Relevant issues to biossimilars licensing

Questões relevantes para a aprovação de medicamentos biossimilares

Beatriz Serrapio Peres[I]

Gabriela Padilha[II]

Cristiane Quental[III]

[I] National Health Surveillance Agency (ANVISA) – Coordination of Intellectual Property.

[II] Oswaldo Cruz Foundation / Health Innovation and Manufacturing Vice-Presidency.

[III] Oswaldo Cruz Foundation / Sérgio Arouca National School of Public Health.

Mailing address: Cristiane Quental. Rua Leopoldo Bulhões, 1480 s. 703, Rio de Janeiro, RJ CEP 21041-210. E-mail: cquental@fiocruz.br

Abstract

When the patent of a drug expires, low cost generics may be introduced in market. Trial results that demonstrate the safety and efficacy of the reference product can be extrapolated to the generic, simplifying the approval process. This paradigm cannot be applied to biopharmaceutical products, large molecules difficult to be characterized. Minor changes in the production process can influence the biological and clinical properties of the product and result in differences in efficacy and safety profiles. It is not possible to demonstrate the identical nature of biopharmaceuticals arising from different manufacturing sources, so they cannot be approved as simple generics and need specific regulation. A bibliographical survey of the main issues involved in the approval of similar versions of biopharmaceuticals was performed as well as a comparative analysis of the regulatory situation in the largests pharmaceutical markets - U.S. and European Union – based on legislation, draft laws, guidelines and technical references issued by their regulatory agencies - FDA (Food and Drug Administration) and EMEA (European Medicines Agency), respectively, in order enlight the discussion now taking place in Brazil. Based on the laws and guidelines studied, it is concluded that, although Brazil, Europe and the United States are at different stages of setting their regulatory framework for biossimilars, it is possible to identify some similarities in approach, such as the need for different treatment for each product class (or a case by case focus) and a step by step comparison exercise, the results of which will define the amount of data and non-clinical and clinical studies required. However, issues such as interchangeability and automatic substitution of biossimilars for reference products are not yet clearly defined. From the sanitary point of view, Europe has a more conservative posture, while the U.S. and Brazil seem to be building a more flexible framework. Besides the health issues, however, we highlight the economic issues, of great importance in Europe and U.S. legislation, and not addressed in the Brazilian regulation - which can bring insecurity to producers interested in this market.

Keywords: Drug approval. Similar drugs. Biological products/therapeutic use.

Resumo

Medicamentos genéricos podem ser introduzidos a baixo custo no mercado quando a patente do medicamento inovador expira. Os resultados dos testes que demonstram a segurança e eficácia do produto inovador podem ser extrapolados para o genérico, simplificando sua aprovação. Este paradigma não pode ser aplicado aos biofármacos, grandes moléculas de difícil caracterização, onde pequenas alterações no processo de manufatura influenciam as propriedades biológicas e clínicas do produto e podem resultar em diferenças nos seus perfis de eficácia e segurança. Não sendo possível demonstrar a identidade entre biofármacos, eles não podem ser aprovados como simples genéricos e necessitam regulamentação específica. Neste trabalho foram feitos um levantamento bibliográfico das principais questões envolvidas na aprovação de versões similares de biofármacos e uma análise comparativa da situação regulatória nos principais mercados – EUA e União Europeia – a partir de legislação, projetos de lei, diretrizes e referências técnicas de suas agências regulatórias – FDA (Food and Drug Administration) e EMEA (European Medicines Agency), respectivamente, visando à discussão do caso brasileiro. A partir da legislação e diretrizes estudadas conclui-se que, apesar de Brasil, Europa e Estados Unidos estarem em estágios distintos de definição de sua estrutura regulatória para biossimilares, é possível identificar algumas semelhanças nas abordagens seguidas, como a necessidade de tratamento diferenciado para cada classe de produto (ou um enfoque caso a caso) e de um exercício de comparabilidade passo a passo, cujos resultados definirão a quantidade de dados e estudos clínicos e não clínicos necessários. Entretanto, questões como intercambialidade e substituição automática dos produtos de referência por biossimilares ainda não estão claramente definidas. Do ponto de vista sanitário, a Europa apresenta uma postura mais conservadora, enquanto que EUA e Brasil parecem estar construindo um arcabouço mais flexível. Ao lado das questões sanitárias, entretanto, destacam-se as questões econômicas, de grande importância na legislação dos EUA e Europa e não abordadas na regulamentação brasileira – o que pode trazer insegurança aos produtores interessados neste mercado.

Palavras-chave: Aprovação de drogas. Medicamentos similares. Produtos biológicos/uso terapêutico.

Introduction

When the patent of an innovator drug expires, as in the case of biopharmochemical drugs, generic drugs may be introduced into the market, assuring patients access to safe, effective and lower cost products. However, drugs developed through modern biotechnical techniques, known as biopharmaceutical drugs, are considered more complex than biopharmochemical drugs, in terms of structure, manufacturing and drug action. Biopharmaceuticals are more difficult to be adequately characterized, considering current analytical techniques. The standard approach applied to generic drugs is scientifically inadequate to the development of biosimilar products and, in general, additional non-clinical and clinical data are required[1].

