substances extracted from tissues, including human, animal and plant tissues, and also products obtained by recombinant DNA or hybridoma technology, and the propagation of microorganisms in embryos or animals, among others [2].

In its most recent definitions, the WHO [2,3] includes the following medicines as biological products: vaccines, allergens, antigens, hormones, cytokines, enzymes, derivatives of human blood and plasma, immunological sera, monoclonal immunoglobulins, antibodies, fermentation products (including products made by recombinant DNA technology) and reagents employed for in vitro diagnosis.

Medicines of biological origin constitute one of the largest sectors of growth of the pharmaceutical industry, and their regulation presents major challenges. Some of these challenges are related to the inherently variable nature of the source materials and the manufacturing methods used [4–6]. Likewise, there is a need for analytical methods, mostly bioassays, for facilitating the characterization of biological products. The use of these methods involves additional special efforts in their standardization and implementation.

Unlike conventional medicines which are produced using technologies able to provide a high degree of homogeneity and manufacturing consistency, the manufacture of biological products involves processes that are difficult to reproduce, and...
the use of natural sources, such as cell cultures or the extraction of materials from live organisms which tend to generate heterogeneous products in the absence of strict manufacturing controls. Thus, one of the main challenges in the manufacture of these products is to achieve consistency in their production. Therefore, the manufacture of biological products implies the need for a comprehensive system of quality management which covers all staffs and stages in the production, to ensure the quality, safety and effectiveness of the final product. The development of such products requires the participation of regulatory agencies in a role different from that which they usually play in relation to conventional medicines. The development of such specialized production methods requires a very specialized process control which rests mainly on the manufacturer. Likewise, provision of evidence of specific quality control in the finished product becomes very complex and sophisticated, and may even have to be tailored for each particular product, which can diminish the value of prescriptive laboratory tests. That is why the assessment of compliance of Good Manufacturing Practices (GMP), the demonstration of effectiveness in clinical trials, and the post-marketing surveillance, become fundamental pillars for the product’s approval by the regulatory agency.

At present, there are multiple reference documents issued by the WHO, as technical report series which are product specific, training manuals, guidelines and other general documents, which provide guidance and direction to the regulators, manufacturers and users of biological medicines. While many of these documents are oriented toward production and control of vaccines as part of the category of biological products, there are also documents aimed at production and control of biotechnological products made by recombinant DNA technology [6–9]. Likewise there are reference preparations available, such as cytokines/growth factors, endocrine substances and recombinant coagulation factors [12].

Despite current availability of multiple reference documents issued by the WHO [6–11], European Commission of Medicines (EMEA) [13–24], and by the International Conference on Harmonization (ICH) [25–28], related to biotechnological and biological products, there is no consensus among these reference institutions for the countries of the Region, on some important definitions used, and the mechanisms for the regulation of biotechnological products.

As an example, we can cite that the WHO uses the name therapeutic biological medicines, while the EMEA and the ICH use the names biological medicinal products containing biotechnology-derived proteins and biological/biotechnological products, respectively, for referring to the same type of biological product.

Considering this international context, the objective of this publication is to present the current picture of biotechnological and biological product regulation in the Latin American and Caribbean Region, in order to offer guidance that will facilitate the regulation of these products in a harmonized manner among the countries of the Member States, as well as responding to the request from some regulatory agencies to address the growing demand for licensing applications of these products.

2. Biological and biotechnological product regulation in Latin American and Caribbean countries

The Pan-American Health Organization (PAHO), with the aim of giving technical support to the National Regulatory Authorities (NRAs) of the Member States, in view of the urgent necessity to rationalize and to harmonize biotechnological and biological product regulation, has begun to develop a series of activities with the countries of the Region, including the meeting on the Biological and Biotechnological Regulation Challenges, held in Montevideo, Uruguay, in November of 2007. This meeting focused especially on the regulation and similarity conditions of these products. At the same time the update on regulation at world-wide level of “biosimilar” products was presented.

Simultaneously and as part of the activities established by the PAHO, the following challenges were established:

- Evaluating the needs and/or strengths of NRAs of the Region in the matter of biotechnological and biological product regulation in general, including “biosimilars” and therapeutic biological medicines.
- Identifying the existing regulatory differences among the Latin America and Caribbean countries for the above products.
- Providing technical support to the NRAs in required areas, as well as to motivate harmonization in the regulation of biological and biotechnological products in the Region of the Americas.

The PAHO, through the Essential Medicines and Vaccines Project, part of the Technology, Health Care and Research Area, has developed a survey to evaluate the needs of NRAs of Latin America and the Caribbean Region in biological and biotechnological product regulation, which was sent to a total of 27 countries: Republic of Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Dominican Republic, Surinam, Trinidad and Tobago, Uruguay, and Bolivarian Republic of Venezuela.

This survey was targeted toward professionals responsible for the evaluation of biological product licensing applications within the regulatory agency of each country. The survey included a series of questions that allowed establishment of a platform to meet the challenges outlined above. The results of that survey are shown below.

