

Biosimilars in the EU

Information guide for healthcare professionals

Prepared jointly by the European Medicines Agency
and the European Commission



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Foreword

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Biological medicines, often produced by cutting-edge biotechnology, have transformed the outlook for patients with many chronic and often disabling conditions. An increasing number of biological medicines are 'biosimilars' - medicines highly similar in all essential aspects to an already approved biological medicine.

The EU has pioneered the regulation of biosimilar medicines by establishing a solid framework for their approval and by shaping biosimilar development globally. Since the EU approved the first biosimilar in 2006, healthcare professionals have gained increasing experience with their use. Today biosimilars are an integral part of the effective biological therapies available in the EU, supported by adequate safeguards protecting patient safety.

As healthcare professionals are at the forefront of patients' care, it is vital that they have access to reliable information on these medicines: what they are and what scientific principles support their clinical development, approval and safety monitoring. This guide has therefore been prepared with the important objective of providing healthcare professionals with reference information on both the science and regulation underpinning the use of biosimilars.



Contributors

This guide has been prepared by the European Medicines Agency in collaboration with the European Commission and scientific experts from EU Member States.

Information needs and feedback from EU healthcare professionals' organisations have been sought throughout the preparation of this document.

Summary

- ▶ Since the EU approved the first biosimilar medicine ('biosimilar') in 2006, the EU has pioneered the regulation of biosimilars. Over the past 10 years, the EU has approved the highest number of biosimilars worldwide, amassing considerable experience of their use and safety.
- ▶ The evidence acquired **over 10 years of clinical experience** shows that biosimilars approved through EMA can be used as **safely and effectively** in all their approved indications as other **biological medicines**.
- ▶ A biosimilar is a biological medicine highly similar to another biological medicine already approved in the EU (the so-called 'reference medicine').
- ▶ Because biosimilars are made in living organisms there may be some minor differences from the reference medicine. These minor differences are not clinically meaningful, i.e. **no differences are expected in safety and efficacy**. Natural variability is inherent to all biological medicines and strict controls are always in place to ensure that it does not affect the way the medicine works or its safety.
- ▶ Biosimilars are approved according to the **same standards of pharmaceutical quality, safety and efficacy** that apply to all biological medicines approved in the EU.
- ▶ The aim of biosimilar development is to demonstrate biosimilarity - **high similarity in terms of structure, biological activity and efficacy, safety and immunogenicity profile**.
- ▶ By demonstrating biosimilarity, a biosimilar can rely on the safety and efficacy experience gained with the reference medicine. This avoids unnecessary repetition of clinical trials already carried out with the reference medicine.
- ▶ Demonstration of biosimilarity relies on comprehensive comparability studies with the reference medicine.
- ▶ If a biosimilar is highly similar to a reference medicine, and has comparable safety and efficacy in one therapeutic indication, safety and efficacy data may be extrapolated to other indications already approved for the reference medicine. **Extrapolation** needs to be **supported by all the scientific evidence** generated in comparability studies (quality, non-clinical and clinical).
- ▶ Extrapolation is not a new concept but a well-established scientific principle used routinely when biological medicines with several approved indications undergo major changes to their manufacturing process (e.g. to introduce a new formulation). In most of these cases, clinical trials are not repeated for all indications and changes are approved based on quality and in vitro comparability studies.
- ▶ All indications of biological medicines (including biosimilars) have been granted based on sound scientific evidence.
- ▶ Safety of biosimilars is monitored through pharmacovigilance activities, in the same way as for any other medicine. There is no specific safety requirement applicable only to biosimilars because of their different development route.

- ▶ Over the last 10 years, the EU monitoring system for safety concerns has **not identified any relevant difference in the nature, severity or frequency of adverse effects** between biosimilars and their reference medicines.
- ▶ Biosimilar competition can offer advantages to EU healthcare systems, as it is expected to improve patients' access to safe and effective biological medicines with proven quality.
- ▶ EMA does not regulate **interchangeability, switching and substitution** of a reference medicine by its biosimilar. These fall within the remit of EU Member States.



Biological medicines: overview

Biological medicines ('biologics') contain active substances from a biological source, such as living cells or organisms. Biological medicines are well established in clinical practice and in many cases they are indispensable for the treatment of serious and chronic conditions such as diabetes, autoimmune diseases and cancers.

Key features of biological medicines

Most biological medicines in current clinical use contain active substances made of proteins. These can differ in size and structural complexity, from simple proteins like insulin or growth hormone to more complex ones such as coagulation factors or monoclonal antibodies (figure 1).

