

Similar biotherapeutic products in Latin America. Regulation and opportunities for patients with autoimmune diseases

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Abstract: Biotherapeutic products have revolutionized medicine, changing the way we can treat some chronic diseases, such as autoimmune diseases. The patent expiry and the high costs of reference biotherapeutic products, among other factors, have promoted interest in similar biotherapeutic products (SBPs), also known as biosimilars. The objective of developing an SBP is to manufacture a “highly similar” molecule to a reference biotherapeutic product, by conducting a comparability exercise that can demonstrate similar quality, safety, and efficacy. Regulations like those of the World Health Organization, the European Medicines Agency, and the Food and Drug Administration are international reference standards. Herein, we aim to point out the current status in Latin America on SBPs, focusing on regulatory issues within the context of autoimmune diseases. The regulations of Argentina, Peru, Chile, Guatemala, Panama and Costa Rica follow the World Health Organization guidelines. Other countries, such as Cuba, Mexico, Venezuela, and Brazil have regulations that take into account international standards combined with local features. In Colombia, a draft decree is under revision and the debate is ongoing. Some countries have already approved SBPs. Mexico, Chile, Ecuador, Bolivia, and Peru market SBPs of rituximab, and Colombia markets an SBP of etanercept. The advent of SBPs is definitely beneficial. Safety and efficacy must be ensured following clear and comprehensive regulations.

Keywords: biological therapy, biotechnology, similar biotherapeutic product, autoimmune disease, Latin America

Introduction

Biotechnology is a growing field within the health sciences that allows the development of new effective therapeutic products.^{1,2} Biotherapeutic products (BPs) have revolutionized modern medicine, introducing new molecules that have changed the way we can treat autoimmune diseases (ADs) and other chronic conditions.³⁻⁵ This revolution has opened optimistic scientific perspectives in a scenario of epidemiological transition from infectious to chronic diseases.⁶ Nevertheless, the production and supply of BPs are a challenge for governments and modern health systems, given the elevated costs and the limited access to these therapies, especially in developing countries.⁴ The recent advent of similar biotherapeutic products (SBPs) has raised much controversy worldwide, because of the implications related with their regulation and subsequent entry to market, and all the different interests of the different parties affected. This is why much attention is currently given to the regulations concerning BPs and SBPs.

BPs are mostly large recombinant proteins derived from life forms.^{3,5} Commercially available BPs include insulin, human growth hormone, erythropoietin, granulocyte

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colony-stimulating factor, interferon- α , and monoclonal antibodies (mAbs), among others.^{2,7} SBP has been defined by the World Health Organization (WHO) as a biotherapeutic products that is similar in terms of quality, safety, and efficacy to an already-licensed reference biotherapeutic product (RBP).⁴ A variety of terms have been used to mention these products, including the term “biosimilars.”^{4,8–14} There is some controversy regarding the proper term for designating these products. What has been highlighted is the fact that all these terms should not be used as synonyms of “generics,” and that the term “biogeneric” is currently obsolete.^{15,16} For the present manuscript, the term SBP(s) will be used to designate biosimilar(s). Relevant definitions used throughout the present manuscript are disclosed in Table 1.

BPs are different from conventional pharmaceuticals in three important aspects: (1) high-complexity manufacturing process (MP), (2) active substances of more structural complexity and larger molecular size, especially in the case of mAbs, and (3) BPs are more likely to induce immunogenicity than conventional medications. Details pertaining to the development of a SBP are beyond the scope of this manuscript and can be consulted elsewhere.^{1,2,5,17} In the MP of BPs, once the protein has been sequenced, recombinant DNA biotechnology permits the production of the molecule on a large commercial scale.² The steps of the MP are: (1) cloning and protein expression, (2) protein production, and (3) purification and validation. Quality control for the confirmation of the DNA sequence of the cloned gene is usually conducted before and after full-scale fermentation. The process ends with the characterization and stability of the purified bulk drug. Additional activities within the MP are those related to storage and handling.⁹

The main objective in the development of an SBP is to manufacture a molecule that can be “highly similar” to the RBP.¹⁸ It is known that RBPs undergo changes over time. These changes provide a distribution of attributes that can be considered acceptable because the product has been administered to patients successfully.¹⁸ The limits to this distribution of the RBP attributes are denominated “goalposts.”¹⁸ These predefined limits of variability (goalposts) can be used as a starting point for comparing SBPs with RBPs. If the attributes of an SBP fall within the variability limits accepted for the RBP, then the SBP can be considered “highly similar” to the RBP.¹⁸ In the development of generic pharmaceuticals, only the chemical structure has to be reproduced. In this case, demonstration of structural similarity and bioequivalence is usually enough to demonstrate therapeutic equivalence.^{2,4} However, the

generic approach is not suitable for licensing SBPs.^{4,16} For that reason, a comprehensive comparability exercise (CE) must be conducted, with the objective of establishing similarity in quality, safety, and efficacy. Products should be compared in the same study using the same procedures.⁴ Within the CE, there are different levels of comparability: quality evaluation (ie, physicochemical and biological characterization, immunochemical properties, and impurities) and nonclinical and clinical evaluation (Figure 1).^{17,18} The nonclinical evaluation comprises the pharmacotoxicological assessment of the SBP, involving *in vitro* and *in vivo* studies.^{4,19} The establishment of safety and efficacy profiles of the SBP usually requires some nonclinical data. The purpose of the clinical evaluation is to demonstrate comparable safety and efficacy of the SBP with the RBP. This evaluation is a stepwise procedure that begins with pharmacokinetic (PK) and pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s).^{4,19} Given that BPs are biologically active molecules that are capable of inducing immune responses, immunogenicity is an important consideration within the evaluation of safety.^{2,4} In the clinical evaluation, similar efficacy between the SBP and the RBP should be demonstrated in adequately powered, randomized, and controlled clinical trial(s), preferably double-blind or at least observer-blind.⁴ For this purpose, equivalence trials (ETs) requiring lower and upper comparability margins are clearly preferred for the comparison of efficacy and safety, as requested by the guidelines of the European Medicines Agency (EMA).^{4,16} However, noninferiority trials (NITs), which require only one margin, may be considered if appropriately justified.⁴ Details on the methods and the levels of the CE can be consulted elsewhere and are well described in the guidelines on SBPs of the WHO.^{1,4,19} Additionally, pharmacovigilance programs are a fundamental issue that must be defined for the approval of every BP.

