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SPECIAL ARTICLE

# Spanish Society of Hospital Pharmacy position paper on biosimilar medicines

## Documento de posicionamiento de la Sociedad Española de Farmacia Hospitalaria sobre los medicamentos biosimilares

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**Abstract:** Biological medicines nowadays have a great impact, as they offer treatment for diverse diseases and suppose a high cost for health system. Biosimilar medicines contain a version of an active substance already authorized as an original biotechnological medicine, whose patent has expired, and they comply with the guidelines published by the European Medicines Agency. These guidelines, where biosimilarity criteria are established, guarantee comparability between biosimilar product and reference one. Biosimilars' authorization is carried out through a centralized procedure based on clinical, non-clinical and quality studies. These studies allow the extrapolation of indications, frequently, without carrying out additional analyses. In several European countries, switching between original and biosimilar medicine is considered safe. In Spain, Pharmacy and Therapeutic Committee of hospitals, as consensus bodies among health professionals, are the most suitable bodies to establish the interchangeability criteria in each center. Biosimilar drugs contribute to sustainability and to improvement of the accessibility to medicines. Faced with this situation, Spanish Society of Hospital Pharmacy considers interesting to express its position about biosimilar medicines' strategies. Spanish Society of Hospital Pharmacy, in September 2015, published an information note about biosimilar medicines, in which its role as medicines similar in quality, safety and efficacy to the originals, but at lower cost, was highlighted. Likewise, it was stressed the role of hospital pharmacists within the Pharmacy and Therapeutic Committee of hospitals, where their knowledge for the selection, evaluation and use

of medicines could be useful, in coordination and permanent collaboration with other units or clinical services of hospitals.

**KEYWORDS:** Biosimilars, Biological medicines, Switching, Hospital pharmacist.

**Resumen:** Los medicamentos biológicos actualmente presentan un gran impacto, ya que ofrecen tratamiento para diversas enfermedades y suponen un elevado coste para el sistema sanitario. Los medicamentos biosimilares contienen una versión de una sustancia activa ya autorizada como medicamento biotecnológico original, cuya patente ha caducado, y cumplen con las guías publicadas por la European Medicines Agency, que establecen los criterios de biosimilitud para garantizar la comparabilidad entre el producto biosimilar y el de referencia. La autorización de los biosimilares se realiza mediante un procedimiento centralizado, a través de estudios comparativos clínicos, no-clínicos y de calidad, que permiten la extrapolación de indicaciones, frecuentemente sin realizar estudios adicionales. Algunos países europeos consideran seguro el intercambio entre medicamento original y biosimilar. En España, las Comisiones de Farmacia y Terapéutica hospitalarias, como órganos de consenso entre profesionales sanitarios, se consideran las más adecuadas para establecer los criterios de intercambiabilidad en cada centro. Los biosimilares contribuyen a la sostenibilidad y a la accesibilidad a los medicamentos. Ante esta situación, la Sociedad Española de Farmacia Hospitalaria considera de interés expresar su posicionamiento sobre las estrategias relacionadas con los medicamentos biosimilares. La Sociedad Española de Farmacia Hospitalaria, en septiembre de 2015, publicó una nota informativa sobre los medicamentos biosimilares, en la que destacó su similitud en calidad, seguridad y eficacia respecto a los originales, pero con menor coste. Igualmente, se recalcó el papel del farmacéutico hospitalario en las Comisiones de Farmacia y Terapéutica hospitalarias, donde sus conocimientos son útiles para la selección, evaluación y empleo de los medicamentos, en coordinación y colaboración permanente con los demás servicios clínicos del hospital.

**PALABRAS CLAVE:** Biosimilares, Medicamentos biológicos, Intercambio terapéutico, Farmacéutico hospitalario.

Currently, biological medicines are having a great impact and will continue do so in the near future, due to their potential to offer treatment alternatives for both frequent and rare diseases and due to the costs of these therapies for the health system. The advantages introduced by the emergence of biosimilar medicines include their contribution to sustainability and improved access to both biological and nonbiological medicines. Given this situation, and the fact that their evaluation and marketing process differs from that of other drugs, including generic drugs, the Spanish Society of Hospital Pharmacy (SEFH) considers it of interest to express its position on the strategies to be followed concerning the processes of selecting, evaluating, and implementing these types of medicines in the health care setting.

