The Portuguese Society of Rheumatology position paper on the use of biosimilars

João Eurico Fonseca, João Gonçalves, Filipe Araújo, Inês Cordeiro, Filipa Teixeira, Helena Canhão, José António Pereira da Silva, Sandra Garcês, Luís Cunha Miranda, Sofia Ramiro, Ana Roxo, Fernando M. Pimentel-Santos, Viviana Tavares, Adriano Neto, Alexandre Sepriano, Armando Malcata, Augusto Faustino, Cândida Silva, Catarina Ambrósio, Cátia Duarte, Cláudia Miguel, Filipe Barcelos, Helena Santos, Inês Cunha, João Carlos Ramos, José António Melo Gomes, José Bravo Pimentão, Lúcia Costa, Luís Maurício, Margarida Silva, Miguel Bernardes, Mónica Bogas, Paulo Clemente Coelho, Paulo Monteiro, Renata Aguiar, Rui André, Rui Leitão, Sofia Pimenta, Tiago Meirinhos, Susana Fernandes, Vera Las, Walter Castelão on behalf of Sociedade Portuguesa de Reumatologia

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ABSTRACT

Biotechnological drugs have become a fundamental resource for the treatment of rheumatic patients. Patent expiry of some of these drugs created the opportunity for biopharmaceutical manufacturers to develop biosimilar drugs intended to be as efficacious as the originator product but with a lower cost to healthcare systems. Due to the complex manufacturing process and highly intricate structure of biologicals, a biosimilar can never be an exact copy of its reference product. Consequently, regulatory authorities issued strict preclinical and clinical guidelines to ensure safety and efficacy equivalence and, in September 2013, the biosimilar of infliximab was the first biosimilar monoclonal antibody to be authorized for use in the European Union. The current document is a position statement of the "Sociedade Portuguesa de Reumatologia" (Portuguese Society of Rheumatology) on the use of biosimilar drugs in rheumatic diseases. Two systematic literature reviews were performed, one concerning clinical trials and the other one concerning international position papers on biosimilars. The results were presented and discussed in a national meeting and a final position document was discussed, written and approved by Portuguese rheumatologists. Briefly, this position statement is contrary to automatic substitution of the originator by the biosimilar, defends either a different INN or the prescription by brand name, supports that switching between biosimilars and the originator molecule should be done after at least 6 months of treatment and based on the attending physician decision and after adequate patient information, recommends the registration of all biosimilar treated patients in Reuma.pt for efficacy, safety and immunogenicity surveillance, following the strategy already ongoing for originators, and opposes to extrapolation of indications approved to the originator to completely different diseases and/or age groups without adequate pre-clinical, safety or efficacy data.

Keywords: Biosimilar; Infliximab; Position paper; Review; Rheumatoid arthritis; Ankylosing spondylitis; Switching; Interchangeability; Automatic substitution; Extrapolation.

INTRODUCTION

Biotechnological medicines have profoundly changed the treatment and prognosis of rheumatic diseases[1]. However, these therapies represent a significant economic burden to healthcare systems worldwide. With some of these biopharmaceutical products approaching patent expiration, the opportunity arises for the development of similar versions whose lower cost is expected not only to improve cost-efficacy ratios, but also to improve drug access, especially in countries with economic restraints[2]. The biopharmaceutical medicines currently used in rheumatology are monoclonal antibodies (mAbs) and soluble receptor fusion proteins (Cepts). They have an inherent complexity and variability that originates from their production in living cells, their highly intricate protein structure (with tertiary and quaternary structures) and their post-translational modifications (such as glycosylation)[3]. In the

context of prescribing any approved biologic, it is important to understand the challenges faced in biologic manufacturing and the potential clinical implications. Information that can assist prescribing decisions concerning the utilization of similar biologics includes clinical trial results, regulatory approvals and product labels[4, 5]. Throughout the product life cycle of an approved biologic molecule, a manufacturer may implement process changes to incorporate technological advances or efficiencies. Regulators evaluate these changes carefully and use scientific comparability criteria to determine whether there is a potential impact on the safety or efficacy that underlies its approval. Most of these manufacturing changes are evaluated with analytic studies designed to assess the potential for an unexpected change in the quality of the commercial product[6]. Information on the changes introduced and the data used to support these changes are generally not available in the public domain. Occasionally, however, a major manufacturing change will require that the manufacturer completes a clinical trial to demonstrate that there is no impact on the product's safety or efficacy.