BPs represent one of the fastest-growing sectors of the pharmaceutical industry.^{2,20} Approximately 30% of pharmaceutical and biotechnology research and development is composed of BPs, and nearly a third of this is related to mAbs.¹⁸ However, the growth of this industry is parallel with the cost that health systems must pay for it. Presently, some phenomena promote interest in SBPs, such as the rapid growth of the biotechnology market and the great lucrative potential of this industry, the expiry of the patents of RBPs, the high costs associated with the commercialization and usage of RBPs, the imperious need of governments and health systems for cost containment and better access to these medicines, and the establishment of regulatory frameworks that favor the entry to market of SBPs.^{2,5,18,20}

Table 1 Summary of the relevant terms and definitions within the context of similar biotherapeutic products

Term	Definition(s)	Related terms (synonyms)	Abbreviation
Biotechnology	Any application of technology that uses biologic systems and living organisms or derivatives for the creation or modification of products or processes for specific purposes ⁸		
Biotherapeutic product	Medications, predominantly large recombinant proteins, that undergo complex posttranslational modifications and are typically produced and manufactured using live organisms ^{5,15} Definition by WHO: Medicines obtained from microorganisms, blood, or other living tissues, the manufacturing procedures of which may include one of the following elements: growth of microorganisms, 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 ⁴	Biological products Biological therapy Biological drugs Biopharmaceuticals Biotechnological products Biologics Biologicals	BP
Reference biotherapeutic product	Definition by WHO: An RBP is used as the comparator for comparability studies with the SBP in order to show similarity in terms of quality, safety, and efficacy. Only an originator product that was licensed on the basis of a full registration dossier can serve as an RBP. It does not refer to measurement standards, such as international, pharmacopoeia, or national standards or reference standards ⁴	Original biopharmaceutical Innovator biopharmaceutical Original biological product Innovator biological product	RBP
Second-generation biopharmaceuticals	Molecules that are structurally different from RBP, which are intended to improve performance while preserving the mechanism of action ³		
	Definition(s)	Related terms (synonyms) – country/territory	Abbreviation
Similar biotherapeutic product	Definition by WHO: Biotherapeutic product that is similar in terms of quality, safety, and efficacy to an already licensed RBP ⁴	Biosimilar product Similar biological medicinal product Subsequent-entry biological Biocomparable Known biological product Other terms ^{2,4,9,15} Biosimilar Biosimilar agent Second entry biologic Follow on biologic Follow on protein product Biocompetitor	SBP
		United States ¹⁰ European Union ¹⁶ Canada ⁸ Mexico ^{6,11,12} Cuba ^{13,14}	

Abbreviation: BP, biotherapeutic product; SBP, similar biotherapeutic product; RBP, reference biotherapeutic product; WHO, World Health Organization.

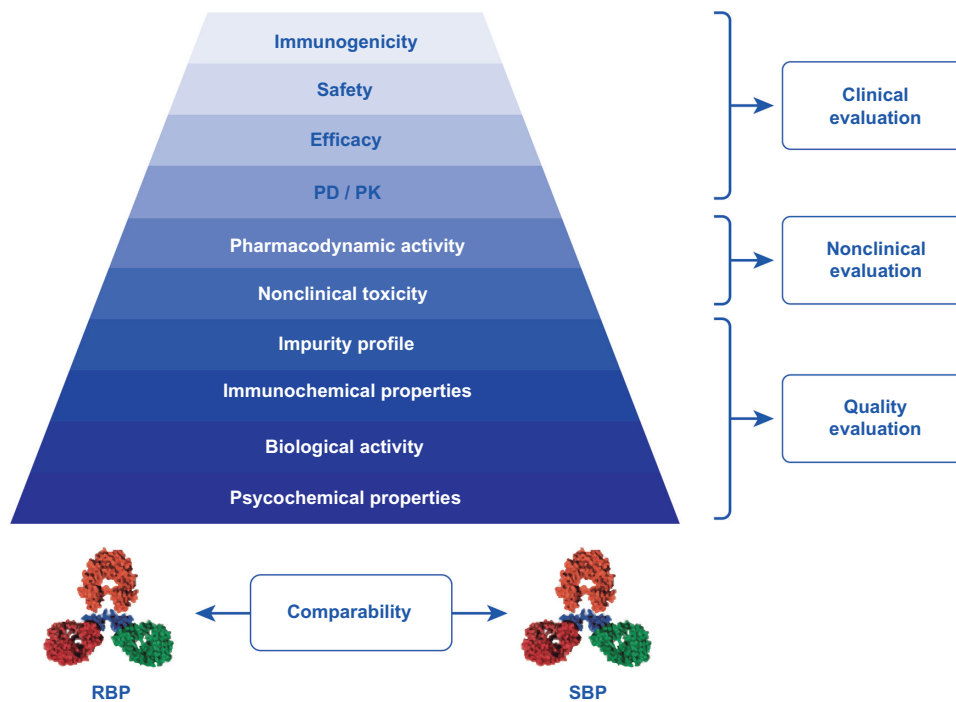


Figure 1 Comparability exercise.

Abbreviations: SBP, similar biotherapeutic product; RBP, reference biotherapeutic product; PK, pharmacokinetics; PD, pharmacodynamics.

Herein, we aim to point out the current status in Latin America (LA) of SBPs, focusing on regulatory issues within the context of ADs, chronic and potentially life-threatening conditions of increasing public health concern. Emerging information regarding molecular and cellular mechanisms about the pathophysiology of ADs has identified many potential targets for the treatment of these common conditions. In diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus, and vasculitis, available BPs are fundamental within the available therapeutics, having an important role in reducing disease progression and improving working productivity and quality of life.^{21,22} Despite these benefits, BPs have a high unit cost and are often used for chronic conditions like ADs that require ongoing treatment, representing significant expenditures for health budgets.^{23,24} The industry of biotechnology and SBPs has raised the interest of many pharmaceutical companies and stakeholders worldwide. Currently, biotechnology companies in Asia, Europe, and Israel are developing SBPs of tumor necrosis factor (TNF) inhibitors, B-cell depletion molecules such as rituximab (RTX), and selective costimulation modulators such as abatacept.³ SBPs of RTX are being marketed in India and some LA countries (Table 2). SBPs have not been approved yet for RA or systemic lupus erythematosus in the European Union (EU) or the United States (US).^{25,26} However, due to all the

known characteristics and important benefits, availability of SBPs in the US and EU is anticipated not only to enhance competition and create better patient access to biotechnology products but also to lower their cost.