Important biopharmaceutical drugs gained patent protection during the 1980's; therefore they will soon be unprotected (e.g. insulin, human growth hormone and erythropoietin). Launching replicas of these innovator products would introduce competitiveness into the market and allow price reduction. In general, biopharmaceuticals cost more per patient than conventional drugs, limiting access to important treatments (diabetes, cancer, chronic renal failure, chronic hepatitis). In Brazil, expiration of the patent term of these products represents an opportunity for domestic manufacturing of these drugs.

This issue becomes more relevant as these products are not only an essential part of the drugs available today, representing 6% of the worldwide pharmaceutical drugs marketed, but mainly because one third of these are biotechnological products[2] indicating exponential growth of this segment.

With no legal boundaries or clear guidelines for biosimilar drug approval, however, patent expiration may be accompanied by the introduction of low price competitor biopharmaceutical drugs in the market. Moreover, the absence of clear guidelines leading to a product comparison in relation to reference products may result in

the approval of products without sufficient proof of safety and efficacy.

In the present study, a revision of the main issues involved in the approval of similar versions of biopharmaceutical drugs in the literature, and a comparative analysis of the regulatory situation in the major markets - U.S. and European Union – based on legislation, draft bills, guidelines and technical references issued by their regulatory agencies - FDA (Food and Drug Administration) and EMEA (European Medicines Agency), respectively, was performed. Both experiences will certainly influence regulatory procedures which other countries may adopt as well as impact on the future global strategy for biosimilar products. The main aspects of the discussion and their relevance to Brazilian regulations are identified. Results are presented as follows.

Main Issues Involved in the Licensing and Clinical Use of Biosimilars

The term "biosimilar" has its origin in the difficulty to compare two versions of the same biopharmaceutical drug whose properties are deeply related to each of their manufacturing processes. Minor changes to the process may lead to contamination, three-dimensional structure changes of protein and changes in the glycosylation profile which affect both biopharmaceutical drug potency and immunogenicity[3].

Given specific manufacturing process information as well as validation and full characterization data of therapeutic proteins are generally a company's intellectual property, it will probably be difficult for another manufacturer to reproduce a biopharmaceutical drug similar enough to the original innovator product, based only on the patent or in published data[4].

Since proteins are complex molecules, it would be difficult to demonstrate the identity between two biological products from different manufacturers or sources[5]. In addition, current analytical techniques cannot detect or predict all clinical and biological properties of proteins, so differences among biopharmaceutical drugs can easily remain hidden[3].

Demonstration of Similarity

Despite the predominant view that comparative studies are essential, there is no consensus as to what extent they would be necessary. In some cases the necessary effort to perform a comparative study between a biosimilar and a reference product may be greater than licensing the potential biosimilar as an independent product[1].

The amount of clinical data depends on numerous factors including drug purpose and mechanism of action. Smaller and non-glycosylated proteins (such as insulin, somatropin) are easier to be completely characterized, whereas highly glycosylated proteins (such as epoetin) or very large proteins (such as monoclonal antibodies and blood factors) cannot generally be completely characterized[6].

Another important issue is the choice of the reference product. In general, countries expect the reference product to be a locally registered drug. However, one must consider the possibility of a company wishing to register a biosimilar in a country in which the reference product is not licensed, increasing the opportunity of access to innovator biological drugs and making it easier to introduce biosimilars in some markets[1].

Safety in Clinical Use

The most important aspect regarding the safety of biosimilars is immunogenicity[5]. All biopharmaceutical drugs demonstrate ability to trigger an immune reaction, as they are polypeptides or proteins. This reaction may be mild but there is potential to cause allergies and anaphylaxis. Moreover, the development of antibodies can neutralize the therapeutic protein, causing loss or reduction in efficacy. Immunogenicity may be influenced by factors related to the

drug, such as the manufacturing process and its formulation, and by factors related to patient, disease and treatment, such as route of administration[7].

Immunogenicity cannot be predicted in preclinical testing and in some cases it is only detectable after long term treatment[5]. A great number of cases of PRCA (Pure Red Cell Aplasia) were caused by the development of neutralizing antibodies against recombinant erythropoietin, detected more than 10 years after the introduction of erythropoietin for the treatment of renal anemia. The likely cause was a small change in the formulation. Furthermore, the replacement of the stabilizer, human serum albumin, for polysorbate 80 may have interacted with the rubber existing in syringes. Modification of syringe material and changing the route of administration led to an almost complete disappearance of PRCA[8]. The only way to measure the immune response of a drug is via clinical trials and it is highly important to have a pharmaceutical surveillance plan for each biological product being introduced into the market.

Automatic Replacement, Naming and Labeling of Biosimilars

Automatic replacement allows dispensing generic drugs instead of a prescribed innovator drug without the knowledge or consent of the doctor. In the case of conventional generic drugs, the risk of this replacement is generally low[8].

If automatic replacement is allowed, patients may receive multiple biopharmaceutical drugs during therapy, which may impair the collection of pharmaceutical surveillance data. Therefore, for safety monitoring, it is essential to know exactly which biopharmaceutical was given to each patient[5].