After patent expiry of an originator medicine, biopharmaceuticals can be developed and marketed by other manufacturers, which must demonstrate similarity to a reference product. Since biosimilars can never be exact copies of their reference product, granting of a market authorization is therefore subject to strict regulatory approval[2-5,7]. Biosimilar-manufacturing companies do not have access to the original process; hence they have to reverse-engineer it from the original molecule. It is unlikely that a perfectly identical molecule can be recreated from the reference product, not only due to developmental differences but also due to molecular micro-heterogeneities common to all biotechnological drugs. Modifications of the primary, secondary, tertiary, or quaternary structure of an approved biologic may impact its potency, purity and safety that underlie its approval. As a result, meticulous attention is required to assure the proper function and integrity of the manufacturing environment for producing approved biologics[4, 5].

While the evaluation of a new manufacturing process for a biosimilar may parallel a manufacturing process change for a biologic, there are important distinctions to consider[2,3,7-9]. The biosimilar manufacturer must develop the manufacturing process in its entirety, from cell line selection to fill and finish. These activities are performed without full access to the innovator manufacturer's product development history. Due to the potential for differences, a biosimilar manufacturer should provide data to ensure that differences between the biosimilar and the innovator biologic will not impact the efficacy or safety of its product. Considering the current limitations of analytical methods, these data should include comparative clinical testing with the reference biopharmaceutical to confirm biosimilarity[2-5,7-9]. Although the extent of clinical testing of the similar biological product is likely to be less than is normally required for an original product (new biological entity), it is essential that the testing of the similar biological product be sufficient to ensure that the product meets acceptable levels of quality, safety and efficacy to ensure public health[10]. Generally, a reduction in data requirements is possible for non-clinical and/or clinical parts of the development program by guaranteeing quality of product, which may vary depending on the characteristics of the already approved reference product[10,11]. A major difference for biosimilar products is that they can be recognized for indications of reference products without performing clinical studies for all the clinical indications that reference products are approved for, supposing the equivalence with reference products by extrapolation of their indications[2, 3, 11].

Therefore, a biosimilar can be defined as a biotherapeutic product, which is similar but not identical in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product[7]. They are, by definition, distinct from generics, whose smaller chemical structure is simple to accurately replicate. Granting marketing authorizations (MA) for biotechnology products falls under the authority of the European Medicines Agency (EMA). However, once authorized through these channels, individual Member States must develop processes regarding the prescription, delivery and use of biological and/or biosimilar products. These processes vary widely across the EU Member States[1-3,7,8]. Europe is ahead of the United States when it comes to biosimilar adoption. The EMA approved its first biosimilar in 2006.

The Guidelines on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality (EMEA/CHMP/49348/05) and Non-clinical & clinical issues (EMEA/CHMP/BMWP/42832/05) lay down the requirements for a biological medicinal product claiming to be similar to another one already marketed. Both these guidelines were adopted by EMA in June 2006. The Committee

for Medicinal Products for Human Use (CHMP) has published over half-a-dozen guidelines related to biosimilar products, including guidelines on specific classes of biological products such as insulin and somatropin, as well as draft guidelines on monoclonal antibodies and a "concept paper" on low-molecular weight heparins. Since then, several biosimilar products have come into the EU market and the number of scientific advices given by the CHMP on the development of biosimilar products has increased significantly. Almost all biosimilars licensed in Europe, thus far, fall into three categories: somatropin, epoetin alpha and filgrastim. These are all relatively small biologics and none of them is as large or complex as mAbs. On the other hand, these approvals have at least demonstrated proof of concept that biosimilars can be manufactured in different expression systems yet still be "similar." For example, the biosimilar Valtropin is expressed in yeast culture, whereas the original Humatrope is expressed in *E. coli* systems. In 2012, EMA issued guidelines for biosimilar mAbs with the mandatory non-clinical (in vitro biological activity) and clinical (in vivo pharmacokinetics, pharmacodynamics, efficacy and safety) studies required for medicine approval[8]. The biosimilar of infliximab, a tumour necrosis factor (TNF) blocker, was first authorized for use in the European Union on September 10th, 2013, as branded names Inflectra and Remsima[12,13].

