



Special Article

Position Paper From the Spanish Society of Rheumatology on Biosimilar Drugs[☆]



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ABSTRACT

A biosimilar (BS) is a biological drug that contains a version of the active substance of an already authorised original biological product. The BSs are marketed after patent period of the original drug has ended and once it has been demonstrated that the differences regarding the innovative medicine have no relevant effect on its safety or clinical efficacy. The Spanish Society of Rheumatology, in line with the European Medicines Agency, considers that because of its nature and complexity of production, a BS cannot be considered to be the same as a generic drug. The Spanish Society of Rheumatology expresses an unequivocal commitment to the sustainability of the health system in our country and our steadfast alignment with all measures designed to ensure continuity, without reducing the quality of care. Therefore, we believe that the advent of BSs will likely facilitate access of patients with rheumatic diseases to the biological drugs. This article reviews the European Medicines Agency requirements for authorisation, the Spanish legal framework and controversies on BS and presents the position paper of the Spanish Society of Rheumatology on these drugs.

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Documento de posicionamiento de la Sociedad Española de Reumatología sobre fármacos biosimilares

RESUMEN

Un biosimilar (BS) es un fármaco biológico que contiene una versión de la sustancia activa de un producto biológico original ya autorizado. Los BS se comercializan al terminar el periodo de patente del fármaco original y tras demostrar que las diferencias con respecto al medicamento innovador no tienen ningún efecto relevante sobre su seguridad y su eficacia clínica. La Sociedad Española de Reumatología, en consonancia con la Agencia Europea del Medicamento, considera que por su naturaleza y complejidad de producción no se puede equiparar un BS a un genérico. La Sociedad Española de Reumatología manifiesta un compromiso inequívoco con la sostenibilidad del sistema sanitario y apoya medidas que, sin reducir la calidad asistencial, estén encaminadas a asegurar su continuidad. Por esto considera que, probablemente, la llegada de los BS mejorará el acceso de los pacientes con enfermedades reumáticas a los fármacos biológicos. Este artículo revisa la normativa de la Agencia Europea del Medicamento, el marco legal español y las controversias sobre los BS, y presenta el posicionamiento de la Sociedad Española de Reumatología sobre estos fármacos.

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Introduction

The growing development, commercialisation and availability of biological therapies have revolutionised the treatment of patients with rheumatic diseases. Biological therapies have been shown to effectively control the activity of these pathologies, while improving patients' physical functions and the ability to modify the progression of these diseases. The risk/benefit and cost/effectiveness ratios of these treatments are favourable when used in the right populations. Their high cost, however, limits their generalised use.¹ In 2012, the top ten most frequently sold biological drugs included 4 medications used in rheumatology (adalimumab, etanercept, rituximab and infliximab).²

In September 2013, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) approved the use of Remsima[®] and Inflectra[®], which are biosimilars of Remicade[®]. They are the first biosimilar drugs of a monoclonal antibody (mAb) approved by the EMA.^{3,4} Likewise, other biosimilar mAb are currently in advanced research phases: adalimumab and etanercept are in stage 3 trials; and, other drugs, such as rituximab and adalimumab, are also being tested in early-stage clinical trials.^{5–11}

According to the EMA,¹² a biosimilar is a biological drug that contains a version of the active ingredient/substance from a previously authorised original biological product (reference drug). During complete comparability testing, it should demonstrate a similarity with the reference drug in terms of quality, biological activity, safety and effectiveness. A biosimilar is not a generic drug with a simpler structure; instead, it is identical to its reference drug.

Until the approval of Remicade[®] biosimilars, the biosimilar drugs that had been approved by the EMA were erythropoietins, colony-stimulating factors and growth hormones, whose structure is very simple compared to monoclonal antibodies. For approval, a biosimilar should demonstrate that the variability and any differences from the innovative drug do not affect its safety or efficacy. Therefore, once a biosimilar has been authorised, the regulatory agencies guarantee that there are no significant differences in quality, effectiveness or safety.

The development of biosimilars by the biotechnological industry is based on:

- (a) The expiration of the first patents for biological therapies in 2001 and the introduction of the concept of biosimilars in European legislation in 2003. These situations induced the biotechnological industry to present the first biosimilar applications in 2004, and the first biosimilars were approved in 2006.¹³
- (b) Economic factors. The cost of biologic drugs is high. In 2012, worldwide sales of the 10 most widely sold drugs reached more than 56 billion dollars.² In this context, the biotechnological industry has found a market opportunity with this type of drugs.
- (c) Sustainability of healthcare systems. Healthcare administrators see biosimilars as a less expensive alternative to reference drugs and an opportunity to cut costs in order to sustain the system. It is estimated that biosimilars are 15%–30% cheaper than reference drugs.
- (d) The accessibility of biological therapy to patients who currently cannot opt for its use due to high costs.