3. Survey results

The responses from 17 countries (Republic of Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru, Dominican Republic, Uruguay and Bolivarian Republic of Venezuela) allowed the identification of the responsible agent for evaluating and granting of the biological product license in each country.
Most of the countries surveyed (75%) have regulations in place for biological products. However, there are often no differences between documents requested for licensing each product (vaccines, blood derivatives, and/or therapeutic biological medicines). In the case of Bolivia, Colombia, Costa Rica, Ecuador, Peru and Dominican Republic, the documents requested for biological products and for pharmaceutical products are exactly the same. Bolivia, Ecuador, and the Dominican Republic, do however demand additional documents for vaccines that are going to be licensed in their countries.

With the exception of Colombia and the Bolivarian Republic of Venezuela, where the duration of the granted license is of 10, and 7 years respectively, for the rest of the surveyed countries the granted license must be renewed every 5 years. In most cases, including Colombia and the Bolivarian Republic of Venezuela, the renewal process involves an exhaustive evaluation of documents.

At present, any change in a licensed product must be notified to the NRAs of all the countries surveyed. In most countries there are established procedures for doing so.

As shown in Fig. 1, few countries provide specific definitions for vaccines (8), blood derivatives (6), biotechnological products (6), biosimilar products (2) and/or biotherapeutic products (3), respectively, in their local regulations.

A total of 12% of the surveyed countries have licensed biosimilar products. The following were licensed under this category of products: recombinant human insulin, coagulation factors (II, VII, VIII, IX, X, XII), plasma activating factor, fibrinogens, specific immunoglobulins, normal immunoglobulins, human albumin, streptokinase, urokinase, sodium enoxaparine, human recombinant erythropoietin (alpha, beta), filgrastim, lenograstim, interferon (alpha 2a, alpha 2b, beta 1a, beta 1b), niseritide, Saccharomyces sp, Lactobacillus sp, and granulocyte stimulating factor.

There are also countries such as the Republic of Argentina, Brazil, the Bolivarian Republic of Venezuela, and soon Costa Rica, whose regulations treat all biological products as new products, given their nature, and process of manufacture. Therefore, full quality dossier, safety and efficacy studies are requested during their license. Also, comparative studies with the innovating product, including impurity profiles of the active principle and finished product, and studies of non-inferiority (if applicable) are requested. The Republic of Argentina, Brazil, Chile and the Bolivarian Republic of Venezuela do not support the term of similarity between biological products.

Although there is a great interest on the part of the countries surveyed in having harmonized documents for the licensing of biotechnological products, there is no clear trend in the acceptance of mutual recognition mechanisms as an alternative to the licensing of these products, by countries that do not have a strong enough infrastructure for this purpose, without undermining the fact that such recognition must be established by each government and in some cases by the various partnerships between countries such as: Mercosur, the Central American Customs Union, the Andean Community of Nations, and the Alba, among others. At present, countries such as the Republic of Argentina, Brazil, Cuba and the Bolivarian Republic of Venezuela do not use this mechanism.

A total of 41% of the countries indicated do not possess legal bases to enable them to identify a mechanism for mutual recognition, indicating that national regulations establish mandatory evaluation of any product that is going to be licensed in the country.

Moreover, some surveyed countries (41%) reported conditions for the acceptability of such a mechanism. Among these conditions, they emphasize the importance of:

- The harmonization of documents requested during the licensing of biological and biotechnological products in Latin America and the Caribbean.
- The granting of recognition by PAHO of the country’s NRA in terms of its regulatory capacity.
- The identification of a regional mechanism of biotechnological and biological product certification.

Fig. 2, shows the number of countries that use documents of reference issued by international entities considered “of reference” for the Region, such as the WHO, ICH, EMEA, FDA, etc.

With regard to background documents related to vaccines, most countries surveyed indicated the use of WHO Technical Report Series, as well as other general documents regarding the batch release process, and cold chain, in addition to specific pharmacopeial monographs.

However, in the case of blood derivatives and biotechnological products, there are many countries that do not mention or are unaware of the existence of reference documents for these products issued by these bodies.

In this context, the PAHO is collecting all available information on biotechnological products to distribute among the NRAs of the Region, and place on the website of Vaccines and Biologicals http://new.paho.org/hq/index.php. Also, during
that ''biosimilar'' products can be approved by an abbreviated product's efficacy and safety. There is also a general agreement on the need to demonstrate and guarantee the ecological and clinical profiles to demonstrate and guarantee the additional data, particularly during the evaluation of the toxicological and clinical profiles to demonstrate and guarantee the product's efficacy and safety. There is also a general agreement on the need to demonstrate and guarantee the additional data, particularly during the evaluation of the toxicological and clinical profiles to demonstrate and guarantee the product's efficacy and safety.

This review, each country indicated the current, most important needs related to biotechnological product regulation. These needs are mostly oriented toward training in various aspects, harmonization and networking, and to the application of reference documents on biotechnological products.