Literature review

After a literature search conducted on PubMed, Embase, Scopus, Lilacs, Scielo, and Biblioteca Virtual en Salud, 18 full-text documents were selected. Inclusion criteria were the following: general documents regarding the situation, perspectives and regulations of SBPs in LA countries, and specific documents related to biotechnology and SBPs in the context of autoimmune rheumatic diseases. Exclusion criteria included topics other than the aforementioned and documents in languages that were not English or Spanish. The chosen documents included reviews, editorials, perspectives, reflections, commentaries, and letters to the editor, amongst others.

Additionally, other sources were manually searched, most corresponding to legislative and regulatory documents, and in some cases newspaper articles. The official government websites of LA countries were consulted, looking for approved SBPs as well as for specific regulations on BPs and/or SBPs.^{12,14,27–60} The websites of ministries of health or equivalent institutions were also consulted, as were the

Table 2 Approved SBPs in the context of autoimmune rheumatic diseases and state of the regulations on SBPs in Latin America

Country	SBPs approved	Specific regulation on SBPs ^a
Mexico	Kikuzubam (RTX) (2010) ^b	Available
Cuba	No	Available
Dominican Republic	Not found	Not found
Puerto Rico	Not found	Not found
Haiti	Not found	Not found
Guatemala	No	Available
Honduras	Not found	Not found
El Salvador	No	Not found
Nicaragua	No	Not found
Costa Rica	No	Available
Panama	Not found	Available
Colombia	Etanar (ETN) (2006)	Available
Venezuela	No	Available
Ecuador	Reditux (RTX) (2012)	No
Peru	Reditux (RTX)	Available
Brazil	Not found ^c	Available
Bolivia	Reditux (RTX) (2009)	Available
Paraguay	Not found	Not found
Uruguay	Not found	Not found
Chile	Reditux (RTX) (2010)	Available
Argentina	No	Available

Notes: ^aSee text for details. In the case of Colombia, regulation is still under review; ^bthe year of approval appears in parentheses; in the case of Peru, this information was not available. Official governmental websites were consulted, looking for approved SBPs and specific regulations on BPs and/or SBPs in all the Latin American countries;^{12,14,27,59} ^cthe official Brazilian website was consulted, but the registries of BPs used in rheumatic diseases could not be viewed.⁶⁰

Abbreviations: SBPs, similar biotherapeutic products; RTX, rituximab; ETN, etanercept; BPs, biotherapeutics products.

websites and databases of public consultation of the authority responsible for drug regulation in each country. Although the latest and most relevant information found is presented in this manuscript, legislation on the matter and approval of SBPs concerns issues that are constantly changing. Additionally, current regulations may be modified, amended, or supplemented at any time by the relevant authorities of each country.

Regulatory background

The first regulatory body in constructing guidelines was the EMA. In 2005, the first official document on the matter was published.¹⁶ In 2006, complementary guidelines on quality issues and nonclinical and clinical issues were published.^{19,61} In 2007, a complementary guideline on immunogenicity assessment was enacted.⁶² Additionally, the EMA has published specific guidelines for each type of medication.⁶³ So far, SBPs of growth hormone, erythropoietin, and granulocyte colony-stimulating factor have been approved in the EU.²⁵ For the approval of an SBP, quality,

nonclinical, and clinical studies are required by the EMA; in the case of clinical trials, ETs are requested.^{16,19,64} Currently, the overarching guideline of the EMA that was enacted in 2005 and the guideline enacted in 2006 about nonclinical and clinical issues are under revision, with the aim of actualizing these documents and discussing in detail some relevant aspects like the terminology regarding SBPs, aspects on the equivalence of efficacy and safety, the possible reduction of the number of animal experiments, the selection of relevant PK markers, recommendations of patient population within pivotal phase III clinical trials, extrapolation of indications, and alternatives to the equivalence design in clinical trials, among other aspects.^{64,65} The draft revision 1 of the EMA guideline on quality issues that was enacted in 2006 is now available.⁶⁶ In May 2012, a guideline on nonclinical and clinical aspects regarding mAbs was published by the EMA.⁶⁷ This guideline recommends a stepwise approach, where the extent and the nature of the nonclinical and clinical evaluation depend on the level of evidence obtained in the previous step.⁶⁷ A case-by-case basis is recommended for nonclinical evaluation to decide the choice and the extent of in vitro and in vivo studies; the necessity of in vivo studies is determined by in vitro studies.⁶⁷ A comparative PK study is the first step in mAb clinical evaluation. PK data can be helpful to extrapolate data on efficacy and safety between different clinical indications of the reference mAb. If dose-comparative and highly sensitive PD studies cannot be performed convincingly showing comparability in a clinically relevant manner, similar clinical efficacy between the SBP and the RBP should be demonstrated in adequately powered, randomized, parallel-group comparative clinical trial(s), preferably double-blind, normally ETs.⁶⁷

In the US, the Patient Protection and Affordable Care Act of 2010 (Public Law no 111–148), through section 7002 of the act, which is known as the Biologics Price Competition and Innovation of 2009 (BPCI Act), amended the creation of an abbreviated approval pathway for the evaluation of SBPs shown to be biosimilar to or interchangeable with an RBP.^{10,68} In February 2012, the Food and Drug Administration (FDA) issued draft guidance for the industry on the implementation of the BPCI Act approval process for SBPs. These included scientific and quality considerations in demonstrating biosimilarity to a reference protein product.^{10,69} In these guidelines, the FDA intends to consider the totality of the evidence provided by a sponsor to support a demonstration of biosimilarity, and recommends sponsors use a stepwise approach in their development of SBPs.¹⁰ The FDA stated that the totality-of-the-evidence approach will be used to review

applications for SBPs. Biosimilarity refers to the fact that the SBP and the RBP "... are highly similar notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the two products in terms of safety, purity, and potency."¹⁰ The clinical evaluation must include a clinical study/studies (including assessment of immunogenicity and PK or PD) sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the RBP is licensed.¹⁰ It was stated that: "The scope and magnitude of clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products, after conducting structural and functional characterization and possible animal studies."¹⁰ A sponsor of an SBP must provide justification for the proposed clinical study design. In the draft guideline, some facts that can influence the choice of the design are stated, as well as some specifications and discussion about ETs and NITs.¹⁰