As some reference drugs have patents with upcoming expiration dates, many manufacturers are developing biosimilars. This could improve patient access to these medications and lower costs in healthcare systems like ours, while stimulating competition that would lead to a reduction in price of original biological therapies.

Regulations of the European Medicines Agency

In accordance with the legislation for medications in the European Union (EU), biosimilars follow a mandatory procedure for centralised registration that is coordinated by the EMA, and they are evaluated by the same experts who evaluate innovative biotechnological products. It is required for the reference drug with which they are compared to be authorised for use in the EU, which should be the same throughout the biosimilar development programme. A workgroup created by the CHMP, the Biological Medicine Working Party, is responsible for writing guidelines for biological medicines. Specifically, the CHMP is in charge of emitting a scientific opinion about their approval and, ultimately, the European Commission (EC) makes the final decision about their authorised commercialisation in the EU. The centralised procedure is valid in all the member countries of the EU.

The EMA has been a pioneer in the development and establishment of a regulated process for the authorisation of biosimilars. This process was created due to the inherent complexity and heterogeneity of biologic drugs. The concept of “biosimilarity” for the fabrication and request for authorised commercialisation of similar versions of innovation medicinal products in the EU was introduced in 2003 by 2 EC directives that modified Directive 2001/83 (basic EU law regulating the authorisation of medications).^{14,15} Afterwards, in 2005, guidelines were published for the general principles of authorisation (“*Guideline on similar biological medicinal products*”),¹² establishing the requirements that products should comply with in order to be considered a biosimilar and which has been recently updated.¹⁶ The EMA then published another 2 guidelines in 2006: one for general production and monitoring as well as quality requirements for biosimilars (“*Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues*”)¹⁷; and, another about the clinical and non-clinical studies necessary to demonstrate comparability (“*Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical & clinical issues*”).¹⁸ The recommendations of these guidelines are, in general, the same that are used in the preclinical development of innovative biological medications. All these guidelines are being revised, published publicly and updated.^{19,20} The basic objective of the development of a biosimilar is to establish the similarity between it and its reference drug, utilising the best available means to guarantee the effectiveness and safety previously demonstrated by its comparative drug.

The immunogenicity of biologic drugs is a subject of great debate in the scientific community and, with the advent of biosimilars, the debate is quite current. Anticipating this controversy, in 2008 the EMA approved a specific guideline about immunogenicity, *Guideline on immunogenicity assessment of biotechnology-derived medical products*,²¹ which is currently being revised and updated.²²

In addition to the general guidelines for the development of biosimilars, the EMA has created specific guidelines for the development of biosimilars of erythropoietins, colony-stimulating factors, insulins, growth hormone, interferon alpha/beta, follitropin and low-molecular weight heparins. In December 2012, specific guidelines were published for mAb biosimilars²³ and for assessing the immunogenicity of mAb.²⁴ The objective of the specific guidelines for mAb biosimilars is to establish the comparability between biosimilars and the reference product. In this manner, the guidelines describe how to plan the studies to detect any differences between biosimilars and their reference product. The process of comparison is done step-by-step through comprehensive comparability testing, in which any relevant difference observed must be justified. Initially, non-clinical studies are done, whose first step is

in vitro studies that should be sufficiently sensitive to detect any difference in the biological activity between the biosimilars and their biological reference product. The second step involves assessing the need to carry out *in vivo* studies to evaluate whether, for example, there are effects mediated by mAb that are not detectable in *in vitro* studies. Nonetheless, they may not be necessary if the comparability of the *in vitro* studies have been satisfactory. The third step is *in vivo* studies, whose focus will depend on the need for additional information, and human toxicity studies are not required.

When the non-clinical development stage has been completed, clinical development is initiated. Clinical studies comparing biosimilars and their reference drug should always be done with a step-by-step approach, as in non-clinical development. In the first step, pharmacokinetics are evaluated to demonstrate pharmacokinetic equivalence between both products. These studies should be done in a sensitive, homogeneous population; several studies may be necessary in patients from different populations, with proper justification for their selection. Afterwards, pharmacodynamic studies are done with pharmacodynamic markers chosen to establish comparability. The next step is clinical development, which should involve: (a) clinical studies following EMA guidelines for clinical requirements of mAb and demonstrating comparability in sensitive clinical models; (b) clinical safety studies; and, (c) pharmacovigilance risk management plan (obligatory). With regards to this last point, biosimilars should be properly monitored, as should all biological drugs, and the manufacturer requesting authorisation should provide a description of the pharmacovigilance system and create a risk management plan including possible risks due to the immunogenicity of these drugs.