Biomanufacturing strictly regulated

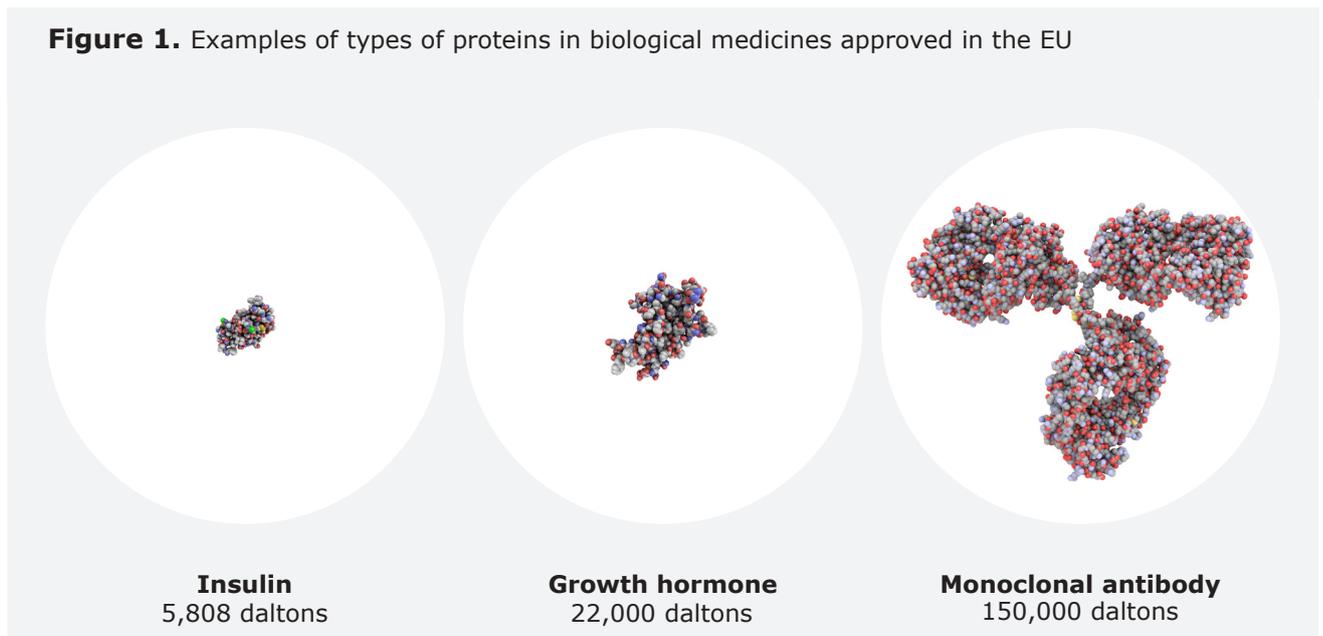
The manufacture of biological medicines tends to be more complex than for chemically-derived molecules. Most biological medicines are made by biotechnology, often using sophisticated

cell systems and recombinant DNA technology. The EU legislation imposes strict requirements for the manufacture of all medicines:

- ▶ EU manufacturers must hold a manufacturer's license and are legally obliged to comply with Good Manufacturing Practice (GMP), the agreed standards to obtain a medicine with proven quality.
- ▶ National regulatory authorities in the EU regularly inspect manufacturing sites for compliance with GMP requirements.
- ▶ If some manufacturing steps take place outside the EU, then non-EU manufacturers, importers and wholesale distributors are obliged to follow the same strict requirements and are also regularly inspected.

For biological medicines, some of the GMP requirements have been adapted to take into account their specific nature (e.g. use of appropriate aseptic techniques, refrigeration and other storage conditions, stability, transport etc.).

Figure 1. Examples of types of proteins in biological medicines approved in the EU



Large molecular structure

Compared with small chemical substances, biological medicines consist of large and often complex molecular structures. Sophisticated analytical methods (e.g. peptide mapping, mass spectrometry and assays in cells) are used to study their physicochemical and functional properties such as molecular structure, protein modifications and biological activity.