The key principles of regulating biosimilars have been the same across different agencies. They all emphasize the fact that the development of a biosimilar involves stepwise, risk based, comparability exercise(s) starting with comparison of the quality characteristics of the biosimilar and original biologic. Demonstration of similarity in terms of quality is a prerequisite for the reduction of the non-clinical and clinical data set required for licensing. After each step of the comparability exercise, the decision to proceed further with the development of the biosimilar should be evaluated. If relevant differences are found in the quality, non-clinical, or clinical studies, the product will not qualify as biosimilar and a more extensive non-clinical and clinical data set will likely be required to support its application for licensing. EMA is emphasizing the need to follow the 3 R principles (replacement, reduction and refinement) and is also considering to potentially revise the existing guidelines. At a minimum, pharmacokinetic and pharmacodynamic (PK/PD) studies would be required to establish sufficient similarity.

Progress in the characterization and understanding of biologics now permits demonstration that some products are highly similar to a reference product. Physicochemical and functional assays have been used to characterize changes in manufacturing processes for some biologics, and then animal or clinical studies are used to resolve any remaining uncertainties about the comparability of the products created before and after such changes and to provide sufficient confidence that safety and efficacy are not diminished. There may be strategies that allow a "fingerprint"-like identification of very similar patterns in two different products. Such strategies were used in supporting the approval of highly complex heparin product, enoxaparin, or low--molecular weight proteins with complex glycosylation like erythropoietins. Although additional animal and clinical studies will generally be needed for protein biosimilars for the foreseeable future, the scope and extent of such studies may be reduced further if more extensive fingerprint-like characterization is used.

With regard to the phase I studies, the general guideline EMEA/CHMP/BMWP/42832/05 and the specific mAb guideline EMA/CHMP/BMWP/403543/ /2010 recommend the selection of relevant pharmacodynamic (PD) markers, but such markers are not always available and/or cannot be shown to reflect efficacy. On the other hand, when relevant surrogate markers do exist, the current guideline includes the possibility of using them (e.g. absolute neutrophil count to assess the effect of granulocyte-colony stimulating factor) as the primary end points in the pivotal phase III studies. This aspect could be expanded to further elaborate on the underlying principles, potentially including examples from other therapeutic areas. Regarding the immunogenicity data, one-year follow-up data are requested in the current guideline (EMA/CHMP/BMWP/ /86289/2010) in case of chronic administration. With regard to the measurement of antibodies, an optimal sampling schedule should be considered in order to take into account e.g. the onset and duration of the antibody formation as shown by the data of the reference product.

EMA regulations do not require the applicant to obtain comprehensive data on patient benefit. It requires, however, the follow-on biologic applicant to demonstrate similar efficacy and safety compared to the reference product. The biosimilar applicant will have to conduct testing and a clinical trial of some sort, but for this pathway to have any practical meaning such trials must be significantly shorter and less comprehensive than the original applicant's. This stand-

point represents a new paradigm in medicines evaluation, where the quality and pre-clinical assessment represents the largest evaluation performed by EMA. The pre-clinical assessment is based on scientifically recognized pharmacokinetic and pharmacodynamic biomarkers for each clinical indication of the original drug. The exploratory clinical development program for assessing patient benefit is substituted by confirmation with clinical studies, where the goal is to show bioequivalence compared to the approved original mAb.

Because biosimilars are approved through an abbreviated clinical trial program and may not be tested in all indications of the originator, extrapolation of indications is an issue of concern. Extrapolation of scientific evidence should be seen as a logical consequence of the comparability exercise principle, which is based in physiochemical and biological characterization. Any uncertainties, such as slight differences of unknown relevance to clinical performance, should be addressed via comparative clinical data. The totality of evidence for each biosimilar applicant should be reviewed as a whole on a case-by-case basis, with extrapolation viewed not as an "extra" for the developer of the biosimilar, but rather as the applicant's burden to collect and demonstrate stringent scientific evidence.

The current document has the goal of expressing the position of the Portuguese Society of Rheumatology (SPR) concerning the use of biosimilars in Portugal, based on the evidence available so far and on the opinion of its affiliates.