Table 1 shows the different EMA guidelines for biosimilars.

Spanish Legislation

In Spain, there is currently no specific legal framework for biosimilars. However, current regulations include different laws and royal decrees that deal with diverse aspects referring to biological therapies and biosimilars in particular (Table 2). The following is a review of these regulations.

Prescription

Royal Decree 1718/2010 for Medical Prescriptions, modified by RD 81/2014, Article 3.2, Sections a and b, states: “Article 3: Formats for common medical prescription data. 2. The prescriber should include, on the prescription as well as one the information sheet for the patient, obligatory basic data that are essential for the medical prescription to be valid, including the following: (a) patient data [...]; (b) medication data: active ingredient, denomination of the medicine if it is a biological medication [...] in compliance with Law 26/2006 from 26th July. The prescription will also briefly mention the commercial name.”

Substitution and Interchangeability

According to Article 86.4 of Law 29/2006, from 26th July, dealing with guarantees and rational use of medications and healthcare products, the Spanish Ministry of Health will establish those medications that, because of their characteristics of bioavailability and narrow therapeutic range, should be an exception to the general criteria for the substitution of the pharmaceutical established in Article 86 of aforesaid Law.

Order SCO/2874/2007, from 28th September, establishes medications that are an exception to the possible substitution by the pharmacist in accordance with Article 86.4 of Law 29/2006, from 26th July, dealing with the guarantees and rational use of medicines

Table 1
Main EMA Biosimilar Guidelines.

Guideline on similar biological medicinal products	CHMP/437/04
Guideline on similar biological medicinal products	CHMP/437/04 Rev 1
Guideline on immunogenicity assessment of biotechnology-derived medical products	EMA/CHMP/BMWP/14327/2006
Concept paper on the revision of the guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (CHMP/BMWP/42832/2005)	EMA/275542/2013
Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non clinical and clinical issues	EMA/CHMP/BMWP/42832/2005
Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non clinical and clinical issues	EMA/CHMP/BMWP/42832/2005Rev1
Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: quality issues	EMA/CHMP/BWP/49348/2005
Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: quality issues	EMA/CHMP/BWP/247713/2012
Similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues	EMA/CHMP/BMWP/403543/2010
Immunogenicity assessment of monoclonal antibodies intended for <i>in vivo</i> clinical use	EMA/CHMP/BMWP/86289/2010

and healthcare products. The list of medications affected by this exception, from the Order of 28th May 1986, which establishes the medications that cannot be substituted for others at dispensation, needs to be updated in accordance with scientific and medical advances. With this proposition and with the primordial objective of safeguarding patient health, this order updates the list of medications that, due to their pharmacologic or therapeutic characteristics, should be excluded from the general rules of possible substitution by the pharmacist.

Its single Article indicates that, in accordance with Article 86.4 of Law 29/2006 from 26 July, dealing with guarantees and rational use of medications and healthcare products, the following medications cannot be substituted at the time of dispensation without the express authorisation of the prescribing physician:

1. Biological medications (insulins, blood products, vaccines, biotechnological medications).

Table 2
Summary of the Legislation in Spain About Biological and Biosimilar Drugs.

Aspect	Regulation	Source/Reference
Prescription by ICD/commercial name	Article 3. Formats for common data in medical prescriptions. 2. The prescribing physician should include the following essential basic data on the prescription and patient information sheet, which are required for the medical prescription to be valid: (a) patient data [. . .]; (b) medicine data: active ingredient. Medicine name if it is a biological medicine [. . .], conforming to Law 26/2006 from 26 July. In these cases, the use of the brand name should be explained.	Royal Decree 1718/2010 for medical prescriptions, modified by RD 81/2014. Article 3.2, Sections A and B, pp. 3 and 4
Pharmacovigilance	Article 5. Functions of the autonomous communities: 12. Implement measures outlined by the Technical Committee of the Spanish Pharmacovigilance System aimed at identifying the name of the medicine and the lot number in notifications involving biological or biotechnological medicines.	Royal Decree 577/2013 Pharmacovigilance. Article 5.12, p. 9
Substitution by the pharmacist	The pharmacist will dispense the medicine prescribed by the physician, with the exception of possible substitution of medicines determined by the Spanish Ministry of Health based on their bioavailability or narrow therapeutic margin.	Law 29/2006, from 26 July, dealing with guarantees and rational use of medicines and healthcare products. Article 86, p. 52.
Prohibited substitution	The following medicines cannot be substituted at the time of dispensation without the express authorisation of the prescribing physician: (a) biological medicines (insulins, blood products, vaccines and biotechnological medicines)	Order SCO/2874/2007 from 28 September, which establishes the medicines that are an exception to the possible substitution by the pharmacist. Article 1.a
Specific regulations for substitution and interchangeability	In the case of biosimilars and related specific regulations, the regulations for substitution and interchangeability will be followed.	Art. 86.5 Ley 29/2006 dealing with Guarantees (modified by Law 10/2013). Pending specific legislation for biological medications, p. 53