In 2009, the WHO published the document *Guidelines on Evaluation of Similar Biotherapeutics Products (SBPs)*. This document was intended to provide guidance to the different national regulatory authorities (NRAs) for the development of evaluation of such products, helping in the harmonization of the requirements worldwide, leading to greater ease and speed of approval and assurance of quality, effectiveness, and security.⁴ The WHO recognizes that some issues like intellectual property matters, interchangeability and substitution of RBPs with SBPs, and labeling and prescribing information need to be defined by NRAs.⁴ This document recommends quality, nonclinical, and clinical (ETs preferred) evaluation within the CE.⁴ The guidance of the WHO can be adopted as a whole or partially by NRAs, or used as a basis for establishing national regulatory frameworks, taking into account that some aspects must be defined locally according to the particular context.^{4,70}

Similar biotherapeutic products in Latin America

In LA, ten countries have current specific regulations concerning the approval of SBPs: Mexico, Cuba, Guatemala, Costa Rica, Panama, Venezuela, Peru, Brazil, Chile, and Argentina. All these regulations have been published in the last 6 years. In Colombia, a second version of a draft decree that is under revision was published in May 2012.⁴⁶ The principal characteristics of the WHO, EMA, FDA, and LA regulations are illustrated in Table 3. To our knowledge, specific regulations or drafts concerning SBPs have not been published in the rest of LA. Countries like Guatemala,

Costa Rica, Panama, Peru, Chile, and Argentina^{35,42,44,51,57,59} follow and/or consider international accepted standards like those of the WHO, FDA, and EMA guidelines.^{4,10,16,19} Mexico, Cuba, Venezuela, and Brazil have regulations that consider international standards in combination with local features.^{12,14,48,52,71} In the Brazilian case, although the regulation addresses the needs of the country, the scientific principles are based on the WHO guideline.⁷¹ In Peru, Ecuador, Chile, and Mexico, SBPs of RTX are currently available: Reditux, an SBP produced by the Indian manufacturer Dr Reddy's Laboratories, is approved in Peru, Ecuador, Bolivia, and Chile, and Kikuzubam, an SBP manufactured by the Mexican company Probiomed, has been commercialized in Mexico since 2010.^{27,50,72} In Colombia, Etaner, an SBP of etanercept (ETN) has been approved since 2006.⁴⁵ However, this SBP was approved before the publication of a regulatory decree, as was Reditux in Ecuador and Chile.^{45,46,57,72} The results of the comprehensive search on SBPs approved in LA and on LA regulations on SBPs are shown in Table 2.

The Pan American Health Organization (PAHO) has been conducting efforts for the harmonization of the regulations on BPs and SBPs in LA and the Caribbean, through specific main objectives: (1) compilation of regulations on the matter in the member states, (2) establishment of a glossary that can facilitate the further development of related documents, (3) identifying regional documents for an appropriate elaboration of guidelines in the short and medium term, (4) establishing related issues, and (5) conducting working plans and developing tools and training programs for NRAs in relation to the regulatory oversight of BPs and related matters.^{73,74} In 2009, Pombo et al studied the state of the regulations of BPs in LA and the Caribbean for that year, through the development of surveys directed to the NRAs of the member countries of the PAHO.⁷⁴ They found that 75% of the countries surveyed had regulations in place for BPs; however, there were no differences in these regulations for licensing different types of BPs, such as SBPs. Additionally, they found that few countries provided specific definitions for BPs and SBPs.⁷⁴ The authors stated that "Although there was a great interest on the part of the countries surveyed in having harmonized documents for the licensing of BPs, there was no clear trend in the acceptance of mutual recognition mechanisms as an alternative to the licensing of BPs 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 partnerships between territories such as Mercosur, the Central American Customs Union, the Andean Community of Nations, the Alba, among others."⁷⁴

Mexico

This nation has been at the forefront of innovation and biotechnology, assuming a leadership role in LA in the matter of regulation of BPs.^{6,11} In 2007, several forums and discussion about SBPs were developed within the Mexican Congress, a process that ended in 2009 with the amendment of article 222 Bis to the General Health Law, which established the general basis for the approval and marketing of SBPs.^{6,11,75} In 2010, Boardman, a Mexican senator and chairman of the health committee of the state of Coahuila, wrote an article in which he described the negotiation and regulation pertaining to BPs and SBPs in Mexico, highlighting the country for being at the vanguard, with legislation that ensures efficacy and safety, allows adequate availability and access, permits competition among manufacturers, leading to price reduction, and fosters the development of biotechnology.¹¹ In 2011, additional dispositions on the previous regulation on BPs and SBPs were incorporated by the Mexican government (Table 3).¹² At the beginning of 2012, the Federal Commission for the Protection against Sanitary Risks announced actualizations on the regulations on BPs and SBPs.^{76,77} On the other hand, Mexico has been heading the manufacturing of SBPs in LA. The foundation Probiomed developed the SBP of RTX (Kikuzubam), which is already being marketed in Mexico, and plans to penetrate other markets.^{27,77,78} However, the commercialization of this SBP has not been without controversy.^{77,79} Probiomed is also developing SBPs of other products like beta-interferon and filgrastim, among others, positioning and contributing to the economic growth of the country in this field.^{9,78,80}

Cuba

This country has developed a pharmaceutical industry capable of responding to the needs of its national health system.¹³ The national industry is regulated by the Center for the Control of the National Quality of Medications (CECMED), which has faced the challenge of regulating a national industry with great scientific and high innovative potential and is dealing currently with the approval of SBPs locally manufactured.¹³ Science parks (SPs) are scientific organizations that link science, manufacturing, and services together. In the case of Cuba, the SP of western Havana brings together various institutions on the basis of a closed-loop strategy, covering all stages of research, development, production, and marketing of a pharmaceutical product.¹³ This SP has sustained important growth in Cuban scientific and technological activity, leading to the development and exportation in some cases of products such as vaccines, cytokines, and mAbs, among others.

