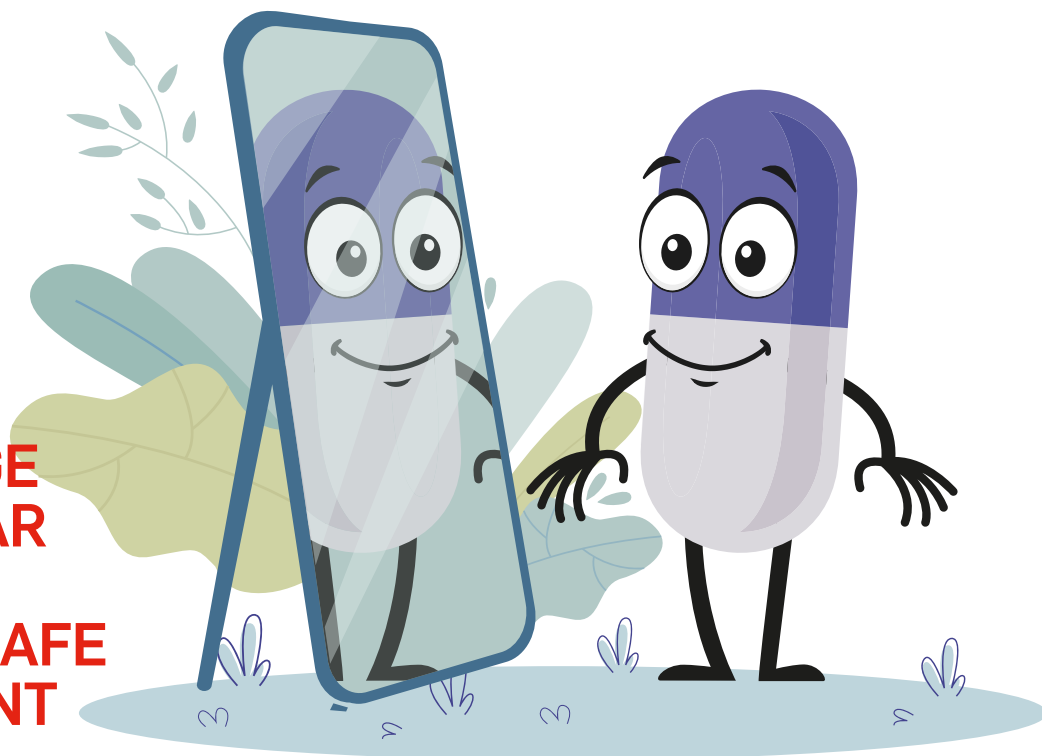




INTERCHANGE OF BIOSIMILAR MEDICINES: EFFECTIVE, SAFE AND EFFICIENT



INTRODUCTION AND OBJECTIVES A biosimilar is a biological medicine that is very similar to another one already marketed in the European Union (EU) whose patent has expired and the differences between which are not clinically significant, in other words do not affect clinical practice. More biosimilars are slowly being developed and, consequently, the experience with their use is increasing. The European Medicines Agency (EMA) considers the biosimilars approved in the EU to be interchangeable, and has signed a statement to reduce the uncertainty regarding interchangeability of biosimilars in clinical practice. The aim of this bulletin is to define the basic concepts, describe the comparability, authorisation and interchangeability processes, evaluate the scientific evidence regarding the efficacy, safety and economic impact of the switch, and to describe the current situation of biosimilars in Spain. **MATERIALS AND METHODS** A literature search was carried out for systematic reviews evaluating the efficacy/effectiveness, safety and immunogenicity or economic impact of the switching in Pubmed and Epistemonikos up to 28/11/2022. Documents from regulatory agencies and other publications of interest were also reviewed. Data regarding the consumption and economic impact of biosimilars in Spain were obtained from the Ministry of Health, and those for Navarre were obtained from the information databases of the Navarre Health Service-Osasunbidea (SNS-O). **RESULTS AND CONCLUSIONS** In general, the evidence available demonstrates that the switching of a reference medicine for a biosimilar does not affect the efficacy, safety or immunogenicity in any significant manner. Some reviews have identified a higher than expected discontinuation rate for the biosimilar after the switch, mainly due to a potential nocebo effect and a lack of confidence of healthcare professionals in the switching. A total of 147 biosimilar medicines are currently marketed in Spain, corresponding to 15 active substances. The introduction of biosimilars in Spain continues to increase, with a penetration of 67.6% having been estimated in a hospital setting in 2021. Similarly, a saving of more than 5 billion € between 2009 and 2022 as a result of their introduction has been estimated.

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Introduction

Since their introduction in 2006, extensive experience in the use of biosimilar medicines has been achieved in almost all the therapeutic areas covered by their indications. However, on occasions, doubts continue to arise in certain situations, especially the switching of these medicines. The aim of this bulletin is to compile the best evidence currently available in this respect to reduce this uncertainty.

Methodology

A literature search for systematic reviews published in Pubmed and Epistemonikos up to 28/11/2022 was carried out. Reviews that evaluated the efficacy/effectiveness, safety and immunogenicity or economic impact of the switch from a reference medicine to a biosimilar, or between biosimilars with the same active substance, were included. Reviews that evaluated the reverse-switch (from a biosimilar medicine to a reference medicine), multiple switching and the impact of the nocebo effect in switching studies were also included.

Similarly, documents from the main regulatory agencies and other publications related to this topic were also reviewed.

Data regarding the consumption and economic impact of biosimilars in Spain were obtained from the Ministry of Health, and those for Navarre were obtained from the information databases of the Navarre Health Service-Osasunbidea (SNS-O).

Concepts

Biological medicine

Biological medicines are those containing active substances extracted or synthesised from a biological source, such as living organisms or cells¹.

Some of these active substances are obtained directly from nature (e.g. albumin), whereas others are synthesised using biotechnological processes.

Biotechnology-derived medicines

Biotechnology-derived medicines are biological medicines that are synthesised using living cells or organisms (mainly yeasts and bacteria) into which genetic material is inserted using recombinant DNA techniques to convert them into producers of the active substance of interest^{2,3}.

Biosimilar medicine

A biosimilar is a biological medicine equivalent to another medicine already marketed in the European Union (EU), whose patent has expired (referred to as the reference medicine), in terms of quality, efficacy and safety^{1,4,5}.

In contrast to conventional medicines synthesised chemically, biosimilar medicines comprise large molecular structures, mainly simple (e.g. insulin, growth hormone) or complex proteins (e.g. coagulation factors, monoclonal antibodies)¹. If the active substance is a protein, both the biosimilar and the reference medicine must contain the same amino acid sequence and same 3D structure (same protein folding), as these are main factors determining biological activity¹.

The active substances in biological medicines exhibit a minor inherent variability (microheterogeneity) as they are obtained from living organisms, which are variable by nature. Similarly, the manufacturing process for biotechnology-derived medicines is more complex than that for conventional medicines synthesised chemically¹. These manufacturing processes are very sensitive, and small changes can lead to a small variability between the molecules of an active substance and between different batches of the same biological medicine, which is why it is often said that "the process is the product"⁴. This means that it is not possible to obtain an exact replica of the molecular microheterogeneity, therefore a biosimilar is not a generic of a reference biological medicine¹.



Biosimilarity

The impact of the variability that a biological medicine candidate for being a biosimilar for a reference medicine may have is evaluated by performing comparability studies with that reference medicine. In order for a biological medicine to be considered biosimilar, this variability must be within an acceptable range to ensure consistent safety and efficacy¹.

The main differences between generic and biosimilar medicines are listed in Table 1^{1,2,4}.