- The Spanish Agency of Medicines and Healthcare Products will create a list of non-substitutable medications, which will be accessible to the public.
- As an exceptional measure and due to reasons of health risks, the Spanish Ministry of Health can establish, by means of a resolution that will be made public, that a medication not included in Section 1 is not substitutable at dispensation.

Law 10/2013, from 24 July, incorporates into Spanish Law Directives 2010/84/EU of the European Parliament and Council, from 15 December 2010, about pharmacovigilance, and 2011/62/EU of the European Parliament and Council, from 8 June 2011, about the prevention of the entrance of counterfeit medications into the legal supply chain, and modifies Law 29/2006, from 26 July, dealing with guarantees and rational use of medications and healthcare products. It states that, in the case of biosimilar medications, current regulations will be respected according to specific regulations in matters of substitution and interchangeability. Currently, this is pending the development of specific legislation about biological medications.

Pharmacovigilance

Royal Decree 577/2013, from 27 July (Article 2, Point 11), indicates what medications are subject to additional follow-up. The medications are included in the list created by the European Medicines Agency, in accordance with the criteria established in Article 23 of EC Regulation no. 726/2004 (by both the Parliament and Council), from 31 March 2004, which establishes EC procedures for the authorisation and control of medicines for human and veterinary use and creates the European Medicines Agency. The creation of this list involves consultation with the European Pharmacovigilance Risk Evaluation Committee and includes all medicines with new active ingredients and biological medicines, including biosimilars. The list may also contain medications that

require post-authorisation studies or conditions or restrictions associated with safe and effective medication use.

Article 5.12 indicates measures that should be adopted as defined by the Technical Committee of the Spanish Pharmacovigilance System, aimed at identifying the medicine name and the lot number of biological or biotechnological medicines.

Recently, a *proposal not of law* was presented in Spanish Parliament (no. 161/002765) referring to the regulation of substituting or interchanging biosimilar medicines, which was unanimously approved to clarify and update these regulations. This proposal identified the need for specific rules and criteria regarding the interchangeability with other biologicals to be included in a general regulation throughout the National Healthcare System as a means to avoid redundant provincial debating about “therapeutic equivalents” because, if not, equal access to biological medicines could be affected among the autonomous communities. This proposal also states that, when a biological is substituted and a biosimilar is implemented in the treatment of a patient, this should be indicated on the patient’s medical file. Likewise, it reiterates the need for specific biosimilar pharmacovigilance programmes and recommends creating a workgroup comprised of representatives from the central government, autonomous communities and pharmaceutical industry to deal with the conformation of the mentioned legislative framework.

Controversies About Biosimilars

Biological therapies currently play a very important role in the treatment of autoimmune and tumour diseases. Although biosimilars have been commercialised since 2006, their implementation has been limited.²⁵ There has been great debate in the medical literature about the risks and benefits of biosimilars, which has increased with the development of LARS mAb.^{26–35} Particularly, there are different aspects that have been the centre of

debate, such as: the structural complexity of biologic drugs, safety, immunogenicity, extrapolation of indications, interchangeability, substitution and prescription by interactional common denomination (ICD or INN) and commercial brand. In 2008, Schneider, the director of the Biological Medicine Working Party of the EMA at that time, enumerated the pros and cons of the development of biosimilars.³⁶ Likewise, numerous scientific associations, both medical and from the pharmaceutical industry, have published position documents about biosimilars.^{37–50}

Structural Complexity and Production of Biologic Drugs

Until the recent approval by the EMA of Remicade® biosimilar drugs, the biosimilars of commercialised biological therapies were structurally much simpler than mAb. There is a marked difference between the sequence and structure of somatotropin (191 amino acids and 22 daltons) and that of IgG monoclonal antibodies (more than 1000 amino acids and 150,000 daltons). Like all biologic drugs, mAb have an inherent variability and a complex structure that is not only defined by their primary (sequence of amino acids), secondary, tertiary and quaternary structure, but also by their grade and pattern of post-translational modification: glycosylation, methylation, fucosylation, etc. These post-translational modifications can influence the tertiary (folding) and quaternary (spatial configuration) structure, changing the conformational integrity of mAb and determining differences in affinity, selectivity, functional activity and immunogenicity. The general structure of an mAb IgG is formed by 2 identical light chains and 2 heavy chains, with some constant regions and other variables. This mAb structure can be subdivided into Fab (fragment antigen binding) region and Fc (fragment crystallisable) region. The Fc region is responsible for producing the effector functions, such as complement dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC); likewise, the union of the Fc region with effector cells through Fc receptors can cause phagocytosis or the release of cytokines and cytotoxic compounds.^{51,52} The activation of these effector functions largely depends on the glycosylation profile of the Fc domain; therefore, the reproduction of the glycosylation profile is a very important datum to consider by laboratories that develop biosimilars, as it can have a large impact on the mechanisms of action of mAb.⁵³