Until October 2010, 133 BPs had been licensed in Cuba, of which 67 were locally manufactured.¹³ The basis for marketing authorization for medicines is based on the ministerial resolution “Rules for marketing authorization of medicinal products for human use,” which classifies medications into categories according to their degree of novelty, where BPs corresponded to category A.¹³ After several years of following this classification, CECMED identified the need to redesign it, taking into account quality, safety, and efficacy, as well as time in the market and therapeutic effects of the product.¹³ As a result, the rules of marketing authorization were updated in 2009, reclassifying medications as follows: class 1 (A and B) for new medicinal products, and class 2 (C) for known medicinal products.¹³ The first draft of the Cuban guideline was released for consultation in 2010.¹³ In 2011, the definitive guidelines and requirements were published (Table 3).¹⁴ In the context of mAbs, only the RTX innovator MabThera has been approved in Cuba for utilization in cancer; none of the BPs used in ADs is currently marketed as RBP or SBP for this indication.^{13,28}

Colombia

The definitive regulation on the approval process of SBPs is under development. In January 2012, the first draft decree was presented and socialized by the Ministry of Health and Social Protection.⁸¹ After receiving opinions and comments on this decree by the different parties, on May 24, 2012, the Ministry of Health and Social Protection presented the second version of the draft decree, inviting the different parties to analyze and comment on this document (Table 3).^{46,82} However, the regulations and entry to market of SBPs have generated numerous biased debates.^{83–86}

In 2006, Etanar, an SBP of ETN, was approved in Colombia for the treatment of RA.⁴⁵ Currently, this is the only SBP of a TNF inhibitor that has been approved in LA (Table 2). In 2007, Forero⁸⁷ brought to the Colombian Rheumatology Association (CRA) attention some concerns about Etanar. In turn, several members of the CRA conducted an observational study and a pharmacoeconomic study about Etanar. These two studies have been discussed elsewhere.^{88–90} “Etanar Therapy in Real-Life Patients with RA” was a multicenter observational study that enrolled 110 patients with active RA who were followed for 20 weeks.⁸⁹ Significant changes in the health assessment questionnaire disability index (HAQ-DI) and the disease activity score (DAS) 28 were observed. HAQ-DI and DAS 28 declined from 2.5 ± 1.1 to 1.1 ± 0.9 ($P < 0.001$) and from 5.76 ± 0.81 to 3.48 ± 1.12 ($P < 0.001$), respectively. Side effects were registered in 10% of the cases.⁸⁹ The authors

Table 3 Contents of regulations on SBPs in Latin American countries and in other reference documents

Country/territory/ institution	Regulatory document/ responsible institution(s)	Year of publication	Term to designate SBP	Definition of SBP
WHO	<i>Guidelines on Evaluation of Similar Biotechnological Products (SBPs)</i> ⁴	2009	Similar biotechnological product	A biotechnological product that is similar in terms of quality, safety, and efficacy to an already-licensed RBP ⁴
European Union	Guideline on similar biological medicinal products/EMA ¹⁶	2005	Similar biological medicinal product	A biological medicinal product claiming to be similar to another already marketed, in terms of quality, safety, and efficacy ^{19,61}
United States	Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product/FDA ¹⁰	Draft 2012	Biosimilar product	Biological product that is highly similar to the reference product, notwithstanding minor differences in clinically inactive components. Additionally, there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency ¹⁰
Mexico	Decree that amends and adds various provisions to the regulation of health supplies/President of the Mexican United States ^{6,11,12}	2011	Biocomparable Biotechnological medicine	Noninnovative biotechnological drug that proves to be biocomparable in terms of safety, quality, and effectiveness, based on the specific tests established by the law for this purpose ¹²
Cuba	Resolution number 56/2011: requisites for the register of known biological products/Ministry of Public Health ¹⁴	2011	Known biological product	A biological product produced by multiple manufacturers, in which the active substance is comparable in terms of quality, safety, and efficacy profiles to the active substance of an already licensed RBP in Cuba or in other countries. The dosage form, strength/concentration/potency, and indications should be the same as those of the RBP ¹⁴
Guatemala	Technical standard 67-2010: Sanitary reference registry of biological and biotechnological products/Ministry of public health and social assistance ³⁵	2010	Biosimilar/ biocomparable	Is a biologic/biotechnological medication that has demonstrated by an exercise of biosimilarity and biocomparability that is similar or comparable in terms of quality, safety, efficacy, and immunogenicity to the reference medication ³⁵
Costa Rica	RTCR 440: 2010. Regulation on the inscription and control of biological medications/Presidency of the Republic – Ministry of Health ⁴²	2010	Biosimilar medication	Biological medication that has been demonstrated by the exercise of biosimilarity to be similar in terms of quality, safety, and efficacy to the reference biological medication ⁴²
Panama	Executive decree no 340: Sanitary registry of biological and biotechnological products/ Presidency of the Republic – Ministry of Health ⁴⁴	2007	Not stated	Not defined

Requirements for approval of an SBP

Considerations/comments

Quality evaluation
 Nonclinical evaluation
 Clinical evaluation: ETs are preferred
 Pharmacovigilance program⁴
 Quality evaluation
 Nonclinical evaluation
 Clinical evaluation: ETs are requested
 Pharmacovigilance program: risk-management program^{19,64}

Guidance can be adopted as a whole or partially by NRAs or used as a basis for establishing national regulatory frameworks⁴

Applicants should note that the CE for an SBP versus the RBP is an additional element to the normal requirements of the quality dossier.⁶¹ The clinical evaluation requirements depend on the existing knowledge about the RBP and the claimed therapeutic indication(s). Available product/disease-specific guidelines should be followed when appropriate.¹⁹ In certain cases, comparative PK/PD studies between the SBP and the RBP may be sufficient to demonstrate clinical comparability, when some conditions specified in the guideline are met.¹⁹ Additionally a guideline on nonclinical and clinical issues of mAbs was published in 2012: a step-wise approach where the extent and the nature of the nonclinical and clinical evaluation depend on the level of evidence obtained in the previous step is recommended⁶⁷
 A totality-of-the-evidence approach is required for approval of SBPs.¹⁰ The type and amount of analyses and testing that will be sufficient to demonstrate biosimilarity will be determined on a product-specific basis¹⁰

Quality evaluation
 Nonclinical evaluation
 Clinical evaluation: at least one clinical trial; evaluation of clinical effectiveness, safety, and immunogenicity
 Pharmacovigilance program¹⁰