Evaluation of comparability

Comparability is evaluated by way of a stepwise process comprising the following steps¹:

Comparative quality studies:

- Analytical: chemical and physical properties
- Functional: biological/pharmacological activity

Comparative non-clinical studies:

- Pharmacodynamics
- Toxicology

Comparative clinical studies:

- Safety and efficacy
- Pharmacokinetics/pharmacodynamics
- Immunogenicity

The authorisation for a biosimilar medicine is based on existing scientific knowledge regarding the safety and efficacy of the reference medicine acquired during its use in clinical practice. In the case of biosimilar medicines, the aim of clinical trials is to evaluate the biosimilarity with the reference medicine rather than to establish the safety and efficacy, as the latter have already been demonstrated for the reference medicine. As such, the comparative clinical trials are designed to rule out that the possible differences may affect the pharmacokinetics, efficacy or safety, including the immunogenicity, in other words to rule out the existence of clinically relevant differences. To that end, appropriate equivalence margins are selected for the primary efficacy endpoint, with these being specific for the indication studied. These margins represent the largest difference in efficacy that would not affect clinical practice and which, therefore, would not have clinical relevance. The difference observed between the candidate biosimilar medicine and the reference medicine will be considered to be acceptable if it falls within this range¹. In that case, a medicine will be considered to be biosimilar.



Table 1. Main differences between generic and biosimilar medicines.

	Generic	Biosimilar
Synthesis	Chemical synthesis	Extraction or synthesis (biotechnology) from a biological source (living cells or organisms)
	Easy to reproduce	Difficult to reproduce
Molecular structure	Identical to reference medicine	High degree of similarity with reference medicine (microheterogeneity)
	Simple	Complex
	Small molecules, low molecular weight	Large molecules, high molecular weight
Immunogenicity	No	Yes
Comparability	Bioequivalence (equivalence in terms of rate and extent of release of the active substance-pharmacokinetics and pharmacodynamics)	Biosimilarity (similarity in terms of chemical structure, biological function, efficacy, safety and immunogenicity) Clinical equivalence
Need for clinical trials for authorisation	Only bioequivalence clinical trials	Yes (pharmaceutical quality, non-clinical and clinical studies comparing with reference medicine)
Development	Shorter time and lower cost	Longer time and higher cost
Authorisation	National or centralised procedure	Biotechnology-derived biosimilars: Centralised procedure (responsibility of the European Medicines Agency, European Commission)
Extrapolation of indications	Authorisation of all indications approved for the reference medicine without the need for additional clinical data	The efficacy and safety must be justified for each indication (although clinical trials for all indications may not always be required)
Interchangeability (switching)	Automatic	Not automatic (competence of EU Member States)

Procedure for approving biosimilar medicines

Biotechnology-derived medicines (reference medicines or biosimilars) are always authorised by way of a centralised procedure. During this procedure, the scientific committees for medicinal products for human use and safety at the European Medicines Agency (EMA) evaluate the registration dossier. If approval is granted, the European Commission issues a marketing authorisation for the medicinal product, which is applicable to all Member States^{1,6}.

Subsequently, in order to be used by the National Health System (SNS), the Ministry of Health must issue a resolution approving funding by the SNS and, if applicable, the Interministerial Pricing Commission must set the price⁶.

Extrapolation of indications

Extrapolation of indications refers to the authorisation of indications of the reference medicine for the biosimilar in the absence of specific clinical data obtained with the biosimilar medicine. This means that, if a biosimilar presents a degree of comparability in terms of safety and efficacy for a specific therapeutic indication, the data concerning its safety and efficacy may be extrapolated to other indications already authorised for the reference medicine¹. The extrapolation of indications is established by the EMA⁷.

Extrapolation may be accepted if all the scientific evidence available from the comparability studies, establishes the biosimilarity and can address all specific aspects of the extrapolated indication (for example, mode of action, potentially unique safety, or immunogenicity aspects).

In the case of biosimilar medicines, the biosimilarity is evaluated to rule out clinically significant differences

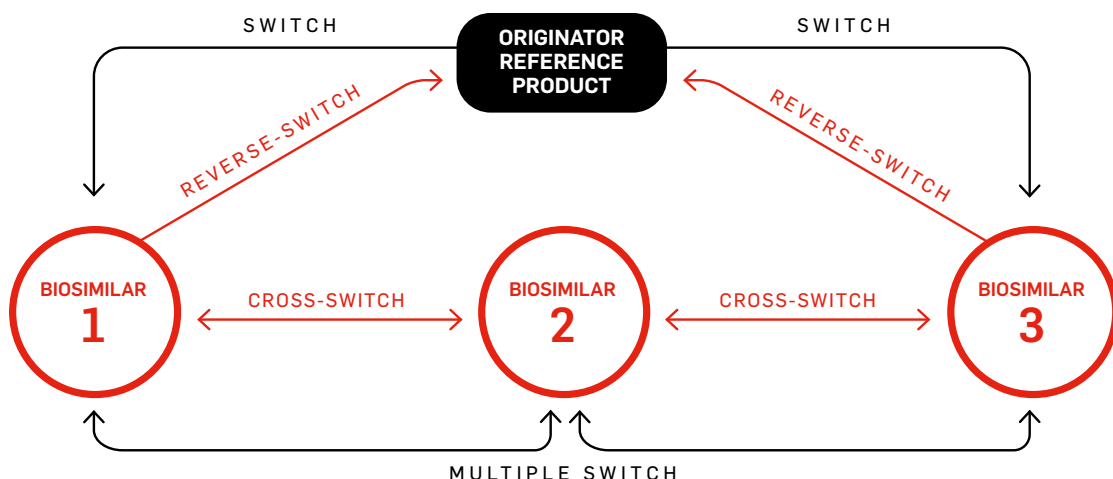
Fewer clinical trials with the biosimilar, or even none in some cases, are required for the extrapolation of certain indications. However, if the data for a specific indication are not directly applicable to the indication to be extrapolated in terms of safety or efficacy (for example if the indication belong to a different therapeutic area where the mode of action, posology or pharmacokinetics vary), additional studies will be required¹.

Interchangeability of biosimilars

This refers to the possibility of changing one medicine for another that is expected to have the same clinical effect. This involves changing a reference medicine for a biosimilar (switching), changing one biosimilar for another (cross-switching) or changing back from the biosimilar to the reference medicine (reverse-switching, retransitioning or switchback).



Figure 1. Switching between biological and biosimilar medicines. Adapted from Solitano et al. 2020⁸



Interchangeability involves a switch, which is when the prescriber decides to exchange one medicine for another with the same therapeutic intent, or a substitution, which is when one medicine is dispensed instead of another equivalent or interchangeable medicine at pharmacy level without consulting the prescriber¹.

Role of the regulatory agencies

The decision regarding whether to allow the interchangeability and replacement of the biological reference medicine by the biosimilar is taken nationally. When the EMA carries out a scientific review for a biosimilar, the evaluations do not include recommendation regarding whether the biosimilar is interchangeable with the reference medicine or, therefore, whether the reference medicine can be switched or substituted with the biosimilar. In the EU, prescribing and advisory practices for drug-prescribing professionals are the responsibility of the Member States, who have the required legal framework and draft regulations, guidelines and recommendations in their areas of competence.

To date, the biosimilars approved by the EMA can be used interchangeably if the national regulatory agency allows this. From a scientific viewpoint, the interchangeability of the biosimilars approved has always been considered to be acceptable, and the agencies have not noticed any warning signs⁹.

The EU medicines regulatory network has recently decided to issue an explicit statement regarding the interchangeability of biosimilars. This is due to the fact that the absence of a clear EU-wide position on interchangeability has been identified as a factor that causes uncertainty among stakeholders on the use of biosimilars in clinical practice. As such, the EMA and the Heads of Medicines Agencies (HMA) consider it necessary to establish a clear and harmonised EU wide position regarding interchangeability to minimise any uncertainty that prescribers may have when deciding to prescribe biological medicines.

Consequently, in September 2022, the EU experts on biosimilar medicines [Biosimilar Medicines Working Party (BMWP)] and the HMA's Biosimilar Working Group have drafted a joint statement in which they explain the rationale for considering the biosimilars approved in the EU as interchangeable from a scientific perspective. This has also been endorsed by the Committee for Medicinal Products for Human Use (CHMP) and the Biologics Working Party (BWP). This joint statement considers that once a biosimilar is approved in the EU it is interchangeable¹⁰.