Furthermore, the process of developing biological drugs is long, complex and done in several stages. The final product depends on each of the phases of this process. For this reason, in biotechnology it is usually said that “the process is the product”, referring to the complexity involved in the manufacture of these products. Any change in the production process or fabrication conditions, such as a change in excipients, the use of new cell banks, storage, etc., could cause significant conformational alterations that would influence the effectiveness and the safety of the final product. Biosimilar manufacturers do not have access to the information of the reference drug production process, so they need to develop their own production process. Although it does not necessarily have to be the same, any changes should be systematically reviewed. As we already commented in the section about EMA regulations, biosimilars undergo detailed comparability testing with their reference drug; however, in spite of this testing, a biosimilar can never be identical to its reference drug. Thus, the same could be said of innovative drugs, since, over the lifetime of any biologic drug, the fabrication process can be changed if properly justified.⁵⁴ In the case of innovative drugs, however, these changes are made regarding a known and patented process, while in the case of biosimilars a new process should be developed. Variations made over the lifetime of an innovative drug should not be compared with a biosimilar produced with different cell lines and production process. The test of being “not quite the

same” is a comparability requirement that the agencies demand for either scenario.⁵⁵

During comparability testing, the biosimilar should demonstrate that there are no differences with the innovative drug, following EMA directives.^{16–18,22,23} Any unjustified difference can mean rejection. One example of this was the non-authorisation of insulins developed as biosimilars in which pharmacodynamics and pharmacokinetic differences were observed, leading to the rejection of the application for Biferonex®, biosimilars of Avonex®,⁵⁶ due to lack of safety information. Therefore, it can be said that a biosimilar that is approved by the EMA has convincingly demonstrated that it is comparable to the reference drug. Thus, it should not be doubted that the EMA may approve a biosimilar, just as it approves new biological drugs. Nonetheless, this does not mean that changes may occur during the lifetime of any biologic drug, and it may even be withdrawn from the market, as has already occurred with other biologic drugs like natalizumab, mepolizumab or nimotuzumab.^{57–59} Furthermore, systems should be established to guarantee their safety and efficacy, as has been done with innovative drugs.

Extrapolation of Indications

The EMA guidelines^{16–18,22,23} state that if a reference medication has more than one therapeutic indication, the extrapolation of the effectiveness and safety profile of the biosimilars to the remaining indications must be justified or, if necessary, demonstrated separately for each of the authorised indications. The justification will depend on clinical experience, bibliographic data available, knowledge about the mechanism of action of the active ingredient and the receptors involved for each indication. If there is evidence that different active sites of the reference medicine or different receptors in the target cells are involved in the different therapeutic indications, or that the product safety profile differs among them, additional data may be necessary to justify the extrapolation of the safety and effectiveness of the indication studied in the pivotal clinical trial. The final decision will be based on the evidence from all the comparability studies and on the possible uncertainties that still remain. Like the EMA, the Canadian agency has developed guidelines to regulate the development of biosimilars.⁶⁰ The Canadian guidelines indicate that extrapolation is possible when the reasoning provided is sufficiently persuasive and justified according to the mechanisms of action, disease physiopathology, safety profile of the respective diseases and clinical experience with the reference drug. Therefore, the laboratory should rationally justify their proposal for extrapolation and provide sufficient data that allow it.

The subject of extrapolation is perhaps what has caused the most debate and controversy, and there are many opinions in favour and against it.^{48–50} Recently, the Portuguese Society of Rheumatology has published a position document with an exhaustive review of the evidence and positions on the extrapolation of indications as well as interchangeability, substitution and immunogenicity by different scientific societies, medicine agencies and laboratories.³⁶