According to Nowick[8], as biotechnological medicines are not identical the original products and biosimilar labels must be different. In the case of biosimilars the reference product must be determined.

It is important to highlight that some European countries such as France, Germany and Spain have prohibited automatic substitution of reference biological medicines by biosimilar drugs[9].

Clinical Data Extrapolation

Extrapolation refers to the approval of a drug for indications for which it has not been evaluated in clinical trials. For example, the approval of the biosimilar growth hormone Omnitrope in Europe included comparability studies with the reference product, Genotropin, conducted only in children with growth disorders. However, the labeling of Omnitrope includes the indication for use in adults. The reasons for data extrapolation between the innovator product and a biosimilar include: long clinical history of safe use of growth hormone; wide therapeutic window for the drug; rare reports of neutralizing antibodies; the ability to characterize the structure and biological activity of growth hormones by physical--chemical and biological methods; and, the variety of tests available to characterize the active substance[5].

European Union and U.S. Position on Licensing of Biosimilars

The regulatory approach of issues involving licensing and use of biosimilars is still being defined in many countries, including Brazil. The path followed in major markets - U.S. and European Union - will undoubtedly influence regulatory procedures that other countries will adopt and will also impact the future global strategy for biosimilar drugs. The following topics will present an overview of the legal and regulatory status in these countries. Chart 1 shows the position of the U.S., the European Union (and Brazil) in relation to the main issues involving the use of biosimilars based on approved legislation in each country/region and guidelines, directions and edited guides published by drug regulating authorities.

The European Union Approach

The European Union has specific legislation which regulates biosimilar product licensing. On this legal basis it has established a regulatory framework which includes guidelines with general directions and additional guidelines, specific to each product class.

The European Community Directives[10-12] provide legal basis to determine that if the required information for similar drugs does not prove the similarity of two biological drug products, additional data must be provided, such as the toxicological and clinical profiles, determined case-by-case by the competent authority, taking into account the specific characteristics of each drug. If the reference drug has more than one indication the safety and efficacy of a biosimilar drug should be demonstrated separately for each of the claimed indications.

The period of exclusivity for the reference product determines that biosimilar drug approval requests can only be filed after the period of data exclusivity, which is of 8 years. Authorized biosimilars can only be introduced in the market after the period of market exclusivity of 10 years. Furthermore, when a request is made for a new indication of a well-established substance, a one-year period of data exclusivity will be granted provided pre-clinical or clinical trials relating to new indications have been conducted. The period of market protection can be extended by one year in case of new therapeutic indications, provided the new application represents significant clinical benefits and has been approved during the first 8 years of the initial marketing authorization.

On this legal basis, the EMEA Committee for Medicinal Products for Human Use - CHMP issued a regulatory framework consisting of a general guideline[13], which brings the concept of similar biological medicine and the adopted principles, in addition to a registration request form; quality guidelines[14]; and clinical and pre-clinical study guidelines[15], in that the latter two refer to specific appendixes for different product classes such as somatropin, insulin, epoetin and G-CSF.

In 2011, documents ("concept papers") were published proposing the review of the three above-mentioned guidelines which form the backbone of the EMEA regulations for licensing of biosimilar drugs. These documents emphasize the need to review these guidelines in relation to the elapsed time since their approval and the experience gained by the Agency in approving various biosimilar drugs[16-19].

There are specific guidelines for recombinant human insulin, somatropin, G-CSF, recombinant interferon alpha, heparin, recombinant erythropoietin. There are also guidelines for recombinant follicle stimulating hormone, monoclonal antibodies and IFN-beta, not yet concluded. These documents require clinical and non-clinical data describing the size of trials needed and the best indication to demonstrate equivalence for each product compared with a reference product[16, 20].

Besides these three main guidelines, the document "Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins"[21] is relevant because it considers the immunogenicity assessment addressing factors that may lead to immunogenicity, from development, planning and interpretation of clinical and non-clinical trials to evaluate the immunogenicity potential and its comparability with other products, to the implementation of a risk management plan.

EMEA Guidelines indicate a comparability exercise which is a step-by-step comparison in terms of quality, safety and efficacy in order to demonstrate that a biosimilar drug and the reference product have similar profiles in these aspects.

U.S. Approach on Biosimilars

In the U.S., the legal basis for biosimilar drug licensing is more recent and the result of intense debate in the U.S. Congress, a forum for competing bills which clearly favors the interests of potential manufacturers of

biosimilar drugs and projects more favorable to the pioneering drug industry - the former more and the latter less flexible as to the requirements for approval of similar products, such as the legal requirement for clinical trials, exclusivity periods, among others[22-24]. The Biologics Price Competition and Innovation Act (BPCI Act) enacted as part of the Patient Protection and Affordable Care Act (PPACA), signed into law by President Obama in March 2010, which underlies the licensing of biosimilar products in the U.S., adopted an intermediate stand between the two positions [25]. Few clinical trials are required by law, small variations are accepted, the approval is concentrated mostly in the hands of the FDA, but the period of exclusivity for innovators is long (Table 1).