In addition, they clarify that decisions regarding the substitution (the practice of dispensing one medicine instead of another without consulting the prescriber) are managed by each Member State and are not within the remit of the EMA.

Interchange or switching refers to the change of a reference medicine for a biosimilar

In Spain, the interchangeability is established by the Pharmacy and Therapeutics Commission at the hospitals and/or the Autonomous Community Commissions

The scientific arguments used to support interchangeability are based on the large number of biosimilar medicines that have been exhaustively reviewed and monitored over the past 15 years and which, based on extensive experience in clinical practice, have been shown to be comparable to their reference medicines in terms of efficacy, safety and immunogenicity.

Although the interchangeability of biosimilars has already been put into practice in many Member States, this joint position harmonises the EU approach, provides greater clarity for healthcare professionals and, therefore, helps patients to access biological medicines. Although this statement has no legal force, it is expected that its proposal can be transposed into each State's interchangeability-related legislation.

Indeed, agencies from several European countries have positioned themselves in favour of the interchangeability of biosimilars under the supervision of the prescribing physician, and support the automatic substitution of these medicines in a hospital setting¹¹.



Interchangeability process in Spain

In Spain, Order SCO/2874/2007 of 28 September establishes that biological medicines are not substitutable by the pharmacist¹². Its interpretation has proved controversial as its scope of application is the dispensing of medicines by community pharmacies¹³. Biological medicines are currently mainly prescribed by specialists and are dispensed by hospital pharmacy services. The drug use policy in a hospital setting is determined by interdisciplinary commissions that promote the rational use of the medicines based on current law and best practice, including therapeutic interchangeability, as clarified by the Spanish Agency of Medicines and Medical Devices (AEMPS)¹³. As such, the choice of biosimilars is generally made by the Pharmacy and Therapeutics Commission (CFyT) at hospitals, and by the commissions of the Autonomous Community concerned.

Consequently, interchangeability in a hospital setting in our country is possible if approved by the CFyT and/or Autonomous Community Commission, and together with the prescriber's opinion, which is represented in this collegiate body⁷. These commissions are responsible for establishing the positioning of biosimilar medicines in the hospital's therapeutic arsenal and for establishing measures to guarantee the traceability and monitoring of adverse effects, as is the case for all other medicines.

In Navarre, [Instruction 7/2018](#) issued by the Managing Director of the Navarre Health Service-Osasunbidea (SNS-O) proposes to always use the biological or biosimilar medicine that is most efficient after the tender process, and places the responsibility for monitoring and control of the recommendations approved in the hands of the Medical Directorates of SNS-O hospitals, through pharmacy services.

Evidence regarding the impact of the switching on health outcomes

Evidence from individual studies

The scientific evidence analysing switching may come from extension studies of randomised clinical trials (RCTs), RCTs for approval by regulatory bodies, registry-based observational studies and real-life studies. Figure 2 shows the different study types by design.

RCT extension studies analyse the differences between at least two groups with or without switching, after an initial period in which the efficacy of a biosimilar is evaluated versus the reference medicine in two randomised groups. Although they study the efficacy and safety of switching, they do not usually have sufficient power to reach robust conclusions, given that the primary outcome is based on efficacy or safety in the first period prior to switching.

The EMA considers biosimilars to be interchangeable

The switch does not significantly affect the efficacy, safety or immunogenicity

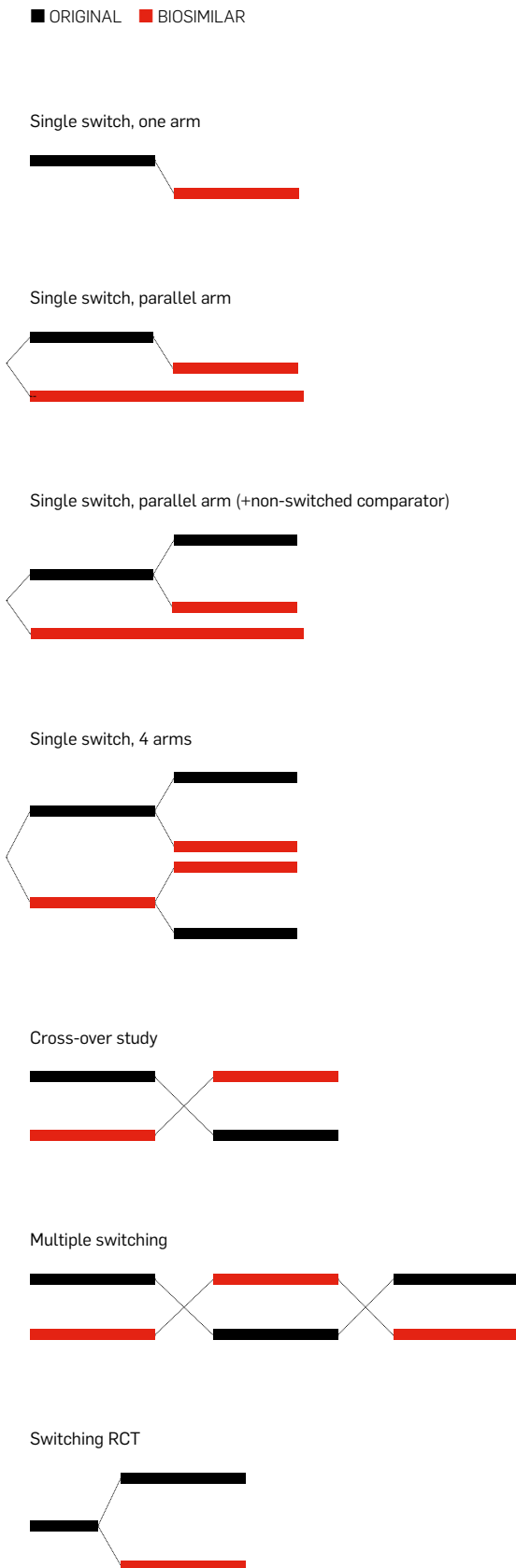
Some compare the safety and efficacy of a maintenance group taking a biosimilar and a group that switches from the reference medicine to the biosimilar, but with no comparator group that continues to take the reference medicine. Other RCT extension studies include three groups, dividing the reference medicine group into two for the extension phase: one group maintaining the reference medicine and the other switching to the biosimilar.

One such example is the study by Ye et al., a randomised, double-blind, phase III, 54-week, non-inferiority study that examined the efficacy and safety of the infliximab biosimilar CT-P¹³ versus the reference medicine in 220 patients with active Crohn's disease¹⁴. Patients were randomised to the biosimilar or the reference medicine and followed-up for 30 weeks. At week 30, participants in each arm were randomised again to continue with treatment or switch, thus leading to a total of four treatment arms. The primary endpoint of the study was to compare the efficacy between the biosimilar and reference medicine in terms of response rate at week 6, with no significant differences being found between the groups. Efficacy was maintained and was similar for all groups at weeks 6, 14, 30 and 54 (after switching), although the study did not have sufficient power to show statistically significant differences in secondary endpoints, including those after week 30, which are the ones that provide information about switching.

Observational studies that analyse the efficacy and safety of switching from a reference medicine to a biosimilar have also been carried out, in either single-arm studies or studies comparing with a comparator group receiving the reference medicine or biosimilar (e.g. cohort studies or studies with historical control).



Figure 2. Types of studies according to their design.



Only one RCT designed specifically to evaluate switching has been found to date:

The NOR-SWITCH study was sponsored by the Norwegian government and was the first randomised, double-blind, phase-IV non-inferiority study to examine the switching from infliximab reference medicine to the biosimilar CT-P13 in 481 patients aged 18 years or older who were clinically stable with infliximab for ≥ 6 months and with any of the following six inflammatory diseases: rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, Crohn's disease and chronic plaque psoriasis¹⁵. This trial had an initial duration of 52 weeks and was designed to evaluate any worsening of the disease (according to specific criteria for each disease) upon switching in comparison with maintenance of the reference medicine.