Inherent degree of variability

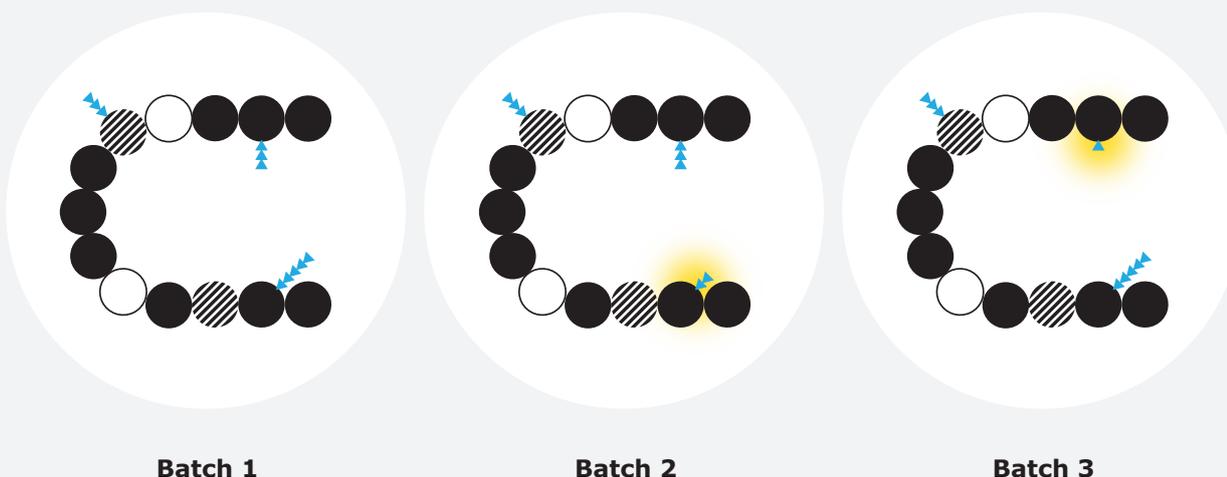
Biological medicines are made by living organisms, which are naturally variable. Thus, the active substance in the final biological medicine can have an inherent degree of minor variability

(‘microheterogeneity’). This minor variability must fall within the acceptable range to ensure consistent safety and efficacy. This is done by adjusting the manufacturing process to guarantee that the active substance fits into the desired specifications range.

This degree of minor variability can be present within or between batches of the same biological medicine (figure 2), particularly when manufacturing processes are modified during the commercial life of the medicine (e.g. increasing production scale). Strict controls are always applied to ensure that despite this variability there is batch-to-batch consistency and that the differences do not affect safety or efficacy. In practice, variability (within a batch or batch-to-batch) is very low when using the same manufacturing process.

Figure 2. Example of variability between different batches of a biological medicine

Consecutive batches of the same biological medicine may show a small degree of variability (yellow shadow) within the accepted ranges, for example in glycosylation (sugar molecules attached to the protein, which are represented by small blue triangles). The amino acid sequence (represented by circles) and biological activity of the protein remain the same in all batches even when these minor differences in sugar chains are present.



Strict control of the quality of biological medicines

The quality of all medicines (biological and non-biological) approved in the EU is rigorously proven. For biological medicines, this includes studying their specific physicochemical properties, biological activity, purity, sterility and stability to ensure that all the required standards are met before batches are released for marketing.

Natural variability is inherent to all biological medicines and strict controls are always in place during manufacturing to ensure that it does not affect the way the medicine works or its safety.

Potential immunogenicity

The immune system has the ability to recognise foreign proteins and react against them. Biological medicines usually cause no or only a limited immune response (e.g. transient appearance of antibodies). Adverse reactions of an immune nature (e.g. infusion-related reactions or injection-site reactions) are normally not severe. Rarely, however, an immune reaction against a biological medicine could be serious and life-threatening.

Also, antibodies directed against the biological medicine ('anti-drug antibodies' or ADAs) could neutralise the medicine's activity and reduce its efficacy. Thus, potential immunogenicity needs always to be evaluated for all biological medicines.



Biosimilar medicines: definition and specific features

A biosimilar medicine ('biosimilar') is a medicine highly similar to another biological medicine already marketed in the EU (the so-called 'reference medicine')^{1, 2}. Companies can market approved biosimilars once the period of market protection of the reference medicine expires (after 10 years).

Since biosimilars are a type of biological medicine, all features pertinent to biological medicines apply.

Due to the natural variability of the biological source and to the manufacturing process unique to each manufacturer, minor differences can occur between the biosimilar and its reference medicine (table 1 and figure 3). Strict controls are always in place during manufacturing to ensure that minor differences do not affect the way the medicine works or its safety. Thus, these differences are not clinically meaningful in terms of safety or efficacy.