Case-by-case basis: the better the quality evaluation and the better comparability is demonstrated, less clinical evidence will be requested for approval of an SBP^{6,12}

Quality evaluation
 Nonclinical evaluation: in vitro studies may not be required if determined by the authorities
 Clinical evaluation: will be determined by the quality evaluation
 Pharmacovigilance program¹²
 Quality evaluation
 Nonclinical evaluation
 Clinical evaluation
 Pharmacovigilance program: postmarketing active surveillance

The magnitude of the nonclinical and clinical data will depend on the previous knowledge on the RBP, the pharmacologic classification, the specific indication requested, and the differences detected during the quality evaluation.¹⁴ The clinical trial design can be that of ETs or NITs, or can be PK/PD studies in certain cases¹⁴

Quality evaluation
 Nonclinical evaluation
 Clinical evaluation: PD, PK, efficacy, safety, and immunogenicity
 Pharmacovigilance program: risk-management program and pharmacovigilance plan postregistration³⁵

The type and the amount of clinical studies will be determined by the knowledge on the RBP and the therapeutic indications that are being requested. A case-by-case approach will be conducted following the guidelines of the WHO, the ICH, the EMA, and the FDA³⁵

Quality evaluation
 Nonclinical evaluation
 Clinical evaluation
 Pharmacovigilance program: risk-management plan and postmarketing pharmacovigilance

The type and the amount of clinical studies will be determined by the knowledge on the RBP and the therapeutic indications that are being requested. A case-by-case approach will be conducted following international guidelines. In the absence of international guidelines, those of the ICH, the EMA, and the FDA could be followed.⁴² In article 6 of this document, five alternatives are stated for selecting the RBP for conducting the CE⁴²
 The national direction of pharmacy and medications will use as a reference for the CE the guidelines of the WHO and other guidelines like those of the FDA, ICH, and EMA⁴⁴

Quality evaluation
 Nonclinical evaluation
 Clinical evaluation
 Pharmacovigilance program: risk management⁴⁴

(Continued)

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Table 3 (Continued)

Country/territory/ institution	Regulatory document/ responsible institution(s)	Year of publication	Term to designate SBP	Definition of SBP
Colombia	Draft decree by which decree 677 of 1995 is partially modified and the register of medications of biological origin for human use is regulated and other dispositions are dictated/ Ministry of Health and Social Protection and the President of the Republic ⁴⁶	Draft 2012 ^a	Medication of successor biological origin	Medication whose entry has been later than a biological medication of first entry, approved by INVIMA supported on proper information of quality, security, and efficacy ⁴⁶
Venezuela	Standard for the registry, batch release and control of biological products/Ministry of the Popular Power for Health – National Institute of Hygiene “Rafael Rangel” ⁴⁸	2008	Not stated	Not specifically defined. May correspond to new product A ₂ : biologic product, whose active principle or combination of active principles are already registered in the country, but the request of approval is requested by a producer different than the pharmaceutical company of the approved product ⁴⁸
Peru	Regulation for the register, control and vigilance of sanitary pharmaceutical products, medical devices, and sanitary products. Chapter V: biological products/ constitutional President of the Republic – Ministry of Economy and Finance – Ministry of Health ⁵¹	2011	Biosimilar biologic product	Not defined
Brazil	Resolution 55 of 2010: Registration of new biological products and biological products and other dispositions/ANVISA ⁵²	2010	Biological product ^b	Not specifically defined ⁵²
Chile	Proposal of rule on technical aspects for the evaluation of biotechnological pharmaceutical products derived from techniques of recombinant DNA/Committee of Biological Products of ANAMED – Public Health Institute of Chile ⁵⁷	2011	Biosimilar	Biotechnological drug that has been demonstrated to be similar in quality, security, efficacy, and immunogenicity to the RBP, relying on its comprehensive characterization, comparative quality studies, nonclinical and clinical comparative studies, ie, a comparability study ⁵⁷
Argentina	Disposition no 7075/Ministry of Health – Secretary of Politics, Regulations, and Institutes – ANMAT ⁵⁹	2011	Not stated	Not defined

Notes: ^aA second version of the draft was published in May 2012 by the Ministry of Health and Social Protection.⁴⁶ ^bin Brazil, biological product refers to BPs that are not new in Brazil; these include SBPs and other types of copies of the RBP.⁵² This table illustrates the principal characteristics and contents of the pertinent regulatory documents. For more details or for additional consultation, the specific regulation of each country can be consulted.

Abbreviations: SBP, similar biotherapeutic product; BP, biotherapeutic product; RBP, reference biotherapeutic product; WHO, World Health Organization; ETs, equivalence trials; NRAs, national regulatory authorities; EMA, European Medicines Agency; CE, comparability exercise; mAbs, monoclonal antibodies; FDA, Food and Drug Administration; NITs, noninferiority trials; ICH, International Conference on Harmonisation; INVIMA, National Institute of Vigilance of Medications and Food; ANVISA, National Agency of Sanitary Vigilance; ANAMED, National Agency of Medications; ANMAT, National Administration of Food, Medications, and Medical Technology.

concluded that “Etaner can effectively control disease activity in real-life patients with active RA and poor responses to MTX but also other disease-modifying antirheumatic drugs. Safety and tolerability assessment indicates Etaner to be well tolerated.”⁸⁹

Brazil

BPs represent 2% of all the medicines covered and distributed by the Brazilian government; however, this represent 41% of the total amount that the Ministry of Health spends annually on medicines through specific health programs; mAbs

Requirements for approval of an SBP**Considerations/comments**

Essential information

Quality evaluation

Immunogenicity testing: according to the guidelines established by the Ministry of Health and Social Protection

Pharmacovigilance program: risk-management plan

The review commission of the chamber of drugs and biologicals of INVIMA will establish conclusive evidence of the safety and the efficacy of the SBP based on the essential information provided by the manufacturer of the SBP. If this evidence is not conclusive, complementary information will be required: comparability exercise, nonclinical evaluation, and clinical trials.⁴⁶ The specific designs or studies within the clinical evaluation are not established⁴⁶

Quality evaluation

Nonclinical evaluation

Clinical evaluation

Pharmacovigilance program: active pharmacovigilance plan during the first year⁴²

BPs are classified in different categories. The requisites for the approval will depend on the specific category. Every biological product will be considered as a new one for obtaining its sanitary registry⁴⁸