The change of the reference medicine to the biosimilar was not inferior to continued treatment with the reference medicine, as per a non-inferiority margin of 15%, for the variable worsening of the disease (29.6% versus 26.2%), with a risk difference of -4.4% (95% confidence interval of -12.7 to 3.9), adjusted for diagnosis and duration of treatment. The frequency of patients who presented adverse events or serious adverse events was similar in both treatment groups and there were more patients with infusion-related reactions who suspended the study drug in the reference medicine group than in the biosimilar group. The immunogenicity, serum drug concentrations and appearance of anti-drug antibodies did not differ significantly between both groups.

The strengths of the NOR-SWITCH study were its randomised design and the inclusion of a large number of participants. Some limitations of the NOR-SWITCH study have also been mentioned, including the inclusion of populations with different diseases, thus requiring different definitions of efficacy to be combined, the lack of statistical power to obtain conclusions for each disease, or a non-inferiority limit that could have been stricter¹⁶.

Evidence from systematic reviews

A total of 26 systematic reviews evaluating the efficacy or effectiveness, safety, immunogenicity and costs related to switching of biosimilars have been identified. Six of these reviews analysed the switching of various drugs in numerous indications, eight analysed the switching of anti-TNF α in various immune-mediated inflammatory diseases, six evaluated the switching of anti-TNF α (infliximab and adalimumab) in inflammatory bowel disease, one analysed the switching of anti-TNF α and rituximab in rheumatoid arthritis, and one concerned the switching of rituximab and trastuzumab in oncological diseases and in rheumatoid arthritis. Two reviews that specifically analysed the switching between biosimilars have also been identified: one analysing the reverse-



switching, and one intended to evaluate the possible existence and impact of a placebo effect associated with switching.

The characteristics and findings of the reviews identified are provided in [Annex 1](#). The majority of the evidence available comes from observational studies and, to a lesser degree, from RCTs and extension studies of them.

The drugs for which the strongest evidence regarding the impact of switching is available are anti-TNF α agents, mainly infliximab and, to a lesser extent, adalimumab and etanercept. With regard to the therapeutic indications, the evidence available mainly concerns inflammatory bowel disease.

This evidence mainly concerns switching from the reference medicine to the biosimilar, and very little evidence is available regarding switching between biosimilars, reverse-switching and multiple switching.

In general, the reviews identified conclude that switching from a reference medicine to a biosimilar does not significantly affect the efficacy, as analysed using clinical variables (clinical response, clinical remission, disease activity, worsening before and after switching, etc.), safety, as measured using the incidence of adverse events, or immunogenicity, as measured using anti-drug or neutralising antibody levels. This conclusion can be generalised to the drugs and indications included in the reviews identified, with no drug or therapeutic area or specific indication showing a different pattern having been identified. In inflammatory bowel disease, no differences in clinical efficacy were found when switching was performed during induction or during the maintenance phase.

However, some reviews identified a higher-than-expected discontinuation rate for the biosimilar after switching, with this tending to increase with time. The discontinuation rate for biosimilars varies markedly between the different reviews. For example, the review by Liu et al. (2022), which included 66 real-life studies, identified an annual discontinuation rate for the biosimilar of 21% (95% CI: 15-25)¹⁷. Similarly, the review by Queiroz et al. (2020), which included 30 observational studies evaluating the switching of infliximab in inflammatory bowel disease, identified a discontinuation rate for the biosimilar of 8%, 14% and 21% at 6, 12 and 24 months, respectively¹⁸. In the review by Bakalos et al. (2019), a discontinuation rate for the biosimilar of more than 10% was identified for 11 of the 14 (78.6%) observational studies included (range: 12.2–28.2%)¹⁹. In the RCTs in the review by Numan et al. (2018), a discontinuation rate of 5–33% was identified for the group of patients with switching vs 4–18% for the control group²⁰.

Both the review by Yoo et al. (2018)²¹ and others noted the main reasons for discontinuation of biosimilars as being

The discontinuations of biosimilar medicines were mainly due to a potential placebo effect and a lack of confidence on the part of health professionals

a potential placebo effect and the lack of confidence of healthcare professionals in the switch, with, in general, no objective clinical or biological evidence of inefficacy or safety problems having been identified.

The majority of publications agree that the switching of a reference medicine for a biosimilar can be considered to be safe in clinical practice, and that not performing switching due to hypothetical risks is disproportionate. There is some uncertainty regarding the actual financial impact of switching, as the cost-effectiveness studies found are generally incomplete, and also given the limitations for extrapolating their findings to other settings.

The two reviews concerning switching between biosimilars^{22,23} concluded that this is a safe and effective practice, with no significant differences in terms of disease activity and response, adverse events or immunogenicity having been observed.

The only review concerning reverse-switching found that, after a follow-up of 12 months, approximately 8% of included patients presented transition²⁴. There were fewer returns to the reference medicine in the studies including only patients with stable disease and in those studies implementing additional laboratory monitoring as part of the biosimilar implementation strategy, amongst other aspects.

However, the reviews available concerning reverse-switching and switching between biosimilars only include observational studies, and very little information concerning multiple switching is available. Consequently, it is not currently possible to extract firm conclusions regarding the possible impact of this type of multiple switches on the efficacy and safety, although relevant differences are not expected.



Impact of the nocebo effect in switching clinical trials

The nocebo effect can be considered to involve undesired results arising from an intervention as a result of negative expectations. As such, it is the opposite of the placebo effect. It has been reported for various medicines, although it has not been widely studied in the field of biosimilars.

The higher treatment discontinuation observed with biosimilars in some studies, especially observational ones, with similar efficacy and adverse event rates, suggests the existence of a nocebo effect²⁵.

A systematic review proposed to evaluate whether patients and/or healthcare professionals being aware of having switched from a reference medicine to a biosimilar was associated with an increase in the adverse events susceptible to a nocebo effect²⁶.

The hypothesis was that the incidence of subjective adverse events (for example, malaise) should be higher in non-blinded biosimilar studies, as it would be more likely for them to be affected by a nocebo effect. In contrast, the incidence of objective adverse events (for example analytical values) in open and double-blind studies should be similar, as they would be less likely to be affected by this effect. The authors reviewed studies reporting the efficacy and safety results for the switch of a reference medicine to a biosimilar, and compared the subjective and objective complications in blinded and open studies. They found that in infliximab studies, which represented the majority, the treatment-interruption rates for any reason, due to adverse effects and due to lack of efficacy were, in general, higher in open trials than in double-blind trials. This suggests that an awareness of a switch to a biosimilar may affect patients' perceptions and subsequent results.

It has been suggested that the relationship between the patient and the healthcare professional is a key factor as regards the acceptance of biosimilars, and that this could limit the nocebo effect²⁷. As such, the awareness of both patients and healthcare professionals regarding the efficacy and safety of biosimilars should be promoted. Education about biosimilars should be adapted to each patient, and a positive focus is recommended.

Biosimilars marketed in Spain

As of 24 January 2023, a total of 147 biosimilar medicines, corresponding to 15 active substances, were marketed in Spain.

Their brand names, grouped by active substance and authorisation date, can be seen in table 2²⁸.

The penetration of biosimilars in Spain has resulted in a saving of more than 5 billion € between 2009 and 2022

Evolution of the consumption and economic impact of the introduction of biosimilars

In Spain

The penetration of biosimilars in Spain is very heterogeneous and depends on the active substance, hospital or community pharmacy dispensing, and the Autonomous Community. The consumption of biosimilars is mainly hospital-based. In 2021, a penetration of biosimilars of around 67.6% has been estimated for hospital settings (national average consumption of packages of biosimilar medicines divided by totals for these active substances)²⁹. Those with the highest penetration in this setting are filgrastim (96%), pegfilgrastim (88.2%), infliximab (82.8%), erythropoietin (82.7%) and rituximab (79.1%). Based on the invoicing of drug prescriptions by the SNS, the national average is 18.2%, with the highest penetration being found for enoxaparin (47%) and follitropin alfa (41.1%)²⁹. Marked variability is also seen between Autonomous Communities, with penetrations in a hospital setting ranging from 89% to 40%, and in primary care from 34.4% to 5.2%²⁹.