METHODS

A systematic literature review of the clinical trials of the biosimilars that are positioned to be used in rheumatic diseases was performed. A MEDLINE search up to September 2013 was done using relevant search terms in order to include all clinical trials assessing the efficacy and safety of biosimilar candidates to be used in the field of rheumatology.

A systematic literature review of the International Position Papers on the use of biosimilar drugs was also carried out. We included the position of other medical, pharmaceutical and scientific organisations concerning the use of biosimilar drugs, particularly those addressing less consensual aspects such as interchangeability, substitution and extrapolation of data. Therefore, we developed a systematic literature search through MEDLINE using relevant search terms ("biosimilars"[MeSH]), without date or language restrictions, for position papers addressing the use of any biosimilar drug. The search was supplemented with a hand search through the websites of several international societies.

The results of this evidence-based approach were presented and discussed during a national meeting of the Portuguese Society of Rheumatology (SPR) that took place during the 5th and 6th of October 2013. During the meeting, a first plenary session was dedicated to an open discussion and to the elaboration of a first draft of a bullet like SPR position on the use of biolosimilars in the field of rheumatology. A steering committee made a final proposal of this position, which was adapted and approved in a second plenary meeting that took place in the following day.

RESULTS

CLINICAL TRIALS IN BIOSIMILAR CANDIDATES TO BE USED IN RHEUMATOLOGY: A SYSTEMATIC LITERATURE REVIEW

Of the 312 articles screened, 6 were selected for detailed review and 2 fulfilled our inclusion criteria. Two abstracts from the EULAR congress were also included.

The first trial was the phase I PLANETAS trial[14], which compared CT-P13 and originator infliximab in patients with active ankylosing spondylitis. The primary endpoint, pharmacokinetics, and clinical efficacy endpoints, including ASAS 20 and ASAS 40 responses, were highly similar between CT-P13 and infliximab groups. CT-P13 had a safety profile comparable to that of infliximab up to the 30th week.

The second trial was the phase III PLANETRA trial[15], which compared CT-P13 and originator infliximab in patients with rheumatoid arthritis. CT-P13 and originator infliximab were shown to be equivalent in terms of ACR 20 response at week 30 in patients with active rheumatoid arthritis despite methotrexate treatment. Overall, CT-P13 was well tolerated and the safety profile of CT-P13 was comparable with that of infliximab.

At the 2013 EULAR meeting, the results at 54 weeks of the PLANETAS and PLANETRA trials were published as abstracts. Once again, CT-P13 showed comparable efficacy and safety to originator infliximab in patients with active ankylosing spondylitis and rheumatoid arthritis with inadequate response to methotrexate treatment.

There are seven ongoing biosimilar clinical trials, all in patients with rheumatoid arthritis: five trials refer to rituximab, one to etanercept and one to infliximab. There is still no published data on these trials.

The clinical trials included in this review have demonstrated a similar efficacy and safety profiles between the tested biosimilars and the original drugs, granting recent approval of CT-P13 by EMA.

INTERNATIONAL POSITION PAPERS ON THE USE OF BIOSIMILAR DRUGS: A SYSTEMATIC LITERATURE REVIEW

We identified a total of 166 papers (MEDLINE - 143 results, hand search – 23 results), of which 137 were excluded after a title and abstract suitability scrutiny. The remaining 29 papers were submitted to detailed review and all were included in our study (Table I).

Approximately half of the position statements were issued by European organizations, while about one fifth of the papers were of North American origin and the remainders were of different multinational provenances. The type of organizations included medical societies/ /colleges, health-related non-profit non-governmental organizations, governmental departments, pharmaceutical associations and pharmaceutical manufacturers. Most (58%) papers were published in the last 2 years and the dates of publication of all included papers were comprised in the last 8 years (2007 to 2013).