Table 1. Specific features of biosimilar medicines

Highly similar to the reference medicine	The biosimilar has physical, chemical and biological properties highly similar to the reference medicine's. There may be minor differences from the reference medicine which are not clinically meaningful in terms of safety or efficacy.
No clinically meaningful differences compared with the reference medicine	No differences are expected in clinical performance. Clinical studies that support the approval of a biosimilar confirm that any differences will not have an effect on safety and efficacy.
Variability of biosimilar kept within strict limits	Minor variability is only allowed when scientific evidence shows that it does not affect the safety and efficacy of the biosimilar. The range of variability allowed for a biosimilar is the same as that allowed between batches of the reference medicine. This is achieved with a robust manufacturing process to ensure that all batches of the medicine are of proven quality.
Same strict standards of quality, safety and efficacy	Biosimilars are approved according to the same strict standards of quality, safety and efficacy as for any other medicine.

Figure 3. Example of variability between a biosimilar and the reference medicine

Variability (yellow shadow) between a biosimilar and the reference medicine is comparable to what may occur between different batches of the same biological medicine (figure 2). Minor variability, e.g. in glycosylation (represented by small blue triangles) may be allowed, while the protein’s amino acid sequence (circles) and biological activity are the same.

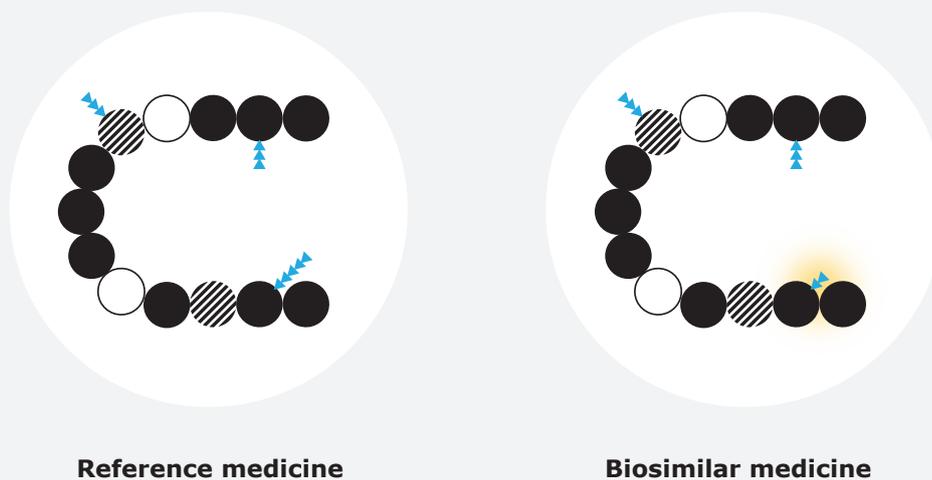


Table 2. Classes of biological medicines for which a biosimilar is currently approved in the EU

Classes of biological medicines	Biosimilar approved in the EU (as at March 2017)
Polysaccharides	
Low-molecular weight heparins	▶ Enoxaparin sodium
Proteins	
Growth factors	▶ Epoetin ▶ Filgrastim
Hormones	▶ Follitropin alfa ▶ Insulin glargine ▶ Somatropin (growth hormone) ▶ Teriparatide
Fusion proteins	▶ Etanercept
Monoclonal antibodies	▶ Adalimumab ▶ Infliximab ▶ Rituximab

Why biosimilars are not considered generic medicines

A biosimilar is not regarded as a generic of a biological medicine. This is mostly because the natural variability and more complex manufacturing of biological medicines do not allow an exact replication of the molecular microheterogeneity.

Consequently, more studies are needed for regulatory approval of biosimilars than for generics to ensure that minor differences do not affect safety or efficacy. Table 3 compares development and characteristics of generics and biosimilars.

Table 3. Comparison of development and characteristics between generics and biosimilars

Generic medicine	Biosimilar medicine
Usually produced by chemical synthesis	Obtained from a biological source
Generally possible to obtain exactly the same molecule	Possible to reproduce the molecule to a high degree of similarity due to unique biomanufacturing methods and natural biological variability
Mostly smaller molecules, easier to characterise	In general, larger, structurally more complex molecules, which require multiple technologies for their characterisation
Full data requirements on pharmaceutical quality	Full data requirements on pharmaceutical quality, plus additional quality studies comparing the structure and biological activity of the biosimilar with the reference medicine
Development based on demonstration of bioequivalence (i.e. that the generic and the reference medicine release the active substance into the body at the same rate and to the same extent under similar conditions)	Development based on demonstration of biosimilarity using comparability studies (comprehensive head-to-head comparison of the biosimilar with the reference medicine to show high similarity in chemical structure, biological function, efficacy, safety and immunogenicity)