Some studies regarding the budgetary impact of the introduction of biosimilars have been carried out both internationally and in Spain. In Spain, a cost saving of more than 5 billion € has been estimated for the period 2009–2022, with somatropin, epoetins, infliximab and adalimumab having the greatest influence on that saving given the time they have been on the market, their consumption volumes and their price³⁰. Around a hundred patents for reference biological medicines will expire between 2024 and 2029, and this may lead to the introduction of a large number of new biosimilars over the next few years. As such, biosimilars represent a major opportunity for promoting the sustainability of the SNS by providing the same quality and safety guarantee as the reference medicine.



Table 2. Biosimilar medicines marketed in Spain.

Active substance	Biosimilar medicine	Authorisation date	Reference medicine
Epoetin Zeta	Retacrit®	2007	Eporatio®
Epoetin Alfa	Binocrit®	2008	Eprex®
Filgrastim	Accofil®, Nivestim®, Zarzio®	2009	Neupogen®
Somatropin Recomb.	Omnitrope®	2014	Genotonorm® Humatrope® Norditropin® Nutropinaq® Saizen® Zomacton®
Infliximab	Flixabi®, Inflectra®, Remsima®, Zessly®	2014	Remicade®
Follitropin Alfa	Bemfola®, Ovaleap®,	2014	Gonal-F®
Etanercept	Benepali®, Erelzi®	2016	Enbrel®
Insulin Glargine	Abasaglar®, Semglee®	2016	Lantus®
Rituximab	Rixathon®, Ruxience®, Truxima®	2017	Mabthera®
Enoxaparin Sodium	Enoxaparina Ledraxen®, Enoxaparina Rovi®, Hepaxane®, Inhixa®,	2018	Clexane®
Trastuzumab	Herzuma®, Kanjinti®, Ogivri®, Ontruzant®, Trazimera®, Zercepac®	2018	Herceptin®
Adalimumab	Amgevita®, Hulio®, Hyrimoz®, Idacio®, Imraldi®, Yuflyma®,	2018	Humira®
Pegfilgrastim	Nyvepria®, Pelgraz®, Pelmeg®, Ziextenzo®	2018	Neulasta®
Teriparatide	Livogiva®, Movymia®, Terrosa®	2019	Forsteo®
Bevacizumab	Alymsys®, Aybintio®, Mvasi®, Oyavas®, Zirabev®	2019	Avastin®



The emergence of biosimilars has allowed competitive tendering in standardised public drug purchasing processes, thus resulting in greater efficiency and contributing to the sustainability of the public health system.

The Ministry of Health has launched an action plan to promote the use of market-regulating drugs in the SNS, especially biosimilar and generic medicines, which aims to develop measures to promote competition as a key element for efficiency and to guarantee the use of the most cost-effective drug³¹.

In Navarre

The consumption of biosimilars in Navarre has increased steadily over the past few years, from 7631 packages of biosimilar medicines consumed in 2017 to 39,702 in 2021, with the expenditure thereof increasing from 2,109,825 € in 2017 to 16 million € in 2021 (table and figure 3).

In the hospital setting, the penetration of biosimilar medicines over the past five years has varied widely. The percentages of packages of biosimilar medicines consumed with respect to all medicines with the same active substance can be seen in table and figure 3.

Biosimilar medicines based on monoclonal antibodies (mAb) have generally been introduced slowly and are well accepted for treatment initiation, but there is more reticence as regards switching from the reference medicine, especially in the early years of their marketing. Even so, they have now reached values of more than 70% in almost all cases. In the case of infliximab, the first mAb to have a biosimilar medicine available, essentially all its consumption is currently the biosimilar. In the case of the biosimilar medicine of bevacizumab, the latest to reach the market, it has been the fastest to be introduced.

In the case of filgrastim, pegfilgrastim and erythropoietin, in contrast, the biosimilar medicines were incorporated immediately and have now completely replaced the reference medicines.

Somatropin reference medicine has not been subjected to an active recommendation to switch to a biosimilar medicine for financial criteria.

In the primary care setting, the penetration of biosimilar medicines over the past six years has been lower. The percentages of packages of biosimilar medicines consumed with respect to all medicines with the same active substance can be seen in table 4, figure 4 and figure 5.

Over this period, the use of biosimilars in primary care has increased slowly, with values still lower than 50% compared with the reference medicines in all cases. In the case of insulin glargine and enoxaparin, the use of the biosimilars has remained stable at around 10% compared with the reference medicines, whereas use of the follitropin and teriparatide biosimilars is increasing, although it still remains at around 50%.

The above results in a marked cost-saving, which in Navarre, in 2021, for the drugs with the highest impact in the hospital setting, can be estimated at approximately 9 million €, with bevacizumab making the greatest contribution to this value.



Table and figure 3. Consumption of biosimilars in Navarre 2017–2021.

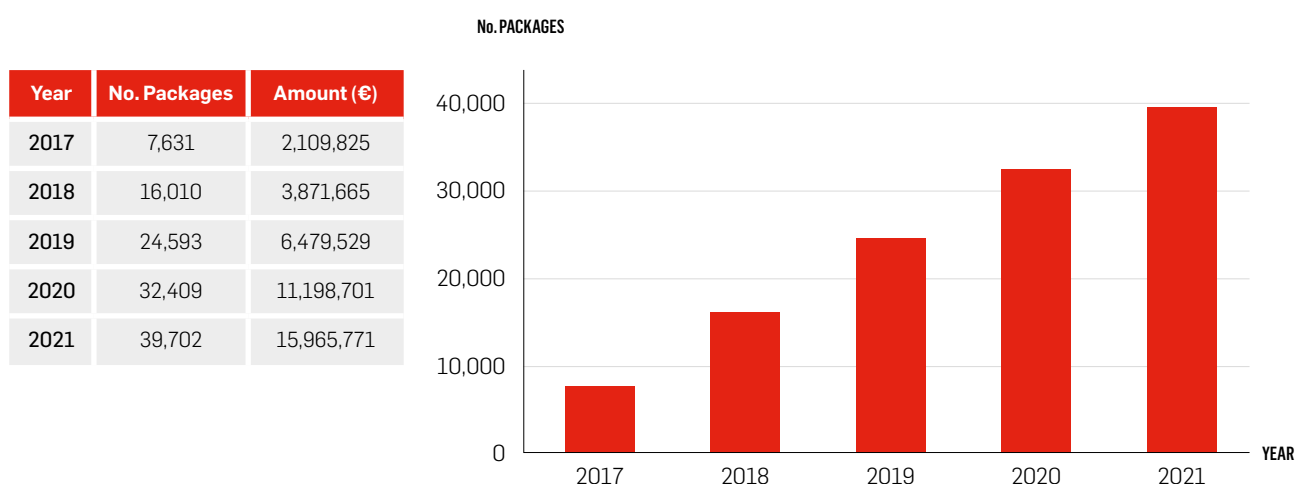


Table 4. Penetration in packages of biosimilars in the hospital setting in Navarre.