All papers were favourable to the use of biosimilars, provided the safety, efficacy and quality of the drugs were assured. Forty-five percent of papers were clearly in opposition to automatic substitution (i.e. the legal authority for a pharmacy filling a prescription to switch the innovator product to the biosimilar without physician approval) and all papers indirectly advised against this practice by restricting interchangeability of biosimilar drugs to the consent of the attending physician (62% of papers), as well as of the patient (14% of papers). The automatic extrapolation of the approval of biosimilar drugs to other indications different from the ones specifically tested in trials gathered low consensus (unacceptable for 44.8% of the papers). Another source of concern was expressed by many position papers regarding the possibility of biosimilars having the same International Non-proprietary Name (INN) as the originator molecule. In such conditions, 41.4% of the papers defended that prescription should be performed by brand name. Safety concerns were expressed by most organisations, particularly regarding immunogenicity and other potentially unexpected drug related adverse events. Table II summarizes the most relevant position trends found.

THE PORTUGUESE SOCIETY OF RHEUMATOLOGY POSITION ON THE USE OF BIOSIMILAR DRUGS IN THE FIELD OF RHEUMATIC DISEASES

DRUG SELECTION

– In patients naïve to biotechnological drugs, the therapeutic choice among the approved biologic drugs (originators or biosimilars) must be dictated by an assessment of the individual risk-benefit profile (i.e. taking into consideration patient's age, co morbidities, previous infections, concomitant treatments and functional status) and should not be based solely on economic aspects;

SUBSTITUTION

– In light of most medical public positions and based on the opinion of most Portuguese rheumatologists, automatic substitution should be currently considered unacceptable;
– If biosimilars have the same INN as the originator molecule, prescription should be performed by brand name;

INTERCHANGEABILITY

– Switching between the originator molecule and biosimilars is not justifiable due to efficacy or safety reasons (it will be only done in the context of an economical advantage of the biosimilar) and must be based on the attending physician decision and after adequate patient information;
– When switching between biosimilars and the originator molecule, safety and efficacy assessments must be performed and registered in Reuma.pt, following a strategy analogue to the current national guidelines when initiating a new biologic drug;
– Switching between the originator molecule and biosimilars should occur after a minimum of 6 months use in order to allow for adequate efficacy, safety and immunogenicity assessment;

EXTRAPOLATION

– Extrapolation of indications approved for the originator drug to completely different diseases and age groups that are not based on adequate pre-clinical, safety and efficacy data (ideally phase I and phase

TABLE I. SUMMARY OF INCLUDED STUDIES
Position Statements assorted according to the type of organization, country of origin of the organization and year of publication

Organisation	Country of origin	Year
Medical Societies/Colleges[9] 31%		
American College of Rheumatology[16]	USA	2010
Colegio Mexicano de Reumatologia[17]	Mexico	2012
American Academy of Dermatology[18]	USA	2012
European Crohn's and Colitis Organization[19]	Europe	2013
Sociedad Española de Patología Digestiva/ Sociedad Española de Farmacología[20]	Spain	2013
Austrian Society of Hematology and Oncology[21]	Austria	2008
Italian Society of Hematology[22]	Italy	2011
International Union of Angiology[23]	International	2012
Société Française de Néphrologie/ Société Francophone de Dyalise[24]	France	2009
Non-profit Non-governmental Organizations[4] 13.8%		
National Psoriasis Foundation[25]	USA	2013
National Comprehensive Cancer Network[26]	USA	2011
National Haemophilia Foundation[27]	USA	2009
Diabetes UK[28]	UK	2013
Pharmaceutical Organizations[8] 27.6%		
European Biopharmaceutical Enterprises/ European Federation of Pharmaceutical Industries and Associations[29]	Europe	2007
Biotechnology Industry Organization Deutschland[30]	Germany	2012
International Federation of Pharmaceutical Manufacturers and Associations[31]	International	2011
Organisation of Pharmaceutical Producers of India[32]	India	2012
Belgian Biotechnology Industry Organization[33]	Belgium	2013
Generic Pharmaceutical Association[34]	USA	2013
Association of the British Pharmaceutical Industry[35]	UK	2013
Apifarma[36]	Portugal	2013
Governmental departments[4] 13.8%		
Department of Health's Ministerial Industry Strategy Group[37]	UK	2009
Agenzia Italiana del Farmaco[38]	Italy	2013
Scottish Medicines Consortium[39]	UK	2011
Health Canada[40]	Canada	2010
Pharmaceutical Manufacturers[4] 13.8%		
Merck Sharp & Dohme[41]	USA	2010
Eli Lilly and Company[42]	USA	2010
F. Hoffmann-La Roche AG[43]	Switzerland	2010
Brystol Meyers Squibb[44]	UA	2013