Quality evaluation

Nonclinical evaluation: in vitro studies will not be required if determined by the pertinent authorities

Clinical evaluation

Pharmacovigilance program: risk-management plan⁵¹

Preclinical and clinical studies must demonstrate comparability between the RBP and the SBP. The degree of similarity in the quality evaluation will determine the extension of the nonclinical and clinical studies⁵¹
The comparability exercise will be based on the guideline of the WHO^{4,51}

Quality evaluation

Nonclinical evaluation

Clinical evaluation

Pharmacovigilance program

The amount of requested studies in each level depends on the pathway (comparability or individual).⁷¹ More emphasis is given to clinical studies. Nonclinical studies are not dispensable⁷¹

Quality evaluation

Nonclinical evaluation: at least one study in vitro and one repeated-dose toxicity study in an animal model

Clinical evaluation: including clinical studies of immunogenicity unless these data can be generated by clinical studies that evaluate safety

Pharmacovigilance program: risk-management plan⁵⁷

BPs can be licensed by a comparative pathway or by an individual development pathway.^{52,71} In the individual pathway, a reduced dossier can be presented; however, at least one comparative NIT with the RBP must be presented. Within this pathway, indications cannot be extrapolated to those of the RBP.⁷¹ Only the copies licensed by the comparability pathway are considered as SBPs and could claim for extrapolation of indications.⁷¹ Brazilian regulation regarding license of SBPs is not related to patent issues⁷¹
For specific class products like mAbs, the specific guidelines developed for this purpose by the EMA must be followed.⁵⁷ Preclinical and clinical studies will be requested on a case-by-case basis according to the comparability in the quality evaluation; for nonclinical studies, at least one study in vitro and one animal model.⁵⁷ For clinical studies, comparative immunogenicity and extension studies must be developed. At least one comparative PK/PD study must be conducted⁵⁷

Within the clinical evaluation, phase I, II, and III studies must be included⁵⁹

Quality evaluation

Nonclinical evaluation

Clinical evaluation

Pharmacovigilance program: integral system of report, epidemiological analysis, and risk management⁵⁹

account for the 32% of the total amount spent on BPs by the Brazilian Ministry of Health.⁷¹ In 2002, the first regulation related to BPs was published; the same pathway was contemplated for RBPs and for SBPs.⁷¹ At the end of 2010, given the national and international interest and questions on SBPs, the

National Health Surveillance Agency (ANVISA) published the current guidelines (Table 3).^{52,71} This guideline established two pathways for the approval of SBPs: comparative and individual.⁵² Special importance is given to the clinical evaluation within both pathways; the nonclinical evaluation

is not dispensable.^{71,91} The Brazilian guidelines follow the same scientific principles as the WHO guidelines, but also have some differences, which are due to specific country needs.⁷¹ Since 2005, the NRAs of Brazil (ANVISA) and Cuba (CECMED), through an agreement between both countries, created the Technical Regulatory Committee (TRC) to follow all the activities related to technology-transfer projects.⁷¹ This TRC has members from different areas of the Brazilian and Cuban NRAs, as well as members from different areas of the Cuban and Brazilian producers.⁷¹ A project for the development of an interferon alpha-2b has already been developed by the TRC.⁷¹ In 2010, Azevedo highlighted the importance of the formulation process of SBPs, which goes from the type of administration to the final use by the patient.⁹² He argued that the possible differences in this aspect between the RBP and the SBP must be clearly and publicly stated by both manufacturers, that safe application of BPs depends on informed and appropriate use by health-care professionals, and that the role of prescribing physicians is of great importance, given that the exchange between RBPs and SBPs is their responsibility, as well as the obligation of promptly communicating loss of efficacy and signs that indicate differences in immunogenicity between the RBP and the SBP.⁹² In 2011, Azevedo et al studied the opinion of some Brazilian rheumatologists about SBPs.⁹³ One-third of the professionals reported not being familiar with what SBPs were and what seemed reasonable, since the subject was relatively new to rheumatologists.⁹³ Most interviewees indicated low price as an undeniable advantage of SBPs. Regarding the approval of SBPs, few professionals considered it important that an SBP had different nomenclature from the RBP.⁹³ Of note, this research evidenced the lack of information on the matter, and claimed for academic and unbiased discussions about differences between RBPs and SBPs among physicians, especially rheumatologists.⁹³

The Brazilian government is supporting two companies, Bionovis and Orygen, wishing to be the first national companies to develop SBPs. On the other hand, Sandoz, which is based in Cambé, Paraná, already markets Omnitrope, the first SBP/rhGH follow-on protein, and also is conducting clinical trials on other SBPs, including RTX.

Chile

Currently, there are guidelines on the approval of SBPs that follow the accepted international standards (Table 3). In 2006, Saavedra and Quiñones⁹⁴ described considerations pertaining to the interchangeability of BPs and the approval of SBPs in Chile. The authors stated that the Public Health

Institute and the Ministry of Health of Chile must consider that for BPs there are no interchangeable generics, and must also consider that the bioequivalence of these medications should be addressed on a case-by-case basis following non-clinical and clinical studies that can demonstrate efficacy and safety.⁹⁴ In 2010, the Chilean Society of Rheumatology issued a statement on the authorization of SBPs, supporting their development based on the patient's right to have better access to appropriate and timely treatment.⁹⁵ The concerns of these two articles mentioned^{94,95} were solved by the current Chilean guidelines on SBPs.⁵⁷

Argentina

In November 2011, the regulation on SBPs was enacted. The document was based on international standards (Table 3).⁵⁹ In this country, no SBPs have been licensed for utilization in RA or other ADs.⁵⁸ In 2009, Matar⁹⁶ highlighted the importance of following updated and specific legislation for the approval of SBPs and also emphasized the importance of conducting clinical trials designed for testing the efficacy and security of SBPs before their approval.⁹⁶ This point of view was published before the enactment of the current regulation.