Active substance	2017	2018	2019	2020	2021
Filgrastim	100.0%	99.6%	100.0%	100.0%	100.0%
Infliximab	36.0%	44.3%	69.3%	92.2%	95.3%
Erythropoietin	31.0%	98.0%	98.0%	98.6%	98.8%
Somatropin	10.5%	.6%	18.4%	24.8%	26.1%
Insulin glargine	2.8%	0.7%	3.6%	3.8%	3.0%
Etanercept	2.1%	9.6%	45.3%	79.2%	76.7%
Rituximab	0.0%	0.0%	43.8%	74.8%	83.5%
Pegfilgrastim	—	0.0%	70.0%	100.0%	100.0%
Trastuzumab	—	0.0%	37.3%	45.8%	71.8%
Adalimumab	—	0.0%	0.3%	30.6%	51.7%
Bevacizumab	—	—	0.0%	6.4%	90.1%
Teriparatide	—	—	0.0%	0.0%	28.6%

Figure 4. Penetration in packages of biosimilar mAbs and related drugs in the hospital setting in Navarre.

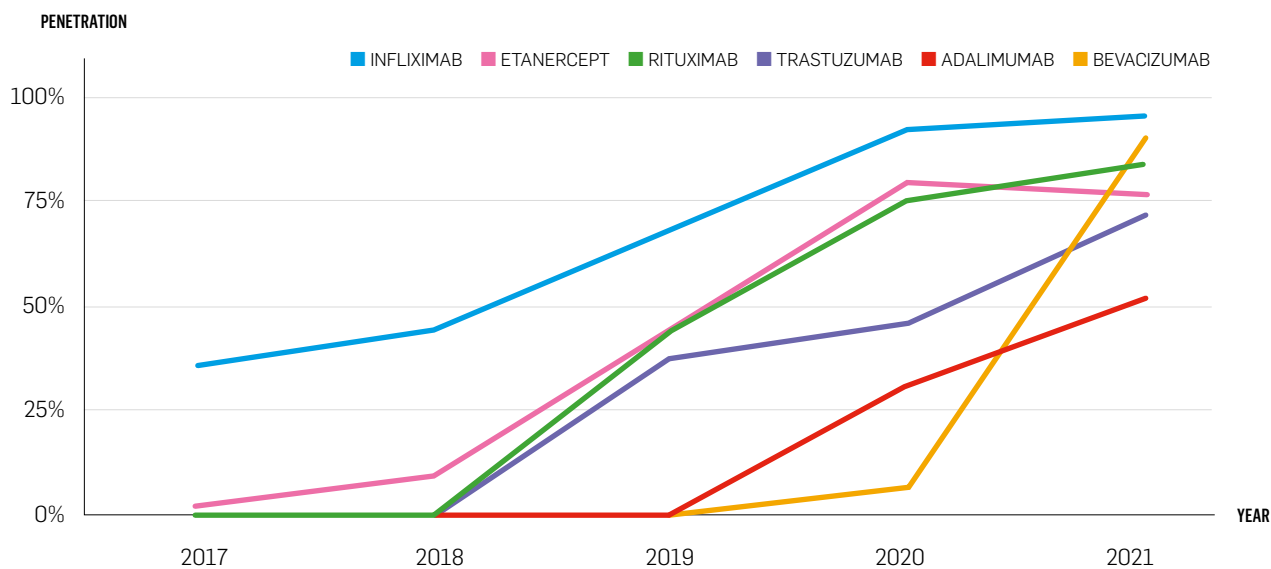


Figure 5. Penetration in packages of other biosimilars in the hospital setting in Navarre.

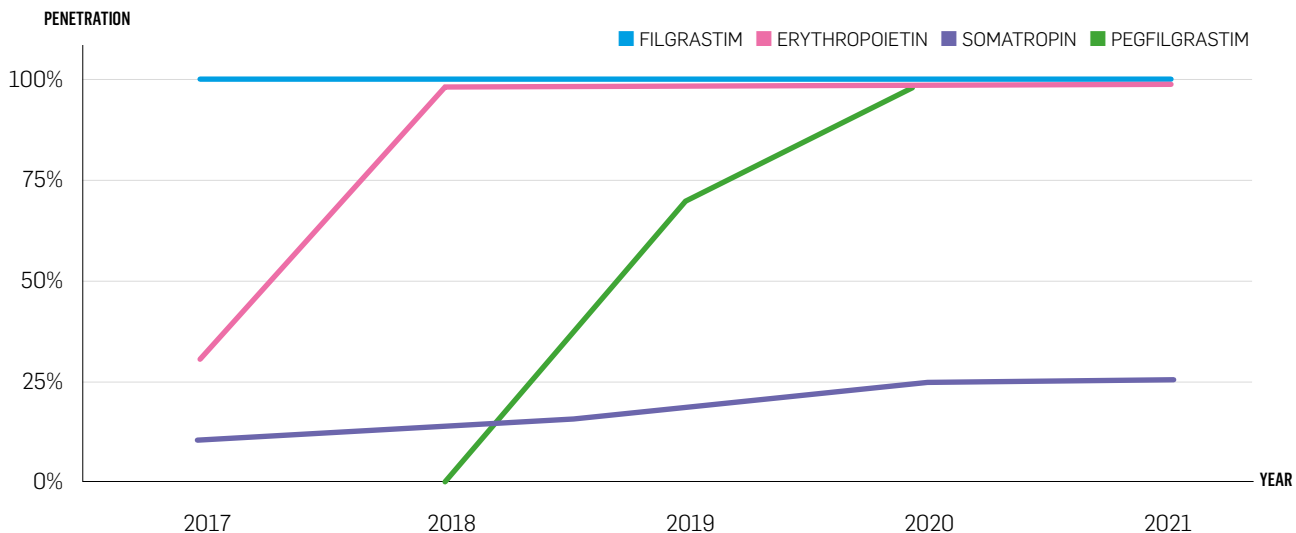


Table 5. Penetration in packages of biosimilars in the primary care setting in Navarre.

Active substance	2017	2018	2019	2020	2021
Insulin glargine	5.5 %	6.4 %	6.6 %	6.6 %	6.7 %
Follitropin	1.3 %	1.2 %	10.7 %	18.9 %	35.2 %
Enoxaparin	—	0.3 %	6.0 %	9.7 %	12.7 %
Teriparatide	—	—	14 %	21.8 %	44.1 %



Figure 6. Penetration in packages of biosimilars in the primary care setting in Navarre.

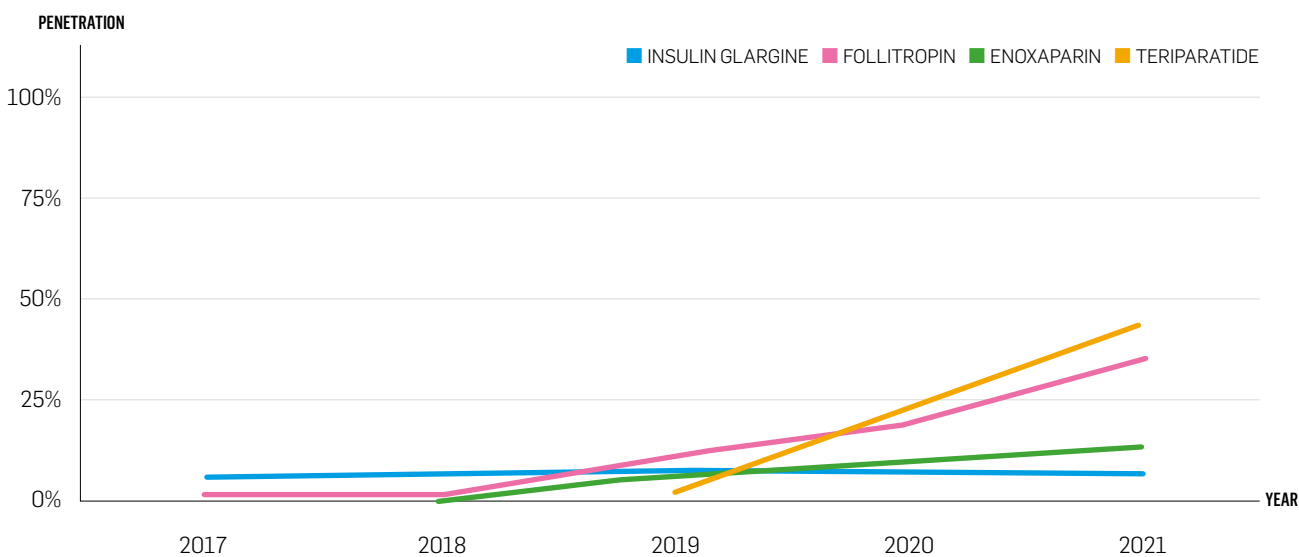


Table 6. Estimated saving with the use of the biosimilars with the greatest impact in the hospital setting in Navarre in 2021.