The BPCI Act amends section 351 of the Public Health Service Act, determining the requirements for approval through an abbreviated pathway for biological products which are highly similar (biosimilars) or interchangeable with a biological product previously licensed by FDA. It also determines that the FDA will license a product as a biosimilar if it considers that the information provided is sufficient to demonstrate biosimilarity and that the manufacturing facilities subject to licensing application are inspected.

The FDA describes a biosimilar product as a biological product highly similar to an already-approved biological product, despite minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the biosimilar product approved in terms of safety, purity and potency. The Agency understands that there are no biological generic products and additional data from clinical safety and efficacy studies required[26].

It is important to highlight that the position adopted by the FDA was to wait for the definition of a legal basis to publish specific guidelines for biosimilar products[4]. Before approval of the BPCI Act, some less complex therapeutic proteins were approved as biosimilars of products registered under the Food, Drug, and Cosmetic Act (FD&C Act), based on a case-by-case analysis, such as human growth hormone and somatotropin. However, the knowledge and technology available would allow the approval of more complex products through an abbreviated pathway[27].

After the approval of the BPCI Act, the FDA held a public hearing and set a public document which addresses the specific issues and challenges associated with the implementing of the legislation on biosimilars[28]. On February 9, 2012, the FDA issued three draft guidelines for discussion and commentaries [29,30,31].

The Scientific Considerations in Demonstrating Biosimilarity to a Reference Product draft guideline points to the factors which will be considered by FDA in the evaluation of biosimilarity, such as product complexity, formulation and stability, and biochemical characterization. The approach will be based on risk considering the totality of the evidence or data, and referring to certain product characteristics, such as the mechanism of action, product structure--function relationships, manufacturing process, and clinical experience with the reference product. The amount of data and information needed will be determined case-by-case.

This draft guideline also stresses that despite advances in the analytical sciences that allowed extensive characterization of some protein products, they may not be able to detect all relevant structural and functional differences between two proteins. Therefore analytical, animal and clinical study data are required for the demonstration of biosimilarity unless the FDA determines that an element is unnecessary.

The Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product draft guideline emphasizes the importance of extensive analytical, physical-chemical and biological characterization. Any differences between the proposed biosimilar product and the

reference product and its potential effects on safety and potency should be described and discussed.

The Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 draft guideline provides questions and answers grouped into three main categories on the themes of: Biosimilarity or Interchangeability, Provisions Related to the Requirement to Submit a BLA for Biological Product and Exclusivity.

Brazil´s Position on Licensing of Biosimilars

In Brazil, regulations on biological and biotechnological products were subject of discussion in different forums with significant involvement of entrepreneurs, class representatives, academics, government laboratories and ANVISA, with a view to draft proposals for the review of the Brazilian regulation.

The National Health Surveillance Agency by Public Consultation 49/10, issued on May 25, 2010, presented a Resolution proposal on the registration of biological products. The final text of Resolution 55/2010[32] was finally published on December 17, 2010.

Brazilian regulation is much more general and simplified than the American and European cases studied. With respect to safety and efficacy it is careful to require, in addition to pivotal clinical trials, pharmaceutical surveillance and immunogenicity studies, but does not go beyond what is currently being done in the European Union, in aspects such as the difficulty to prove the identity of these products in relation to the reference products; the extent and nature of clinical and preclinical data required, taking into account the characteristics of the product, the ability to characterize it with current analytical techniques (which depends on its structural complexity), dosing regimen, target population etc.; establishing an appropriate approach for evaluation of immunogenicity, including comparability test validation; naming, labeling and interchangeability issues.

Resolution 55/2010 determines that biological products can be registered through a development pathway by similarity. It is defined as the "regulatory pathway that can be used for a biological product to obtain registration with the regulatory authority, in which similarity was determined in terms of quality, safety and efficacy between the product developed and to be compared, and the biosimilar reference product". The biosimilar reference product must be an Anvisa-registered product with a full registration-based dossier*, where the same reference product must be used in all stages.

Under Resolution 55/2010 the application for registration of a biological product by a development pathway by similarity should provide information such as: description of the analytical techniques used to detect potential differences between the biological product and the biosimilar reference product, biological and physical-chemical characterization data related to the biological product quality attributes; information on the expression system used to manufacture the biological product and the biosimilar reference product; molecule similarity between the biological product and biosimilar reference product; detailed description of the similarity assessment stages; accelerated and stress comparative stability studies; description of the observed differences in purity and impurity profile between the biological product and biosimilar reference product; evaluation of the contaminants and impurities identified in the biological product, discussing the potential impact on quality, safety and efficacy; analytical characterization of the biological and biosimilar reference product; results of comparative biological tests needed to determine the degree of

* The Complete Dossier "is the total set of documents submitted to ANVISA for demonstrating the attributes of quality, safety and efficacy of a biological product. This file consists of the complete characterization of the product and detailed description of the manufacturing process, demonstrating consistency in drug manufacturing, further to substantial safety and efficacy clinical evidence demonstrated by means of clinical and non-clinical phase I, II and III studies. "(Resolution 55/10 of the National Health Surveillance Agency dated of December 17, 2010).

comparability; and conclusive report with demonstration of comparability, containing sufficient information to predict whether the detected differences in the quality attributes result in adverse impacts on the safety and efficacy of the biological product.