There are several factors that can influence the extrapolation de indications. First of all, it is well known that mAb can cause a clinical effect through a wide variety of mechanisms: blocking ligands or receptors, cell depletion (ADCC or CDC) or signal induction. The action of mAb can be due to one or several of these mechanisms and the participation of each of these mechanisms can vary in each of these indications. Specifically, infliximab and adalimumab act fundamentally by blocking soluble TNF- α ; nonetheless, in patients with intestinal inflammatory disease, both have demonstrated to bind with membrane TNF- α .⁶¹ The binding of membrane TNF α can cause different actions, such as cell death through ADCC or CDC, or

apoptosis, although the contribution of each of these mechanisms is unknown.^{62,63} Due to these multifactorial mechanisms of action in patients with intestinal inflammatory disease, the extrapolation from other indications in which the effector functions do not seem to play a central role (for example, rheumatoid arthritis and ankylosing spondylitis) is questionable. There are also other factors that should be considered with regards to extrapolation, such as the different doses and posologies in each indication, the concomitant use of immunosuppressants, the use of different administration pathways for different indications and the physiopathology of the disease.

The EMA indicates that the development of biosimilars should be done in a sensitive, homogenous population. But, is rheumatoid arthritis the most sensitive model? Some authors do not believe so. According to Lee,⁴⁹ the most sensitive model for detecting differences is cutaneous psoriasis; the author goes on to state that the extrapolation of indications using a less sensitive model is, at best, very questionable. Lee also indicates that, even with the same mAb, the mechanisms of action can be different in different diseases and refers to possible problems of safety and immunogenicity. Other authors state that, although the rheumatoid arthritis population is not the most sensitive, it seems that the formation of anti-drug-antibodies (ADA) is similar between both drugs. Also, preliminary laboratory data from an observational study of 23 patients with intestinal inflammatory disease suggest a similar effectiveness between CT-P13 and Remicade®.⁵⁰

Based on laboratory results, the EMA has approved the biosimilars of infliximab (European Public Assessment Report–EPAR) for all the indications of Remicade® (rheumatoid arthritis, ankylosing spondylitis, Crohn's disease and ulcerative colitis, in adults and in patients with paediatric disease, psoriatic arthritis and cutaneous psoriasis) after considering trials in rheumatoid arthritis and ankylosing spondylitis.^{64,65} The extrapolation is based on extensive study of physical-chemical comparability in combination with demonstrated pharmacokinetic equivalence in rheumatologic diseases. Nevertheless, the laboratory is required to do a double-blind randomised clinical trial between Remsima® and Remicade® in patients with active Crohn's disease as well as a prospective observational study to assess the effectiveness and safety in patients with Crohn's disease and ulcerative colitis. In this comparability exercise, the only difference observed between CT-P13 and Remicade® was a lower level of fucosylation, which means less affinity to FcγRIIIa and, therefore, less ADCC activity in their most sensitive *in vitro* experimental model, using the NK cells of patients with Crohn's disease (CD) and with high-affinity genotypes (VV and VF). However, the EMA does not consider these differences clinically relevant.

In contrast, another regulatory agency (Health Canada), using the same EMA data, has not approved the extrapolation of indications to Crohn's disease, ulcerative colitis or paediatric patients.⁶⁶ The summary from its approval states that the safety profile has not been established in paediatric patients, and it is not recommended to extrapolate the data to Crohn's disease and ulcerative colitis due to the differences found between biosimilars and their reference product. It does not recommend extrapolation due to the differences in the levels of fucosylation, binding to FcγRIIIa receptors and some *in vitro* trials for ADCC. The document indicates that the laboratory has provided arguments, indicating that ADCC is not an important mediator in the efficacy of Remicade®. Nonetheless, after a review of the reasons supporting extrapolation and after reviewing the literature, it was considered that the fact could not be dismissed that ADCC plays an important role as mechanism of action in inflammatory bowel disease. Furthermore, this position is supported by the observation that certolizumab pegol, another anti-TNF without the capability to induce ADCC,

has only marginal benefits in Crohn's disease compared with other anti-TNF. Therefore, and given these data, extrapolation is not recommended due to the lack of studies in inflammatory bowel disease.

In short, in the issue of extrapolating indications, there are 2 prestigious regulatory agencies that, with the same data, have their reasons for reaching different conclusions. Who is right? The Canadian agency has been more conservative than the EMA, but the latter has also recommended doing clinical trials and observational studies in patients with inflammatory bowel disease.

Substitution and Interchangeability

With regards to this aspect, the EMA affirms that decisions regarding interchangeability and/or substitution depend on the corresponding authorities from each country and are outside the realm of the EMA and CHMP. In order to base their decisions, the member states have access to the scientific evaluations done by the CHMP and all the information presented.⁶⁷ The Canadian agency states that the authorisation of a biosimilar is not a declaration in favour of interchangeability, substitution or therapeutic equivalence. This statement is based on possible differences between both drugs, as they are not identical, and on the possible differences in the safety profile and immunogenicity of both drugs, recommending that physicians participate in the decisions for exchanging biosimilars for their reference drugs.^{68,69} A review has recently been published evaluating the safety profile of biological drugs (erythropoietins, growth hormone and colony-stimulating factors). There were few studies about interchangeability, most of which dealt with erythropoietins, although no safety problems were observed.⁷⁰ Nonetheless, these data should be assessed with caution because the complexity of these drugs is not comparable with that of mAb.