## Biosimilars: concepts and criteria of the European Medicines Agency

A biosimilar medicinal product is defined as one containing a version of an active substance already authorized as an original biotechnological medicine (reference medicine) in the European Economic Area, whose patent rights have expired, and which complies with the principles established in the European Medicines Agency (EMA) guidelines[2-3]. These publications describe and establish guidelines for the evaluation of a biosimilar, the choice of reference product, and the principles that

establish biosimilarity. The guidelines guarantee the following aspects, among others, concerning the biosimilar medicine:

Comparability between the reference medicine and the biosimilar. Biological medicines are made from living organisms that are naturally variable, and so the active substance of a biological medicine is subject to a degree of interbatch variability, which is inherent to the way they are obtained. The approval of a biosimilar shares the same regulation concerning comparability with the reference medicine as that applied to changes in the manufacturing process of biotechnological drugs (ICH Q5E, November 2004)[4]. The main aim of this regulation is to provide the basic principles governing the comparability of a product, before and after making a change in the manufacturing process. For example, the regulation was applied to each of the 50 times the Remicade® manufacturing process was changed, including 3 high-risk occasions, and each of the 23 times the Mabthera® manufacturing process was changed, including 1 high-risk occasion[5]. This was done to ensure that the active substance obtained was comparable to that before the change in the manufacturing process.

The molecular and biological characteristics of the active substance of a biosimilar must be the same as those of the reference medicine. For example, when an active substance is a protein, the amino acid sequence must be the same.

The biosimilar and biological reference medicine must have the same posology and route of administration.

Any deviation in terms of strength, pharmaceutical formulation, excipients, or presentation must be fully justified and in no case can it compromise safety. Changes that involve an improvement in the efficacy of the biosimilar versus the reference product are incompatible with the biosimilar authorization procedure. However, changes that include improvements in safety (such as decreased impurities or reduced immuno-genicity) should be notified and do not rule out biosimilarity.

## Biosimilar authorization process

The approval of biosimilars in the European Union (EU) is based on a solid legal framework, which was developed in 2004. All medicines produced using biotechnology and those for specific indications, such as cancer, degenerative diseases, and so on, are approved via a centralized procedure, and therefore most biosimilars are approved through the EMA. The EMA has specific regulations on the data required for the authorization of biosimilars, as well as general and specific technical guidelines according to the type of product to be developed. These guidelines are available on the EMA website[6] and each time they are updated a draft is published to which comments are invited. This procedure is therefore based on transparency and communication between regulatory bodies, the pharmaceutical industry, and scientific organizations and associations, which can request changes should they

deem them necessary. If a biosimilar does not fulfil the criteria needed to establish its similarity to the reference medicine, the biosimilar must undergo the same approval process as that of a new medication and will have an active substance with a different name[2].

Biosimilars are approved for marketing when a positive benefit-risk balance has been demonstrated based on proven biosimilarity. Comparative studies are used to establish biosimilarity between the biosimilar and the reference medicine. These studies involve different levels of complexity depending on the medicine[3]:

1st level. Comparative quality studies: These studies are in vitro studies comparing protein structure and biological function using sufficiently sensitive techniques to detect any relevant clinical difference between the biosimilar and the reference medicine.

2nd level. Comparative nonclinical studies: These studies include in vitro pharmacodynamic and toxicology studies on the binding and activation (or inhibition) of physiological targets and their effect on cells. If there are no in vitro models, in vivo studies (in animal models) are conducted.

3rd level. Comparative clinical studies: The objective of these studies is not to demonstrate safety and efficacy in patients, because these aspects have already been demonstrated for the reference medicine. These studies are conducted to confirm biosimilarity or to clarify any questions that were not resolved by the analytical or functional tests. The 3rd level includes the following studies:

-- Pharmacokinetic studies in healthy volunteers (if there are no toxicity issues) and in patients.

-- Pharmacodynamic studies (PD). If available for the reference medicine, PDs provide endpoints by which to compare pharmacodynamic activity. In many cases, pharmacodynamic variables are more sensitive than clinical variables for the purposes of comparison.

-- If PD endpoints are not available to compare drugs, a clinical efficacy trial should be conducted in a homogeneous population to detect any differences in clinical outcomes (the trial should be adequately powered, randomized, parallel-group, preferably double-blind, and use efficacy endpoints). The endpoints should preferably measure the pharmacological activity of the medicine and be less influenced by factors related to the patient or disease. The same equivalence margins are established that are used to compare therapeutic alternatives in equivalence studies. The need for clinical trials, and the number and type to be conducted for the approval of a biosimilar, are determined according to the complexity of the molecule, the availability of PD endpoints that correlate with efficacy, safety issues concerning the reference medicine (possible severity of adverse reactions and immunogenicity), and the possibility of extrapolating to other indications.