In addition, the applicant company should present non-comparative clinical studies, designed to detect significant differences between the biological product and biosimilar reference product. Relevant pharmacodynamic studies for the intended therapeutic indications and studies of cumulative toxicity (repeated dose) are required. In reference to clinical studies, pharmacokinetic and pharmacodynamic studies are mandatory; along with a pivotal study of clinical safety and efficacy.

In 2011, ANVISA issued the "Guideline for Conducting Comparability Exercise for Biological Products Licensing"[33], with directions to perform the comparability exercise for biological product registration by the development pathway of comparability according to RDC55/2010. As in the guidelines proposed by the FDA, the guideline issued by ANVISA proposes a gradual approach, in stages, starting with the characterization and assessment of quality attributes of the product, followed by clinical and nonclinical studies. The characterization and comparison at a quality level would be the basis for a possible reduction of studies in the clinical and nonclinical development stage. If differences are found between the biological product and the biosimilar reference product the reasons should be investigated and justified, which may lead to additional data requirement. The amount of clinical and nonclinical data required will depend on the product; on the degree of characterization possibly undertaken with modern analytical methods; on the differences observed in relation to the clinical experience reference product and the product class. The guideline stresses the need for a case-by-case analysis for each product class.

Table 1 compares the Brazilian position in relation to that of the U.S. and the European Union.

Final Considerations: Implications for Regulating Biosimilar Drug Licensing in Brazil

Most biopharmaceutical drugs are

Chart 1 – Comparison of United States, Europe and Brazil's position in relation to the approval of biossimilars and the issues related to their use, based in the applied legislation and regulation
Quadro 1 *– Comparação do posicionamento dos Estados Unidos, Europa e Brasil em relação à aprovação dos biossimilares e de questões envolvendo o uso dos mesmos, com base na legislação e regulamentação aplicadas.*

	American Legislation	European Legislation	ANVISA Resolution
Definition of a biosimilar	The term biosimilar is used in the legislation and is applied to a biological product that is highly similar to the reference biological product notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency. FDA also uses the term "follow-on biologics (FOBs)" to designate these products.	Uses the concept of "similar biological medicinal product". Refers to the product claiming to be "similar" reference product (authorized in the European Community via a complete dossier), based on safety, quality and efficacy comparability studies.	Resolution 55/2010 determines a development pathway by comparability, which can be used to obtain the registration of a biological product, using a comparability exercise in terms of quality, safety and efficacy between the product developed to be compared and the reference biological product. Comparability is the scientific comparison of clinical and nonclinical parameters in terms of quality, safety and efficacy of a biological product with a reference biological product with the objective of determining that there are no detectable differences in terms of quality, safety and efficacy.

Chart 1– continuation
Quadro 1 *– continuação*

	American Legislation	European Legislation	ANVISA Resolution
Similarity requirements (safety/ efficacy)	An application for licensure should contain: analytical studies, animal studies (including the assessment of toxicity) one or more clinical studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics), that are sufficient to demonstrate safety, purity and potency. It should be demonstrated that the similar product and the reference product utilize the same mechanism of action. The condition or conditions of use proposed for the biosimilar shall have been previously approved for the reference product.	Similarity is demonstrated by comparability exercises or studies carried out with the chosen reference product which should be used throughout the study. In vitro and in vivo non-clinical studies using animal models are necessary, such as non--clinical toxicity studies. Clinical comparability should include pharmacokinetic, pharmacodynamic, and if necessary, pharmacokinetic/pharmacodynamic studies followed by safety and efficacy assays as well as by an immunogenicity assessment. If the reference medication has more than one indication, safety and efficacy for the biosimilar candidate should be justified or, if necessary, demonstrated separately for each one of the requested indications. Any observed differences between the biosimilar and the reference products will have to be justified with appropriate studies, on a case-by-case basis.	Comparability studies are required. Analytical techniques should be utilized to detect potential differences between the biological product and the reference product, as well as the complete biological, physical and chemical characterization. The same reference biological product should be used throughout the study. Complete reports on non-clinical comparability studies are required, as well as pharmacodynamic studies for the intended therapeutic indications and cumulative toxicity studies. Pharmacokinetic, pharmacodynamic and pivotal studies of clinical safety e efficacy are mandatory. Regardless of the development pathway used, when the registration application is filed for a new biological product or a biological product, the company should present an immunogenicity study report.
Naming/ labeling	The FDA guideline proposal presented determines that the labeling of a biosimilar shall contain all necessary information so that the health care professional can prescribe; this includes the information that the product is biosimilar to a specific reference product, its indication, and route of administration, as well as if the product has been considered interchangeable or non-interchangeable.	There are no specific provisions, but it is clearly determined that the biosimilar should be "clearly identified", in order to allow for pharmaceutical surveillance.	There are no specific provisions.
Guidelines	To date no Guidelines have been enforced. The FDA has published three guideline proposals for comments. Proposals indicate the adoption of an approach based on risk and on total evidence. Proposed guidelines also provide a panorama of analytical factors to be considered in the assessment of therapeutic protein biosimilarity, highlighting the importance of extensive analytical, physical-chemical and biological characterization. There is also a proposed Guideline with a Q&A format, directed to those interested in filing biosimilar licensing applications.	Legislation indicates that overall principles to be applied are covered in the guidance norms published by the Agency, considering the biological medicinal product's characteristics. The EMEA recognizes the great variability in the complexity of biopharmaceutical drugs and establishes specific guidelines for each product class. The EMEA has published specific guidelines for biosimilar products. The regulatory structure is composed of general guidelines relating to basic principles, quality and clinical and non-clinical aspects. There are also specific guidelines for product classes, some of which are in effect and other under elaboration.	Anvisa published the guide "Guidelines on how to conduct the comparability exercise to register a biological product", which instructs on how to carry out the comparability exercise in order to register a biological product via development through comparability as per resolution RDC55/2010. The Guideline makes reference to the WHO and Canadian guidelines and proposes a gradual, step-by-step approach which starts with the characterization and assessment of the quality attributes of the product, followed by clinical and non-clinical studies.