III trials) should not be performed;

IMMUNOGENICITY

– Immunogenicity evaluation should be performed when clinically relevant and available. As laboratorial methods of assessing immunogenicity are not routinely available in clinical practice, immunogenicity must be inferred from the adverse events and secondary loss of efficacy data reported in the Reuma.pt register and this information should be reported to health authorities;

ADVERSE EVENTS

– In face of the Portuguese law number 242/2002 (November 5 2002), the regulatory authorities, the marketing authorization holder (former product license holder) and the healthcare professionals must

TABLE II. SUMMARY OF THE POSITION STATEMENTS FOUND

Position statements assorted by modality of use. The name and number of organizations that support the position are stated in the columns on the right-hand side. Although we performed a comprehensive search, for the sake of intelligibility, only the most relevant positions are displayed

Use	Position statements	Organizations that support the position	Total, n (%)
Drug selection	Therapeutic choice must primarily be dictated by patient safety concerns	Apifarma	1 (3.4)
	The less expensive drug is a reasonable first therapeutic choice in *naïve* patients	Agenzia Italiana del Farmaco	1 (3.4)
Substitution	Automatic substitution is unacceptable	Apifarma Austrian Society of Hematology and Oncology Brystol-Meyers-Squibb Colegio Mexicano de Reumatología Eli Lilly and Company F. Hoffmann- La Roche AG Health Canada Italian Society of Hematology, Italian Society of Experimental Hematology, and Italian Group for Bone Marrow Transplantation National Psoriasis Foundation Scottish Medicines Consortium Sociedad Española de Patología Digestiva/ /Sociedad Española de Farmacología Société Française de Néphrologie	13 (44.8)
	When biosimilars have the same INN, prescription must be performed by brand name	Apifarma Association of the British Pharmaceutical Industry Belgian Biotechnology Industry Organization/ /Essenscia Brystol-Meyers-Squibb Diabetes UK Generic Pharmaceutical Association Health Canada Italian Society of Hematology, Italian Society of Experimental Hematology, and Italian Group for Bone Marrow Transplantation Lilly Scottish Medicines Consortium Sociedad Española de Patología Digestiva/ /Sociedad Española de Farmacología Société Française de Néphrologie, Société Francophone de Dyalise	12 (41.4)
Interchangeability	Switching between biosimilars and the original product must be performed only upon consent of the attending physician	Agenzia Italiana del Farmaco American Academy of Dermatology American College of Rheumatology Apifarma Association of the British Pharmaceutical Industry Biotechnology Industry Organization Deutschland	

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TABLE II. CONTINUATION

Use	Position statements	Organizations that support the position	Total, n (%)
		Brystol Meyers Squibb Colegio Mexicano de Reumatología Department of Health's Ministerial Industry Strategy Group Eli Lilly & company European Biopharmaceutical Enterprises/ /European Federation of Pharmaceutical Industries and Associations European Crohn's and Colitis Organization Merck National Haemofilia Foundation National Psoriasis Foundation Organisation of Pharmaceutical Producers of India Sociedad Española de Patología Digestiva, Sociedad Española de Farmacología Société Française de Néphrologie, Société Francophone de Dyalise	18 (62.1)
	Switching requires informed consent of the patient	Association of the British Pharmaceutical Industry European Crohn's and Colitis Organization National Haemofilia Foundation National Psoriasis Foundation	4 (13.8)
Extrapolation of approval (to other indications of the originator drug)	Automatic extrapolation of safety and efficacy data from the original drug should not be performed	American College of Rheumatology Apifarma Biotechnology Industry Organization Deutschland European Crohn's and Colitis Organization Sociedad Española de Patología Digestiva/ /Sociedad Española de Farmacología	5 (17.2)
	Extrapolation must be decided on a case-by-case basis	Association of the British Pharmaceutical Industry Austrian Society of Hematology and Oncology Health Canada Société Française de Néphrologie	4 (13.8)
	The approval of the biosimilar drug automatically extends to all the indications of the originator drug	Agenzia Italiana del Farmaco Italian Society of Hematology, Italian Society of Experimental Hematology, and Italian Group for Bone Marrow Transplantation Scottish Medicines Consortium	3 (10.3)
Immunogenicity	Immunogenicity must be adequately assessed	Diabetes UK Health Canada International Federation of Pharmaceutical Manufacturers and Associations Italian Society of Hematology, Italian Society of Experimental Hematology, and Italian Group for Bone Marrow Transplantation Merck National Haemofilia Foundation Organisation of Pharmaceutical Producers of India Société Française de Néphrologie	8 (27.6)