In Spain, biological drugs are on the list of non-substitutable medicines.⁷¹ However, in standard clinical practice, biologicals are often changed due to adverse effects or ineffectiveness. There are limited data in the literature about the change in biological therapy in controlled patients. The only article published is a clinical study in patients with Crohn's disease controlled with infliximab who were randomised to continue with infliximab or initiate adalimumab, with an observed loss of efficacy and tolerance in the adalimumab group.⁷² Preliminary data were presented at the ACR 2013 congress about the safety of the substitution between CT-P13 and Remicade®, with no observed safety problems.^{73,74} Likewise, an observational study is underway to assess the effectiveness and safety of the substitution of infliximab for a biosimilar in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, Crohn's disease and cutaneous psoriasis.⁷⁵

Current experience with biosimilars is relatively limited. Therefore, until pharmacovigilance practices improve and there is complete support for interchangeability with biosimilars, it seems prudent for physicians to make therapeutic decisions for biologic drug substitutions on an individualised basis.⁷⁶

Immunogenicity, Safety and Pharmacovigilance

During comparability testing within the process of biosimilar development, safety and immunogenicity are key aspects and are considered throughout the entire process of drug development (see section on EMA guidelines).

Like all medicines approved for human use in the EU, biosimilars are required to be provided with a risk management plan (RMP) under current EU legislation for pharmacovigilance.⁷⁷ The laboratory requesting approval of a biosimilar should provide the RMP, including safety data for all approved indications, including

long-term safety, steps for detecting known and unknown safety problems associated with the use of the drug, as well as additional data on immunogenicity. Remicade® biosimilars provided an RMP that was considered acceptable by the Pharmacovigilance Risk Assessment Committee.^{3,4} This RMP gives details about all the steps and studies that the manufacturing laboratory will carry out to control potential safety problems. The Pharmacovigilance Risk Assessment Committee recommends considering inclusion in other European biological registries, such as the Swedish and Spanish registries, apart from those already included in the RMP provided by the laboratory: British (BSRBR-RA) and German (RABBIT) registries.

Immunogenicity is the ability to induce a humoral and/or cell mediated immune response. All exogenous proteins, including mAb, have the potential capability of triggering an immune response, especially when used repetitively for long period of time.^{78,79} The incidence of ADA is very variable among the different drugs and studies, and it depends on the techniques used to detect them. Clinical consequences are also variable and depend on whether the ADA is neutralising or non-neutralising. Neutralising ADA bind with the drug and do not allow it to carry out its biological or therapeutic function; this reduces its efficacy and is associated with increased adverse effects.^{80,81} A classic example is the appearance of red cell aplasia in patients with renal failure after the change in the process of fabrication of erythropoietin.⁸² There are multiple factors that influence the development of immunogenicity. Some depend on the drug and its fabrication process: variation in protein sequence folding, degree of humanisation, alteration in the glycosylation process, formulation processes, excipients used, storage, administration pathways and treatment time. Others depend on the patient: genetic factors, age, previous exposure to similar drugs, patient disease and use of associated immunosuppressants.⁸³ Therefore, the most sensitive population for detecting differences in the immunogenic response to mAb would be that in which the immunogenicity was not suppressed by concomitant immunosuppressant therapies.⁶⁹

The EMA guidelines about immunogenicity^{21,24} discuss in detail the problems of the immunoanalysis utilised for measuring ADA, and recommendations are provided for the types of assays to use in order to comparatively assess the development of neutralising and non-neutralising ADA. The comparative assessment of immunogenicity should include not only the incidence of ADA, but also ADA titres and distribution among the population, as well as their effect on pharmacokinetics, effectiveness and safety.⁶⁹

The EPAR for Remsima® and Inflectra®^{3,4} affirm that the immunogenicity profile is well characterised in the 2 clinical trials that have been done. They observe that the immune response to Remicade® and its impact on safety and effectiveness are comparable to the biosimilars; therefore, these data can be extrapolated to other indications for the reference product. In the efficacy analysis, the development of ADA in both drugs was seen to be associated with an increase in the frequency of hypersensitivity reaction related with the infusions. In the RA trial, it was observed that the complete loss of effectiveness (defined as a loss of ACR 20 response) is slightly greater in biosimilars vs Remicade® at week 30 (14% vs 10%) and at week 54 (13% vs 11%); the same is true for the loss of effectiveness and discontinuation of treatment (10% vs 65%). Nonetheless, in the AS study, the opposite was observed.