Chart 1– continuation
Quadro 1 *– continuação*

	American Legislation	European Legislation	ANVISA Resolution
Interchangeability/ automatic replacement	This guideline considers that a biosimilar is interchangeable when it can replace a reference product without the intervention of a health care professional who prescribed the reference product. The FDA BCPI Act allows a biosimilar to be determined as interchangeable. This is achieved by demonstrating that: a biological product is biosimilar to the reference product; produces the same clinical results as the reference product, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biosimilar and the reference product is not greater than the risk of using the reference product without such alternation or switch. However, the information which shall be necessary to allow determining interchangeability has not yet been defined by the FDA. A biosimilar product which does not meet the necessary requirements to be determined interchangeable is determined to contain a new active ingredient.	There is no specific determination dealing with biosimilar and reference product interchangeability or automatic substitution. The definition of biosimilar per se differentiates it from a generic and leaves it clear that differences related to raw-materials or the manufacturing process can exist and therefore they are not identical products. EMEA clarifies that decisions on interchangeability and/or substitution are the responsibility of proper local authorities and not within its competence. French legislation on biosimilars prohibits automatic substitution of a biological medicine by another. Other countries such as Germany and Spain also prohibit automatic substitution.	There are no specific provisions.
Exclusivity periods for the innovator product	The BPCI Act determines that until the date that is 12 years after the date on which the biological reference product was first licensed, the approval of a biosimilar may not be made effective; and until the date that is 4 years after the date on which the biological reference product was first licensed, no biosimilar application may be submitted which has this product as reference. Exclusivity periods also apply to certain biological products for which pediatric studies are being conducted.	Application for biosimilars can only be filed after an 8-year period of data exclusivity. Authorized biosimilars can only be introduced in the market after a period of market data exclusivity of 10 years. When an application for a new indication for a well-established substance is made, a period of one year of data exclusivity shall be granted, provided that pre-clinical or clinical studies were carried out in relation to the new indication; the new application represents significant clinical benefits in comparison to existing therapies; and that it has been approved during the first 8 years which followed the initial marketing authorization. The period of exclusivity cannot exceed a total of 11 years; therefore this provision may only be used once.	There are no specific provisions.
Exclusivity period for the first biosimilar	The BPCI Act grants exclusivity periods for the first biosimilar determined interchangeable with the reference product.	There are no specific provisions	There are no specific provisions.

Chart 1– continuation
Quadro 1 *– continuação*

	American Legislation	European Legislation	ANVISA Resolution
Clinical data extrapolation	FDA regulating proposals allow data extrapolation provided that sufficient scientific justification is given for each condition of use for which licensure is sought. The following aspects shall be considered: The mechanism of action in each condition of use, the PK and biodistribution of the product in different patient populations; differences in toxicities in each condition of use, as well as any other factor that may affect the safety or efficacy.	Legislation determines that if the originally authorized medication has more than one indication, biosimilar safety and efficacy should be justified separately for each one of the requested indications. This position is confirmed by the guidelines, which allow data extrapolation from one indication to another and therefore allow its use for indications with no formal studies, provided there is a rationale.	Determines that safety and efficacy data extrapolation for other therapeutic indications for registered biological products via the comparability pathway will be defined by specific guidelines. Data extrapolation will only be possible after safety and efficacy comparability has been demonstrated between the products. The involved mechanism of action and receptors in the different indications must be the same and the biological products' safety and immunogenicity should be sufficiently characterized.
Pharmaceutical surveillance	Post commercial marketing safety monitoring is an important component to ensure biological product safety and efficacy, biosimilar protein products included.	The EMEA recognizes the possibility of existing issues related to immunogenicity which were not detected in the clinical trials and which do not occur with the reference product and which therefore require immunogenicity tests and pharmaceutical surveillance programs to monitor the safety and efficacy of the biosimilar after its approval.	Regardless of the development pathway utilized, when the registration application is filed for a new biological product or a biological product, the applicant company should present a drug surveillance plan and a minimizing risk plan according to health regulation in effect.

complex products with high added value, and patent term expiry for innovator products represent the opportunity for replica of these products, increasing the population's access to new treatment possibilities. If on one hand there is all this potential, on the other hand the regulatory barriers for biosimilars are still significant. The main aspect is the difficulty in predicting the safety and efficacy of these products.