Generic medicine	Biosimilar medicine
Clinical data requirements are mainly pharmacokinetic bioequivalence studies	In addition to comparative pharmacokinetic and pharmacodynamic studies, safety and efficacy data may be required, particularly for more complex biological medicines
All indications approved for the reference medicine can be granted based on demonstrated bioequivalence, without the need for further clinical data	Efficacy and safety have to be justified in each indication. However, confirmatory clinical trials with the biosimilar are usually not needed in every indication that has been approved for the reference medicine. After demonstration of biosimilarity, extrapolation of data to other indications is possible if the scientific evidence available addresses all specific aspects of these indications



Development and approval of biosimilars in the EU

A robust regulatory framework for biosimilars

Approval of medicines in the EU relies on a solid legal framework, which in 2004 introduced a dedicated route for the approval of biosimilars. The EU has pioneered the regulation of biosimilars since the approval of the first one (the growth hormone somatropin) in 2006. Since then, the EU has approved the highest number of biosimilars worldwide, and consequently has the most extensive experience of their use and safety.

Over the years, EMA has issued scientific guidelines to help developers conform to the strict regulatory requirements for approving biosimilars. The guidelines have evolved to keep pace with rapid advances in biotechnology and analytical sciences, and they take on board increasing experience of clinical use.

The expertise acquired over the last 10 years has enabled EU regulators to integrate experience-based knowledge with the initial science-driven concept. This has helped to shape current requirements for approval.

Process for approval of biosimilars in the EU

All medicines produced using biotechnology and those for specific indications (e.g. for cancer, neurodegeneration and auto-immune diseases) must be approved in the EU through EMA (via the so-called 'centralised procedure'). Nearly all biosimilars approved for use in the EU have been approved centrally, as they use biotechnology for their production. Some biosimilars may be approved at national level, such as some low-molecular weight heparins derived from porcine intestinal mucosa.

When a company applies for marketing authorisation at EMA, data are evaluated by EMA's scientific committees on human medicines and on safety (the CHMP and PRAC), as well as by EU experts in biological medicines (Biologics Working Party) and specialists in biosimilars (Biosimilar Working Party).

The review by EMA results in a scientific opinion, which is then sent to the European Commission, which ultimately grants an EU-wide marketing authorisation.

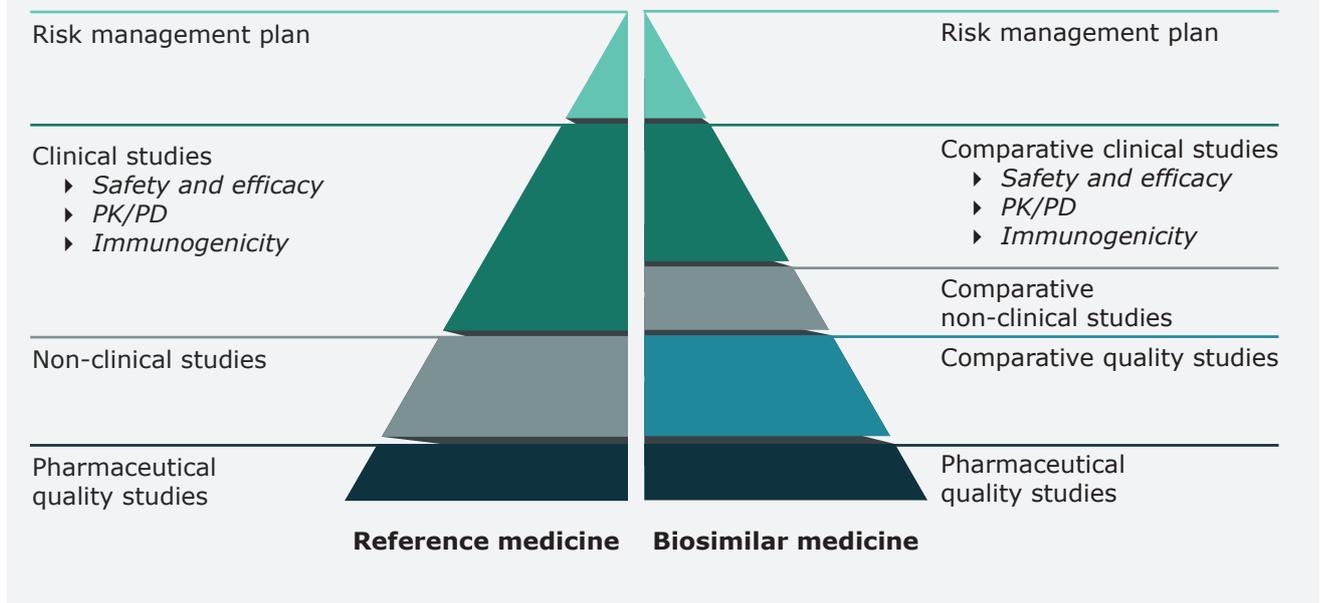
Data requirements for approval: a scientifically tailored package