International Common Denomination or Brand Name

The traceability of biological medicines is a quality element in patient care as it is able to specifically assign potential adverse reactions to each product. Once a biological goes on the market, appropriate systems should be established to ensure traceability.

Currently, biological drugs are assigned the same international common denominator (ICD or INN) as the innovative drug. There are opinions that this nomenclature can hinder correct identification of biosimilars. To avoid this problem, some experts believe that the ICD should include some type of differential identifier for biosimilars. Other sources believe that traceability is not lost even though several biosimilars have the same ICD because each biological has its own commercial name.⁸⁴

The WHO document “Guidelines on Evaluation of Similar Biotherapeutic Products” indicates that, like all biotherapeutic products, biologicals require an appropriate system to guarantee their specific identification (*i.e.*, traceability). National regulatory agencies should provide a legal framework for the proper supervision of pharmacovigilance and guarantee the capability to identify any biotherapeutic product commercialised in their territory with associated adverse reactions. All reports of adverse reactions of any biotherapy product should include, in addition to the ICD, other important indicators, including the product/brand name, manufacturer name, lot number and country of origin.⁸⁵

This is an open debate that should be resolved.^{86,87}

Position of the Spanish Society of Rheumatology on Biosimilars

The Spanish Society of Rheumatology (*Sociedad Española de Reumatología*–SER) has expressed its unwavering commitment to the sustainability of the healthcare system of our country and supports measures that are aimed at ensuring its future without altering the quality of care. In this context, SER considers that the arrival of biosimilars is going to improve the access of rheumatoid arthritis patients to biological therapies.

In this new scenario of increased therapeutic offer of biologicals, the SER considers it essential to preserve the freedom of physicians to prescribe drugs according to individual patient characteristics, while taking into account the economic aspects of these decisions.

The requirements for the commercialisation of biosimilar drugs are very strict. There is much consensus among the main regulatory agencies, which guarantees that the authorisation of a biosimilar is based on the demonstration that its differences from the innovative drug have no relevant effect on the safety and clinical effectiveness of the product.

In agreement with the EMA, the SER considers that biosimilars should not be equated with generic drugs. While a generic drug is an exact chemical copy of its model drug, biosimilars can show potentially relevant differences in their structure with regards to the innovative reference drug because the production processes are not identical.

Regarding biosimilars, the position of SER is as follows:

1. A biosimilar is a biologic drug that is produced according to the specific requirements of the EMA and should have demonstrated similarity with its reference drug for quality, biological activity, safety and effectiveness in double-blind, randomised, direct comparison clinical trials.
2. The choice of either an innovative reference drug or its biosimilar is the exclusive responsibility of the prescribing physician.
3. Biosimilar drugs are not generic versions of their reference drugs, so they are not substitutable. The substitution of a biological with a biosimilar is a medical decision that should be made exclusively by the prescribing physician and with patient consent.
4. SER understands that, for top-quality care, hospitals should guarantee that all biological drugs and biosimilars that are financed by the healthcare system of our country for the management of

rheumatic diseases should be available in all National Healthcare System hospitals.

5. Since biosimilar drugs are subject to a safety follow-up like that of reference drugs, it is necessary to create specific pharmacovigilance registries. SER has extensive experience in these registries and has offered to perform these safety studies.
6. The traceability of biological medicines is a quality element that allows each specific product and lot to be assigned suspected adverse reactions. Currently, biosimilars are assigned the same ICD as their innovative reference drugs, so prescriptions should be written with Brand names for adequate traceability.
7. In the case that the biological reference drug has more than one indication, the extrapolation of indications should be justified in accordance with EMA standards. If necessary, each authorised indication should be individually demonstrated with double-blind, randomised, direct comparison clinical trials with the reference drug. The demonstration of effectiveness and safety of a biosimilar for a certain indication may not be the same as for a second indication in which the biological reference drug has been shown to be safe and effective.
8. The optimal use of biosimilars requires continuous dialogue and interactions between physicians, pharmacologists and regulatory entities, with the intention of preserving the right to health of patients while offering them safe, effective, quality products.
9. This position of SER will be periodically updated in approximately 2 years' time as new evidence becomes available.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of Interests

Miguel Ángel Abad Hernández has received professional fees for conferences from Abbvie, MSD, Pfizer and Roche, and for scientific consulting from MSD and Abbvie.

José Luis Andreu has received professional fees for conferences from Abbvie, MSD, Pfizer, Roche and UCB, and for scientific consulting from Abbvie, Sanofi and UCB.

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