Case analysis clearly demonstrates that a regulatory procedure for biosimilars will be different from that existing for generic drugs and that the tendency is to seek specific guidelines for product categories, and it is the regulatory authority's competence to assess the extent of required data as well as the appropriateness of a study, deciding on interchangeability.

Although Brazil, Europe and the United States are each at a distinct stage of definition and establishment of their regulatory framework for biosimilar drugs, similarities in the approach can be identified: the need for differential treatment for each product class, with specific guidelines (as in Europe) or a case-by-case focus (as indicated in the proposed American Guidelines and Anvisa Guidelines); the indication of the importance of full and extensive analytical studies, as the first stage of a step-by-step approach when it identifies potential differences between the biosimilar candidate and the reference product, which will dictate the data and the extent of the clinical and nonclinical studies of later stages. From a health point of view, Europe has a more conservative position, whereas the U.S. and Brazil seem to be building a more flexible framework.

However, based on the European and American legislation and guideline analysis we can state that the discussion goes beyond the issue of safety and efficacy, reaching the economic aspects of investment in biosimilar drug manufacturing. In this sense, one of the most controversial aspects is the existence of periods for data and market exclusivity, justified by the need to promote innovation. It is possible to anticipate that this issue is still the subject of intense debate, which has not yet been considered in Brazilian regulations and which can bring insecurity

to manufacturers interested in this market.

The great challenge for regulatory agencies will be to deal with the risks and benefits inherent to biosimilar drugs, while not introducing excessive barriers to development and approval, in order to promote domestic production and greater access to safe and effective products for the Brazilian population.

References

1. World Health Organization. Challenges in biotherapeutics: regulatory pathways for biossimilar products. *Who Drug Inform* 2008; 22(1): 3-5**.**

2. European Generic Medicines Association. *Frequently asked questions about biossimilar medicines.* Brussels: EGA; 2006. Disponível em: http://www.egagenerics.com/FAQ-biossimilars.htm [Accessed em 05 de agosto de 2009].

3. Adrian C, Cannata-Andia J, Cancarini G, Coppo R, Frazão JM, Goldsmith D et al. Biossimilars and biopharmaceuticals: what the nephrologists need to know-a position paper by the ERA-EDTA Council. *Nephrol Dial Transplantation* 2008; 23(12): 3731-7.

4. Schellekens H. The first biossimilar Epoetin: but how similar is it? *Clin J Am Soc Nephrol* 2008; 3(1):174-8.

5. Mellstedt H, Niederwieser D, Ludwig H. The challenge of biossimilars. Ann Oncol 2007; 19(3): 411-9. Disponível em: http://annonc.oxfordjournals.org/cgi/reprint/19/3/411 [Accessed em 18 de fevereiro de 2009].

6. Nick C. *Biossimilars: growing the concept.* RAJ Pharma; 2008. Disponível em: http://www.egagenerics.com/doc/Biossimilars_RAJPharmaOct08.pdf [Accessed em 28 de janeiro de 2009].

7. European Generic Association. *EGA handbook on biossimilars medicines.* Brussels: Palgrave Macmillan; 2007.

8. Nowick M. What do nephrologists need to know about Biossimilars? *Port J Nephrol Hypertension* 2007; 21(3): 201-7. Disponível em: http://www.spnefro.pt/RPNH/PDFs/n3_2007/artigo_05.pdf [Accessed em 29 de janeiro de 2009].

9. Barroso et al. Biossimilares em oncologia. *Acta Med Port* 2009; 22: 203-6. Disponível em www.actamedicaportuguesa.com/pdf/2009-22/3/203-206.pdf [Accessed em 18 de abril de 2012].

10. European Union. Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use. 06 nov. 2001. Official *Journal***,** L 311, 28 de novembro de 2001, p. 67. Disponível em: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_83_cons/dir2001_83_cons_20081230_en.pdf [Accessed in April 14, 2009].

11. European Union. Regulation (EC) No 726/2004 of the European Parliament and of the Council. 31 mar. 2004. *Official Journal***,** L 136, 30 abr. 2004, p. 1. Disponível em: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726_cons/reg_2004_726_cons_en.pdf [Accessed in April 14, 2009].

12. European Union. Comission Regulation (EC) No 1085/2003. 03 jun. 2003. Official Journal, L 159, 27 jun. 2003, p. 24. Disponível em: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2003_1085/reg_2003_1085_en.pdf [Accessed in April 14, 2009].

13. European Medicines Agency. *Committee for Medicinal Products for Human Use.* Guideline on similar biological medicinal products. London: EMEA; 30 oct. 2005. (CHMP/437/04). Disponível em: http://www.emea.europa.eu/pdfs/human/biossimilar/043704en.pdf [Accessed in April 14, 2009].

14. European Medicines Agency. *Committee for Medicinal Products for Human Use.* Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. London: EMEA; 22 fev. 2006. (EMEA/CHMP/BWP/49348/200). Disponível em: http://www.emea.europa.eu/pdfs/human/biossimilar/4934805en.pdf [Accessed in April 14, 2009].