## Biosimilars: extrapolation to other indications

Extrapolation to other indications is the responsibility of the EMA. If a medicine proves to be biosimilar to a reference product and has comparable safety and efficacy in one of its indications, these data may be extrapolated to other indications approved for the reference medicine. Given that the mechanism of action, posology, and pharmacokinetics of the biosimilar may vary for each indication, if it is destined for use in different therapeutic areas (e.g. rituximab in rheumatoid arthritis and in follicular lymphoma), additional studies may be needed in each therapeutic area. Safety data can be extrapolated once a similar safety profile has been demonstrated in one of its indications. The extrapolation of the immunogenicity data is not automatic. The data needed for approval include incidence, titre and persistence of antibodies, neutralization assays, assessment of clinical impact, and measures to manage the potential risk of immunogenicity[3]. However, data are routinely extrapolated to other indications when the route of administration of a biological medicine is changed. For example, a presentation of rituximab for subcutaneous administration has recently been marketed.

## Interchangeability of reference medicines and biosimilars

Decisions on interchangeability and substitution are the responsibility of national competent authorities rather than that of the EMA. The EU member states have access to the scientific evaluations conducted by the EMA and to all the data presented in support of its decisions[7]. In line with the previous points on the characteristics and approval process of any biosimilar medicine in the EU, Dutch, Finnish, Scottish, Irish, and German regulatory agencies have presented their position statements on switching biosimilars under the supervision of prescribers[8]. Given the high similarity between the reference medicine and the biosimilar, they consider that there is no evidence to suggest that the immune system would react differently following a switch between the reference medicine and the biosimilar. Therefore, any switch between the two products can be considered safe. Switching must always be conducted under the supervision of the prescriber, with adequate clinical monitoring of the patient, who should be informed of the change and trained in the administration of the new medicine if needed. There is increasingly more evidence in support of switching[9-14].

## Evaluation of biosimilars in reports by the GENESIS group

When the GENESIS group prepares a report on a medicine for which a biosimilar is available, either as the main target of the evaluation or as one of the alternatives to be compared (biosimilar and new), they are analysed as a single drug based on proven biosimilarity. The report identifies each

drug by the active substance, in line with current legislation (Directive 2010/84/EU on pharmacovigilance and Royal Decree 1718/2010). The choice of the final position of the biosimilar and reference medicine is based on efficacy criteria and, in line with the principle of transparency endorsed by the GENESIS group, the laboratories that produce the reference product and the biosimilars are invited to comment on the report.

## The SEFH position statement on biosimilars

Taking into account the foregoing points on biosimilars, the SEFH would like to state its position.

*A strong regulatory framework is available*

The EU pioneered the development of the first regulatory framework for biosimilars that includes general and specific guidelines. This regulatory framework has been recognized by various international organizations such as the FDA and the WHO, which have adopted its key regulatory aspects. The guidelines developed by the EMA guarantee comparability between the reference medicine and the biosimilar and their similarity in molecular and biological terms. The approval of a biosimilar shares the same criterion of comparability with the reference medicine as that applied to changes in the manufacturing process of the original biological medicine. The equivalence margins used in comparative clinical studies of biosimilars are the same as those used to compare alternatives in clinical trials.

*Biosimilars are safe*

The EMA has developed a rigorous safety regulatory system that includes the analysis of immunogenicity of the biosimilar compared to that of the reference medicine. The specific guidelines of the EMA on immunogenicity guarantee that the use of the biosimilar would not entail a greater risk of immunogenicity than that presented by the original if its manufacturing process is modified. As with any biological medicine, biosimilars are subject to the regulations governing comparability that apply when there are changes in the manufacturing process of these medicines. Pharmacovigilance programs that include safety and adverse drug reaction (ADR) reporting should be promoted for any new medication, including biosimilars.

Extrapolation to other indications can be carried out if similarity and comparable safety and efficacy have been demonstrated between the reference drug and the biosimilar in a given indication[3]

As mentioned above, extrapolation to other indications is the responsibility of the EMA. When a medication has proven biosimilarity to a reference product for a certain indication, with comparable safety

and efficacy, its indications can be extrapolated to others approved for the reference medicine. However, given that the mechanism of action, posology, and pharmacokinetics of a medication vary for each indication, when a biosimilar is used in other therapeutic areas, additional clinical efficacy and safety trials may be needed to detect any differences in clinical outcomes in the relevant populations. In most cases safety data can be extrapolated after a similar safety profile has been demonstrated in one indication. The extrapolation of immunogenicity data is not automatic. The data needed for approval include several parameters and measures to manage the potential risk of immunogenicity. Data are routinely extrapolated to other indications when the route of administration of a biological medicine is changed.

Interchangeability between the reference medicine and the biosimilar is increasingly based on better evidence

In Europe, national regulatory agencies are responsible for defining the criteria on interchangeability and substitution. In several countries, these agencies have issued position statements in favour of the interchangeability of biosimilars under the supervision of the prescribing physician and have endorsed the direct exchange of these medicines in the hospital setting. These decisions are based on the high similarity between the reference medicine and the biosimilar. These agencies consider that there is no evidence to suggest that the immune system would react differently following a switch between the reference medicine and the biosimilar. Therefore, any switch between them can be considered safe.