Active substance	Saving (€)
Bevacizumab	3,081,245
Infliximab	1,814,896
Adalimumab	1,252,320
Trastuzumab	1,098,176
Rituximab	918,694
Etanercept	702,038
Total	8,867,369



Annex 2

Biological medicine and biosimilar medicine

BIOLOGICAL MEDICINE AND BIOSIMILAR MEDICINE. WHO IS WHO?



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–What is a biological medicine and a biosimilar medicine?
 Biological medicines are those obtained from living cells and organisms. A biosimilar is a medicine equivalent to another biological medicine that already exists.

–Is a biosimilar medicine the same as a generic medicine?

A generic medicine contains exactly the same active substance as the reference medicine. Biosimilar medicines are very similar versions of the reference medicines, although they are not identical. In both cases, the safety and efficacy are similar to those of the reference medicine.

–Is there any difference in quality, safety and efficacy between a reference medicine and a biosimilar medicine?

No, as a biosimilar medicine must meet the same quality, safety and efficacy standards as its reference medicine.

–If I start a biological treatment, is there any difference between doing so with the reference medicine or with a biosimilar in terms of quality, safety and efficacy?

No, as both medicines (reference and biosimilar) are biological medicines subjected to the same quality, efficacy and safety requirements by the regulatory agencies.

–Can a biological medicine be changed for another?

Yes. Your doctor, based on his/her own criteria and having informed you beforehand, may change one biological medicine for another with the same therapeutic goal.

–Must the doctor inform me of a change of biological medicine?

Yes. As is the case when starting any treatment, your doctor will inform you about the new treatment, its administration and any other relevant information.

Biosimilar medicines contribute to the sustainability of the public health system while maintaining treatment safety and efficacy.

–Is the safety of biosimilar medicines monitored once they are marketed?

Yes. Safety is controlled permanently by official drug regulatory agencies. That is why it is important for you to notify any adverse reaction to your doctor, pharmacist or nurse, or directly via <https://www.ram.navarra.es>. If possible, save the package, as it is useful when notifying the adverse reaction.

–Are the side-effects of the reference medicine and the biosimilar medicine the same?

Yes. The possible side-effects of a reference biological medicine and its biosimilar are the same.

–What is the best way to obtain information about biosimilar medicines?

The main source of information should be your doctor, pharmacist or nurse.



Conclusions

A biosimilar is a biological medicine that is very similar to another medicine already marketed in the European Union (EU) whose patent has expired.

In the case of biosimilars, studies evaluate the biosimilarity with the reference medicine.

To be considered biosimilar, the existence of clinically relevant differences must be ruled out.

Biotechnology-derived medicines are authorised by the EMA through a centralised procedure.

The extrapolation of indications is established by the EMA.

Interchange or switching refers to the change of a reference medicine for a biosimilar.

Interchange or switching is the competence of the EU Member States.

In Spain, the interchangeability is established by the Pharmacy and Therapeutics Commission at the hospitals and/or the Autonomous Community Commissions.

The EMA considers biosimilars approved in the EU to be interchangeable.

In general, the evidence available shows that switching does not significantly affect the efficacy, safety or immunogenicity.

In the reviews identified, discontinuation of biosimilars was mainly due to a potential nocebo effect and a lack of confidence on behalf of healthcare professionals.

In the Spanish hospital setting, a penetration of biosimilars of 67.6% has been estimated for 2021.

It is estimated that the introduction of biosimilars in Spain has represented a cost-saving of more than 5 billion € between 2009 and 2022.

Biosimilars contribute to the sustainability of the public health system while maintaining treatment efficacy and safety.



References

- EMA, Comisión Europea. Los biosimilares en la UE: Guía informativa para profesionales sanitarios. Published 2019. https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_es.pdf
- Larrayoz B. Medicamentos biosimilares. Concepto, regulación y controversia en su utilización. BIT Navarra 2015;23(3).
- Herrero Ambrosio A. Biosimilares: situación regulatoria para su autorización. Farm Hosp. 2010;34(Supl 1):16-18.
- Medicamentos biosimilares: aclarando conceptos. INFAC. 2016;24(3).
- ¿Qué es un medicamento biosimilar?. BioSim. <https://www.biosim.es/que-es-un-medicamento-biosimilar>
- Guía de biosimilares para farmacéuticos. BioSim. 2020. www.biosim.es/documentos/GUIA-BIOSIMILARES-FARMA-CEUTICOS.pdf
- Martínez-López de Castro N, Matilla-Fernández M, Fraga-Fuentes M, Mangues-Bafalluy I, Asensi-Díez R, Cajaraville-Ordoñana G. Grupos GENESIS y GEDEFO y proyecto MAPEX de la SEFH. Documento de posicionamiento de la Sociedad Española de Farmacia Hospitalaria sobre los medicamentos biosimilares. Farm Hosp. 2018;42(4):180-183.
- Solitano V, D'Amico F, Fiorino G, Peyrin-Biroulet L, Danese S. Biosimilar switching in inflammatory bowel disease: from evidence to clinical practice. Expert Rev Clin Immunol. 2020;16(10):1019-1028. doi:10.1080/1744666X.2021.1826311
- Kurki P, van Aerts L, Wolff-Holz E, Giezen T, Skibeli V, Weise M. Interchangeability of Biosimilars: A European Perspective. BioDrugs. 2017;31(2):83-91. doi:10.1007/s40259-017-0210-0
- EMA - HMA. Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU. 2022. https://www.ema.europa.eu/en/documents/public-statement/statement-scientific-rationale-supporting-interchangeability-biosimilar-medicines-eu_en.pdf
- Medicines for Europe. Positioning statements on physician-led switching for biosimilar medicines (October 2021). https://www.medicinesforeurope.com/docs/20210825_FINAL_Overview_of_switching_positions.pdf
- Orden SCO/2874/2007, de 28 de septiembre, por la que se establecen los medicamentos que constituyen excepción a la posible sustitución por el farmacéutico con arreglo al artículo 86.4 de la Ley 29/2006, de 26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios.
- Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Medicamentos no sustituibles. <https://www.aemps.gob.es/medicamentos-de-uso-humano/medicamentos-no-sustituibles/>
- Ye BD, Pesegova M, Alexeeva O, et al. Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: an international, randomised, double-blind, phase 3 non-inferiority study. Lancet. 2019;393(10182):1699-1707. doi:10.1016/S0140-6736(18)32196-2
- Jørgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017;389(10086):2304-2316. doi:10.1016/S0140-6736(17)30068-5
- Gisbert JP, Chaparro M. Switching from an originator anti-TNF to a biosimilar in patients with inflammatory bowel disease: Can it be recommended? A systematic review. Gastroenterol Hepatol. 2018;41(6):389-405. doi:10.1016/J.GASTROHEP.2018.04.005
- Liu Y, Skup M, Yang M, Qi CZ, Wu EQ. Discontinuation and Switchback After Non-Medical Switching from Originator Tumor Necrosis Factor Alpha (TNF) Inhibitors to Biosimilars: A Meta-Analysis of Real-World Studies from 2012 to 2018. Adv Ther. 2022;39(8):3711-3734. doi:10.1007/s12325-022-02173-7
- Queiroz NSF, Saad-Hossne R, Fróes R de SB, et al. Discontinuation rates following a switch from a reference to a biosimilar biologic in patients with inflammatory bowel disease: a systematic review and meta-analysis. Arq gastroenterol. 2020;57(3):232-243. <http://www.epistemonikos.org/documents/43be1cde0bec62d6d60495d5576a0b0c2921185f>
- Bakalos G, Zintzaras E. Drug Discontinuation in Studies Including a Switch From an Originator to a Biosimilar Monoclonal Antibody: a Systematic Literature Review. Clin Ther. 2019;41(1):155. doi:10.1016/j.clinthera.2018.11.002
- Numan S, Faccin F. Non-medical Switching from Originator Tumor Necrosis Factor Inhibitors to Their Biosimilars: Systematic Review of Randomized Controlled Trials and Real-World Studies. Adv Ther. 2018;35(9):1295-1332. doi:10.1007/s12325-018-0742-9
- Yoo DH, Choe JY, Shim SC, Suh CH. Switching to biosimilars in the treatment of rheumatic diseases. Expert Rev Clin Immunol. 2018;14(7):557-571. doi:10.1080/1744666X.2018.1490178
- Allocati E, Godman B, Gobbi M, Garattini S, Banzi R. Switching Among Biosimilars: A Review of Clinical Evidence. Front Pharmacol. 2022;13:917814. doi:10.3389/fphar.2022.917814
- Cohen HP, Hachaichi S, Bodenmueller W, Kavien TK, Danese S, Blauvelt A. Switching from One Biosimilar to Another Biosimilar of the Same Reference Biologic: A Systematic Review of Studies. BioDrugs. 2022;36(5):625-637. doi:10.1007/s40259-022-00546-6
- Meijboom RW, Gardarsdottir H, Egberts TCG, Giezen TJ. Patients Retransitioning from Biosimilar TNF α Inhibitor to the Corresponding Originator After Initial Transitioning to the Biosimilar: A Systematic Review. BioDrugs. 2022;36(1):27-39. doi:10.1007/s40259-021-00508-4
- Kristensen LE, Alten R, Puig L, et al. Non-pharmacological Effects in Switching Medication: The Nocebo Effect in Switching from Originator to Biosimilar Agent. BioDrugs. 2018;32(5):397-404. doi:10.1007/s40259-018-0306-1