15. European Medicines Agency. *Committee for Medicinal Products for Human Use*. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. London: EMEA; 22 feb. 2006. (EMEA/CHMP/BMWP/42832/2005). Disponível em: http://www.emea.europa.eu/pdfs/human/biossimilar/4283205en.pdf [Accessed in April 14, 2009].

16. European Medicines Agency. Multidisciplinary: Biossimilar. Disponível em: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c [Accessed em 28 de maio de 2012].

17. European Medicines Agency. *Committee for Medicinal Products for Human Use.* Revision of the guideline on similar biological medicinal product. London: EMEA; 17 nov. 2011 (CHMP/BMWP/572643/2011). Disponível em: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/11/WC500117987.pdf [Accessed in May 16, 2012].

18. European Medicines Agency. *Committee for Medicinal Products for Human Use*. Revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. London: EMEA; 22 sep. 2011 (EMA/CHMP/BMWP/572828/2011). Disponível em: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/10/WC500115611.pdf [Accessed in May 16, 2012].

19. European Medicines Agency. *Committee for Medicinal Products for Human Use*. Revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. London: EMEA; 7 feb. 2011 (EMA/CHMP/BMWP/572828/2011). Disponível em: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500102285.pdf [Accessed in May 16, 2012].

20. Schellekens H. Biossimilar therapeutics: what do we need to consider? *Nephrol Dial Transplant Plus*, 2009 Jan; 2(Suppl 1):i27-i36. Disponível em: http://ndtplus.oxfordjournals.org/cgi/reprint/2/suppl_1/i27 [Accessed in February 11, 2009].

21. European Medicines Agency. *Committee for Medicinal Products for Human Use*. Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins. London: IMEA; 13 Dec. 2007. (CHMP/BMWP/14327/2006). Disponível em: http://www.ema.europa.eu/pdfs/human/biossimilar/1432706enfin.pdf [Accessed in April 14, 2009].

22. Promoting Innovation and Access to Life-Saving Medicine Act, HR 1427. In: 111th Cong, Mar. 11 2009. Disponível em: http://www.govtrack.us/congress/billtext.xpd?bill=h111-1427 [Accessed em in July 10, 2009].

23. Pathway for Biossimilars Act**,** HR 1548. In: 111th Cong, Mar. 17 2009. Disponível em: http://www.govtrack.us/congress/billtext.xpd?bill=h111-1548 [Accessed in July 10, 2009].

24. Tabtiang R, Attwell G, Millauer B, Ren S. Congress considers competing biossimilars legislation. Fish News. Disponível em: http://www.fr.com/news/articledetail.cfm?articleid=939 [Accessed in July 15, 2009].

25. Patient Protection and Affordable Care Act**,** HR 3590. In: 111th Cong, Sep. 17 2009. Disponível em: http://www.govtrack.us/congress/bills/111/hr3590 [Accessed in May 16, 2012].

26. Woodcock J. Food and drug administration. Follow-on protein products. In: The House Committee on Oversight and Government Reform. 26 mar. 2007. Disponível em: http://www.fda.gov/NewsEvents/Testimony/ucm154070.htm [Accessed in August 1, 16, 2009].

27. Young D. FDA, Congress to Jointly Form Follow-on Biologics Proposal. *Bioworld Today: the daily biotechnology newspaper* 2008; p. 1-4.

28. Federal Register. Notices. Department of Health and Human Services. Food and Drug Administration [Docket No. FDA–2010–N–0477]. Approval Pathway for Biossimilar and Interchangeable Biological Products; Public Hearing; Request for Comments. Oct 5 2010; 75(192): 61497-501. Disponível em: http://www.gpo.gov/fdsys/pkg/FR-2010-10-05/pdf/2010-24853.pdf [Accessed in May 17, 2012].

29. Food and Drug Administration. Scientific Considerations in Demonstrating Biossimilarity to a Reference Product. Disponível em: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf [Accessed in May 16, 2012].

30. Food and Drug Administration. Quality Considerations in Demonstrating Biossimilarity to a Reference Protein Product. Disponível em: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf [Accessed in May 16, 2012].

31. Food and Drug Administration. Biossimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009. Disponível em: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf [Accessed in May 16, 2012].

32. Brasil. Agência Nacional de Vigilância Sanitária. Resolução RDC nº. 55, de 16 de dezembro de 2010. Dispõe sobre o registro de produtos biológicos novos e produtos biológicos e dá outras providências. Disponivel em http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2010/res0055_16_12_2010.html [Accessed em 4 de agosto de 2011].

33. Brasil. Agência Nacional de Vigilância Sanitária. Guia para Realização do Exercício de Comparabilidade para Registro de Produtos Biológicos. Disponível em: http://portal.anvisa.gov.br/wps/wcm/connect/321df88048bd2560a7c3af9a6e94f0d0/produtos_biologicos_exercicio.pdf?MOD=AJPERES [Accessed in May 16, 2012].

Received: 02/09/11
Final version: 29/05/12
Approved: 10/07/12