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TABLE II. CONTINUATION

Use	Position statements	Organizations that support the position	Total, n (%)
Adverse events	Robust pharmacovigilance strategies must be assured	American College of Rheumatology Apifarma Austrian Society of Hematology and Oncology Belgian Biotechnology Industry Organization/ /Essenscia Biotechnology Industry Organization Deutschland Colegio Mexicano de Reumatología Diabetes UK Health Canada International Federation of Pharmaceutical Manufacturers and Associations International Union of Angiology Italian Society of Hematology, Italian Society of Experimental Hematology, and Italian Group for Bone Marrow Transplantation Lilly Merck Organisation of Pharmaceutical Producers of India Scottish Medicines Consortium Sociedad Española de Patología Digestiva/ /Sociedad Española de Farmacología Société Française de Néphrologie	17 (58.6)
	Patient registries and clinical databases are important sources of data concerning rare adverse events	American College of Rheumatology	1 (3.4)

assure rigorous pharmacovigilance mechanisms;
- The brand name, batch number and date of administration must be registered in the Reuma.pt database upon every biosimilar drug administration;
- Biosimilar-related adverse events registered in Reuma.pt must be periodically monitored through a formal evaluation.

GLOSSARY

BIOSIMILAR PRODUCTS

Biological products that demonstrated its equivalence to an already approved reference product with regard to quality, safety, and efficacy

REFERENCE PRODUCT

A medicinal product that was approved on the basis of a full data package (registration file). Reference products are used as the comparators in head-to-head studies to show similarity in terms of quality, non-clinical and clinical studies of biosimilar products.

ORIGINATOR PRODUCT

A medicine that is the first to be approved by the national regulatory authorities on the basis of a full registration dossier. The originator product is usually used as a reference product as it tends to be the product with publicly available safety information and long market experience.

COMPARABILITY

The scientific evaluation of a comparison of a biosimilar product and a reference product to determine absence of any detectable differences at the level of quality, non-clinical and clinical studies.

CLINICAL EQUIVALENCE

Clinical equivalence is granted when the evaluation based on major clinical parameters is equivalent and when any observed differences are clinically non-relevant.

IMMUNOGENICITY

The ability of a substance to trigger an immune response or reaction (e.g., development of specific antibodies, T cell response, allergic or anaphylactic reaction).

INTERCHANGEABILITY

This term means that the biosimilar product produces the same clinical result as the reference product in any given patient and, for a product administered more than once, the safety and efficacy is not compromised by alternating or switching between the reference product and the biosimilar. An interchangeable biosimilar has the potential to be used under the concept of automatic substitution.

AUTOMATIC SUBSTITUTION

This is the legal authority for a pharmacy filling a prescription to switch the innovator product to the biosimilar without physician approval. This is not regulated by EMA and was left to member states decision.

EXTRAPOLATION

Biosimilar products can be recognized for indications of reference products without performing clinical studies for all the clinical indications that reference products are approved for, supposing the equivalence with reference products by extrapolation of indications of reference products. If equivalence on efficacy and safety of the biosimilar and the reference product have been demonstrated in a particular indication, extrapolation of these data to other indications of the reference product may be possible if:

– A sensitive test model has been used, which is able to detect potential differences between the biosimilar and the reference product and
– The mechanism of action and/or involved receptor(s) is the same
– Safety and immunogenicity have been sufficiently characterized

CORRESPONDENCE TO
João Eurico Fonseca
Instituto de Medicina Molecular
Reumatology Research Unit
Fac. Medicina da Universidade de Lisboa
Av. Prof. Egas Moniz, Lisboa – Portugal
E-mail: jecfonseca@gmail.com

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