26. Odinet JS, Day CE, Cruz JL, Heindel GA. The Biosimilar Nocebo Effect? A Systematic Review of Double-Blinded Versus Open-Label Studies. *J Manag care Spec Pharm*. 2018;24(10):952-959. doi:10.18553/JMCP.2018.24.10.952
27. Pouillon L, Danese S, Hart A, et al. Consensus report: clinical recommendations for the prevention and management of the nocebo effect in biosimilar-treated IBD patients. *Aliment Pharmacol Ther*. 2019;49(9):1181-1187. doi:10.1111/apt.15223
28. Centro de Información Online de Medicamentos de la AEMPS (CIMA). Agencia Española de Medicamentos y Productos Sanitarios (AEMPS).
29. Oferta y consumo de medicamentos biosimilares. Años 2017-2021. Dirección General de Cartera Común de Servicios del SNS y Farmacia.
30. Análisis de impacto presupuestario de los medicamentos biosimilares en el Sistema Nacional de Salud de España (2009-2022). <https://www.biosim.es/analisis-de-impacto-presupuestario-de-los-medicamentos-biosimilares-en-el-sistema-nacional-de-salud-de-espana-2009-2022/>
31. Ministerio de Sanidad. Plan de acción para fomentar la utilización de los medicamentos reguladores del mercado en el Sistema Nacional de Salud: medicamentos biosimilares y medicamentos genéricos. <https://www.sanidad.gob.es/profesionales/farmacia/pdf/PlanAccionSNSmedicamentos-ReguladoresMercado.pdf>
32. Barbier L, Ebbers HC, Declerck P, Simoens S, Vulto AG, Huys I. The Efficacy, Safety, and Immunogenicity of Switching Between Reference Biopharmaceuticals and Biosimilars: A Systematic Review. *Clin Pharmacol Ther*. 2020;108(4):734-755. doi:10.1002/cpt.1836
33. Cohen HP, Blauvelt A, Rifkin RM, Danese S, Gokhale SB, Woollett G. Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes. *Drugs*. 2018;78(4):463-478. doi:10.1007/s40265-018-0881-y
34. Inotai A, Prins CPJ, Csanádi M, Vitezic D, Codreanu C, Kaló Z. Is there a reason for concern or is it just hype?—A systematic literature review of the clinical consequences of switching from originator biologics to biosimilars. *Expert Opin Biol Ther*. 2017;17(8):915-926. doi:10.1080/14712598.2017.1341486
35. Liu Y, Yang M, Garg V, Wu EQ, Wang J, Skup M. Economic Impact of Non-Medical Switching from Originator Biologics to Biosimilars: A Systematic Literature Review. *Adv Ther*. 2019;36(8):1851-1877. doi:10.1007/s12325-019-00998-3
36. McKinnon RA, Cook M, Liauw W, et al. Biosimilarity and Interchangeability: Principles and Evidence: A Systematic Review. *BioDrugs*. 2018;32(1):27-52. doi:10.1007/s40259-017-0256-z
37. Hillhouse E, Mathurin K, Bibeau J, et al. The Economic Impact of Originator-to-Biosimilar Non-medical Switching in the Real-World Setting: A Systematic Literature Review. *Adv Ther*. 2022;39(1):455-487. doi:10.1007/s12325-021-01951-z
38. Ebbers HC, Pieper B, Issa A, Addison J, Freudensprung U, Rezk MF. Real-World Evidence on Etanercept Biosimilar SB4 in Etanercept-Naive or Switching Patients: A Systematic Review. *Rheumatol Ther*. 2019;6(3):317-338. doi:10.1007/s40744-019-00169-4
39. Feagan BG, Lam G, Ma C, Lichtenstein GR. Systematic review: efficacy and safety of switching patients between reference and biosimilar infliximab. *Aliment Pharmacol Ther*. 2019;49(1):31-40. doi:10.1111/apt.14997
40. García-Beloso N, Altabás-González I, Samartín-Ucha M, et al. Switching between reference adalimumab and biosimilars in chronic immune-mediated inflammatory diseases: A systematic literature review. *Br J Clin Pharmacol*. 2022;88(4):1529-1550. doi:10.1111/bcp.15101
41. Lauret A, Moltó A, Abitbol V, et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. *Semin Arthritis Rheum*. 2020;50(6):1449-1456. doi:10.1016/j.semarthrit.2020.02.007
42. Mezones-Holguin E, Gamboa-Cardenas RV, Sanchez-Felix G, et al. Efficacy and safety in the continued treatment with a biosimilar drug in patients receiving infliximab: A systematic review in the context of decision-making from a Latin-American country. *Front Pharmacol*. 2019;10(November):1-15. doi:10.3389/fphar.2019.01010
43. Bernard EJ, Fedorak RN, Jairath V. Systematic Review: Non-medical Switching of Infliximab to CT-P13 in Inflammatory Bowel Disease. *Dig Dis Sci*. 2020;65(8):2354-2372. doi:10.1007/s10620-019-06036-0
44. Dipasquale V, Cicala G, Spina E, Romano C. Biosimilars in Pediatric Inflammatory Bowel Diseases: A Systematic Review and Real Life-Based Evidence. *Front Pharmacol*. 2022;13(March):1-9. doi:10.3389/fphar.2022.846151
45. Milassin Á, Fábíán A, Molnár T. Switching from infliximab to biosimilar in inflammatory bowel disease: overview of the literature and perspective. *Therap Adv Gastroenterol*. 2019;12:1-11. doi:10.1177/1756284819842748
46. Declerck P, Bakalos G, Zintzaras E, Barton B, Schreitmüller T. Monoclonal Antibody Biosimilars in Oncology: Critical Appraisal of Available Data on Switching. *Clin Ther*. 2018;40(5):798-809.e2. doi:10.1016/j.clinthera.2018.03.018





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