In parallel, the PAHO organized a meeting for the NRAs of the Region, in the Dominican Republic, on June 2008, where a total of 15 countries participated (Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, Guatemala, Mexico, Nicaragua, Panama, Peru, Dominican Republic, and Bolivarian Republic of Venezuela). In this meeting the review on biotechnological and biological product regulation in Latin America and the Caribbean described in this article, was presented. Furthermore, updates and the current challenges on biotechnological product regulation, as well as the future activities on this subject to ultimately promote harmonized processes in the Region were discussed.

There is particular interest in the use of the term “biosimilars”, a designation that, until now, has been adopted in an arbitrary manner at the global level. For instance, the EMEA uses the phrase similar biological medicinal products containing biotechnology-derived proteins, in the United States of America and Japan they are referred to as follow-on/protein products, in Canada they are subsequent entry biologics and in India and Iran these are called biogeneric products.

The consensus rests on the fact that the simple term “generic” does not apply, for “biosimilars”. These products cannot be regulated in the same way as generic pharmaceuticals due to the complex nature of biologics, their manufacture and additional data, particularly during the evaluation of the toxicological and clinical profiles to demonstrate and guarantee the product’s efficacy and safety. There is also a general agreement that “biosimilar” products can be approved by an abbreviated regulatory process based on a claim of similarity to a reference product (an existing licensed product) [11]. The conflict arises when term similarity in itself and the similarity of one biological product to another have to be defined.

During the twelfth meeting of the International Conference of Drug Regulatory Authorities, ICDRA, held in Seoul, Republic of Korea in April 2006, a session was dedicated to the global challenges in regulation of vaccines and other biologicals [29]. The following recommendations summarize the requests to WHO:

- Facilitate the process through establishment of regional and global networks of regulators.
- Develop global regulatory consensus and guidance for “biosimilars”.
- Facilitate the work of the National Laboratories of Control (NLC) through a global review of batch release strategies, and
- Ensure sustainability of its international biological reference preparation program, among others.

In April 2007, in Geneva, Switzerland, the WHO initiated specific activities related to the regulation of “biosimilars”, conducting an informal consultation on therapeutic biological medicines' regulation. Some of the objectives were to discuss the current status in the regulation of biological (biosimilars) and to review the alternatives and challenges in quality evaluation, safety and efficacy of these products.

The consultation recognized the importance of the terminology as well as determining a definition of “biosimilars”. However, achieving a global consensus on the terminology for these new challenging products was not attempted at the consultation, and it was decided that a future WHO working group should act on this issue as a next step [11]. Also it was agreed that WHO should develop a global regulatory guideline for biosimilar products, including issues of critical importance as principles of evaluation of these products, and regulatory pathways for their licensing oversight. Due to the great interest and the important consequences to the industry and consumers of adopting the concept of biosimilars and its regulation, this document is currently still in development.

This publication fulfills one of the objectives of the project on biotechnological and biological products started by the PAHO. It presents the results of the review of the regulation of these products in the Region, which is the starting point for any process of harmonization.

4. Conclusions

The regulation of biological/biotechnological products is facing new challenges in comparison with conventional pharmaceutical products. Strong pressure from pharmaceutical companies who recently have incorporated these products into their portfolios, looking for innovation and favorable economic consequences, is making regulators seek for easier and not always adequate pathways to face the new challenges.
Main regulatory agencies are aware that they are not prepared to regulate properly these products which are invading markets all around the world with a major impact and consequences which could affect negatively mainly developing countries.

With the intention to give the first steps for supporting countries in the Pan American Region, the PAHO has conducted a survey to make a review of the current situation for the regulation of these products.

This review gives an overview of the current scene related to the regulation of biological and biotechnological products in 17 Latin American and Caribbean countries, which can be used as an indicator of the current picture at a regional level.

This overview indicates that there are preliminary regulatory activities in the Region which can be used as a platform for the establishment of harmonized documents, harmonized procedures and guidelines relating to this subject, which will support the improvement of existing regulatory mechanisms and facilitate the information exchange among the regulators of the Americas. Despite the existing strengths in some countries of the Region regarding regulatory matters, there are also shortcomings, some of which are related to a lack of definitions for each type of product, and/or specific training, not allowing the establishment of harmonized procedures, and also enabling evaluators at the regulatory level to face the specific challenges of biotechnological and biological product regulation.

Generally, during the design and development of international reference documents the objective is to resolve precise needs in regulatory matters of countries with strong regulatory agencies. Nevertheless, these proposals of modifications are not always applicable to developing countries, because in the majority of the cases these proposals do not consider the existing basic deficiencies that span the establishment of definitions and procedures to carry out these proposals. In order to be able to face the challenges posed by the regulation of new biologicals, such as biotechnological products, the regulatory agencies of developing countries should strengthen their regulatory systems through networking work, harmonization of regulations and assessment procedures, among others [30].

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References