The Pharmacy and Therapeutics Committee of hospitals and the Autonomic Committees play a key role in the evaluation and inclusion of biosimilars in hospitals. As with any other biological medicine, these commissions establish the criteria of use, therapeutic exchange and monitoring

The Pharmacy and Therapeutics Committees (PTC) of hospitals and Autonomic Committees are consensus bodies whose primary function is to promote the rational use of medicines. As with other medicines, these committees are responsible for determining the position of the biosimilar product within the therapeutic arsenal of the hospital and for establishing the appropriate measures to guarantee traceability and ADR reporting (Royal Legislative Decree 1/2015, July 24, approving the revised text of the Law on Guarantees and Rational Use of Medicines and Medical Devices. Chapter III, Article 84). Each PTC establishes whether a biosimilar can be interchanged and the criteria to be applied through the consensus of all interested agents (prescribing physicians, hospital pharmacists, primary care pharmacists, healthcare managers, and patients). Interchangeability in the hospital setting is permitted if it is approved by the PTCs of the hospitals, the Autonomic Committees, and the prescribing physician, who is represented in these Committees.

*The traceability of biosimilar medicines must be guaranteed*

Since biological drugs are made from living organisms, the active substance of a biological medicine can have a degree of variability between batches. As with other biological medicines, in order to guarantee the unambiguous identification and traceability of a prescribed, prepared, dispensed, and administered biosimilar, mechanisms must be established that, while guaranteeing the prescription by active principle, also allow the trademark, batch number, and expiration date of the medicine to be registered[15]. These data should appear in the primary and secondary packaging of the medication and should be included in the patient's medical record. This procedure would be facilitated by the implementation of automated mechanisms. These measures not only guarantee the accurate traceability of medicines, but also ensure pharmacovigilance activities and the safety of them. These aspects should be promoted for any new medicine, including biosimilars.

*Information on biosimilar medicines should be offered*

We consider that the appropriate health authorities should take responsibility for the dissemination of impartial and objective information on biosimilars and promote the mutual transmission of knowledge in this area. In this process, the experience of hospital pharmacists in selecting medicines should be taken into consideration, as well as their experience in passing on information and educating health carers and patients regarding medications. When biosimilar or reference products are interchanged, the patient should be informed and, if needed, trained in the administration of the new drug. Patients should take part in therapeutic decisions that influence their health. To achieve this aim, they require adequate training and information from all the health professionals involved in their treatment.

*Biosimilars support the sustainability of the health system*

The interest of the SEFH in participating in improving access to new drugs and improving the efficiency of the Spanish Health System has been made explicit on many occasions, as evidenced by the position document on access to antineoplastic drugs[16]. The introduction of biosimilars in health care allows pharmaceutical costs to be controlled more efficiently by achieving health outcomes similar to those obtained with reference medicines but at a lower cost. Access to new drugs that provide clinical benefit can be improved by the introduction of biosimilars given their lower costs. The Spanish Law on Public Sector Contracts promotes access to new drugs and contracting through public tender. The acquisition of medicines for state hospitals is subject to public tender in which process biosimilars compete on equal terms with the reference medicines. In some cases (e.g. filgrastim, erythropoietins, and insulins), the change of

medicine in health care practice has not compromised effectiveness or safety, but has been shown to have positive effects on efficiency, leading to marked economic savings for the Spanish Health System[1].

*The hospital pharmacist plays a key role in the pharmacotherapeutic management of biosimilars*

Hospital pharmacists support active and consensual collaboration with all health professionals in the PTC of each health centre or at the regional level in the selection of biosimilar medicines, the transfer of information and knowledge between health professionals and patients, and the establishment of protocols that determine when and under what conditions an original biological is interchangeable with the corresponding biosimilar. As with other medicines, hospital pharmacists will actively participate in pharmacovigilance tasks through the notification of suspected ADRs with biosimilar medicines and in safety programs linked to the registration of new medicines. As with other biological medicines, the hospital pharmacist plays a key role in ensuring traceability during all stages of the use of a biosimilar.

The SEFH is aware that the judicious introduction of biosimilars contributes to improved patient access to biological treatments and to the sustainability of the Health System. The strict authorization procedure conducted by the EMA guarantees the efficacy and safety of biosimilars. The application of this authorization in hospitals must be conducted with transparency under appropriate professional consensus, which is ensured by the fact that the position of these medicines in the therapeutic arsenal is determined by a competent body, such as the PTC.

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