Discussion

The regulation and marketing of competing SBPs has aroused much controversy worldwide, especially regarding the number and the stringency of the requirements for their approval. This aspect is complex given the different interests involved: transnational pharmaceutical companies producers of RBPs, pharmaceutical companies producers of SBPs, local markets and importers of SBPs, governments and health authorities, patients and health professionals, as well as scientific societies. The debate regarding the regulation of SBPs should consider effectiveness, safety, cost containment, and reasonable profits. On one side, the effectiveness and safety of the new molecules and SBPs must be guaranteed, and on the other side access to these medicines must be sought. Cost containment is also critical given that the sustainability of modern health systems in a scenario of advanced medicine and expensive interventions is a great challenge.⁹⁷ Satisfying patent exclusivity and reasonable profits of the manufacturers of RBPs has to be weighed against the sustainability of the health systems and the entry to market of SBPs, also in the context of reasonable profits for manufacturers of SBPs. Some authors believe that the current controversy is artificial and promoted, probably by the pharmaceutical companies that produce the RBPs, who perceive the entry of SBPs as a menace to their profits and monopoly.⁸ These authors argue

that it should not be controversial, because the entry of SBPs is beneficial as long as these products can achieve the requisites of quality and comparability that have been defined by serious regulatory institutions like the EMA.⁸

The debate can be more difficult when the context is that of low- and middle-income countries, like most of the nations of LA. In this case, the necessity of adequate access to BPs is high, and the opportunity for the community and for patients of low resources to obtain expensive treatment for ADs and other chronic diseases is low. Then, some questions appear. How much stringency in the evaluation of SBPs are LA countries willing to sacrifice for cost containment and sustainability of health systems? How much uncertainty on effectiveness and security of SBPs are health authorities in LA willing to sacrifice for better access to high-cost medications such as BPs? Some LA countries like Mexico, Peru, Ecuador, Chile, Bolivia, and Colombia are already marketing SBPs of biological therapies used for autoimmune rheumatic diseases (Table 2). In Colombia and Chile, these SBPs were approved before the publishing of current regulations or drafts.^{45,72} In China and India, some SBPs for RA have also been approved.⁹

Some LA countries have shown important growth in their biotechnology industries: Mexico, through the local manufacturer Probiomed, developed an SBP of RTX that is already being marketed in the country, contributing to the growth of the Mexican biotechnology industry.⁷⁸ Cuba has a structured national industry that produces around half of the BPs that are approved and marketed in the country, specifically vaccines, and it also exports some of these BPs.¹³ In Brazil, there are some national producers of BPs with broad experience in the production of vaccines, and that recently have begun to produce other BPs like erythropoietin and interferon.⁷¹ In this country, the interest and investment of private and public national producers in the biological market has increased in an important way in the last few years.⁷¹ An agreement was reached in 2005 between Cuba and Brazil for the development and follow-up of BPs.⁷¹ These cases are examples of the important role that biotechnology can have on national scientific and economic growth in Latin American countries.

In the case of Colombia, the average cost per patient per year of therapy with TNF inhibitors was estimated for 2009 as US\$23,464 from the payer's perspective,⁹⁸ which is more than four times the Colombian gross domestic product per capita for that period.⁹⁹ Colombian health funds have been seriously affected by BPs and high-cost medicines. In the last 3 years, eight of the ten principal medications reimbursed by

Fund of Solidarity and Guarantees (FOSYGA) corresponded to BPs; between 2008 and 2011, around \$334,728,000 was paid by FOSYGA for reimbursements of 15 BPs.¹⁰⁰ Part of this phenomenon has been blamed on the multinational pharmaceutical industry through attempting to impose rules that prevent entry of drugs that can compete with those already being sold in the country.¹⁰⁰ It is noteworthy that BPs in Colombia are much more expensive than in other countries.^{85,101} For example, RTX and infliximab have been estimated to be much more expensive in Colombia than in the United Kingdom: 1.217% and 94.2%, respectively.¹⁰¹ Another concern that has been stated by the Colombian media is the possible negative effects that the free-trade agreement with the US may have on the national market of biotechnology and on access to BPs and SBPs¹⁰² because of the specifications on patents and intellectual property established in the free-trade agreement.^{102,103}

The entry of SBPs is a phenomenon prone to controversy, given the different affected parties. In Colombia, the approval of Etaner raised different opinions among health professionals, as was discussed previously.^{87,89,90} In Mexico, a similar controversy was seen when Kikuzubam was approved, which involved the local manufacturer, the manufacturer of the innovator RBP, the government, and other parties.^{77,79} Yet in a panorama like the present Colombian scenario, where the prices of BPs are exorbitant, the funding of the health system is affected by reimbursements of BPs, and where access to these medicines is restricted, it is undoubtedly the case that the entry of SBPs will be beneficial. Nevertheless, this entry of SBPs must be framed within a clear and consistent regulation that ensures quality, effectiveness, and safety.

Conclusion

The advent of SBPs is definitely beneficial, because it promotes cost containment favoring the sustainability of modern health systems in a panorama of aging population, demographic transition towards chronic diseases like ADs, costly health technologies, and limited resources. Additionally, SBPs promote better access to BPs, benefiting affected individuals and promoting competition within the market of biotechnology, favoring some parties of local Latin American markets and economies, as in the case of Mexico, Brazil, and Cuba. The advent of these medications gains more importance in Latin American countries, given that most of these nations are low- and middle-income countries.

Nowadays, the trend in LA is toward the adoption of accepted international standards, like those presented by the WHO.¹⁰⁴ This tendency has been seen in regional experiences

like those of Guatemala, Panama, Costa Rica, Peru, Chile, Brazil, and Argentina, where recent guidelines have been developed based on and/or contemplating internationally accepted standards. For the rest of LA countries where specific regulations on SBPs have not been developed, efforts must be conducted for the construction of updated and consistent guidelines in the short term, given the necessity for clear legislation on this matter.

Case-by-case bases, if performed in a transparent way and guided by scientific and objective standards, can allow simplification of the approval of SBPs in specific cases, which favors the efficiency of the approval process by reducing the extent of the requisites. Losing certainty on efficacy and safety by improving patient access with exceptionally abbreviated approval processes is a risk that can be assumed by some governments, but that would be outside the accepted current recommendations on the approval of SBPs. The future perspectives in Europe, US, LA, and other regions are toward the accelerated growth of the industry of biotechnology and toward the increasing entry of SBPs for use in ADs, given the expiry of the patents of RBP and the advent of rising investment in the industry and the manufacturing of SBPs. These factors are expected to be beneficial, because they can promote innovation, competition, access, and efficiency at affordable prices.

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