Medicines are approved when studies on their pharmaceutical quality, safety and efficacy convincingly demonstrate that the medicine's benefits outweigh the risks ('positive benefit-risk balance'). For any biological medicine with a new active substance, a positive benefit-risk balance is determined mainly from evidence of safety and efficacy in pivotal trials in humans (figure 4), supported by solid pharmaceutical quality data and non-clinical data.

For biosimilars, a positive benefit-risk balance is based on demonstrating biosimilarity, i.e. that the active substance is highly similar to the reference medicine (figure 4). This is achieved via comprehensive comparability studies with the reference medicine (figure 5), and on the basis of solid pharmaceutical quality data. By demonstrating high similarity with the reference medicine, the biosimilar can largely rely on the efficacy and safety experience gained with the reference medicine.

An overview of biosimilar development compared with the development of reference medicines is provided in table 4.

Figure 4. Comparison of data requirements for approval of a biosimilar versus the reference medicine



The non-clinical and clinical data needed to approve a biosimilar are different from those needed for a biological medicine with a new active substance.

This is because, by demonstrating biosimilarity, the biosimilar relies on the safety and efficacy experience gained with the reference medicine.

Table 4. Overview of biosimilar development compared with a reference medicine

Biological medicine with new active substance (e.g. reference medicine)	Biosimilar medicine
No previous knowledge of safety and efficacy	Builds on knowledge of safety and efficacy from years of clinical use with reference medicine
Development aims at demonstrating safety and efficacy directly in patients	Development aims at demonstrating comparable safety and efficacy by establishing biosimilarity
Comparability studies only for manufacturing changes during development (e.g. producing larger batches for clinical trials)	Comprehensive comparability studies with the reference medicine
Full non-clinical data (pharmacology and toxicology)	Amount of non-clinical data determined by the outcome of quality studies
Conventional clinical trials to demonstrate efficacy and safety in all claimed therapeutic indications	Comparative clinical trials to exclude clinically meaningful differences
Trials designed mainly to compare with placebo or current standard of therapy using 'hard' endpoints (e.g. long-term outcome, mortality, structural damage) and a relevant patient population to demonstrate benefit	Trials designed mainly to show clinical equivalence with the reference medicine using sensitive endpoints in a population where product-related differences in clinical performance can be detected
Positive benefit-risk mainly established on the basis of safety and efficacy studies in the intended population	Positive benefit-risk based on demonstrating biosimilarity (using comparability studies)

Same pharmaceutical quality standards for all medicines

Companies developing medicines in the EU, including biosimilars, must demonstrate with a large body of data that the medicine is manufactured to agreed standards and that it is suitable for its intended clinical use (what is known as 'pharmaceutical quality').

The studies to prove pharmaceutical quality should provide detailed data on:

- ▶ structural characterisation and other physicochemical properties
- ▶ purity (traces of residues from the manufacturing process have to be controlled and must not exceed acceptable levels)
- ▶ biological activity
- ▶ excipients and starting materials
- ▶ strength and formulation
- ▶ the control of the manufacturing process (to ensure that the active substance and finished product conform with the accepted ranges for technical specifications)
- ▶ stability of the active substance and finished product during shelf-life under defined storage conditions

Comparability studies: the cornerstone of biosimilar development

Biosimilar development relies heavily on 'comparability studies' to establish biosimilarity to the reference medicine. This involves a comprehensive head-to-head comparison of the biosimilar and the reference medicine (figure 5).

Comparability is conceived as a step-wise process that is tailor-made for each product (figure 5); knowledge from the initial quality comparability

studies¹ (step 1) is used to determine the extent and type of non-clinical (step 2) and clinical studies² (step 3) required in the next step of development, always with the aim of ruling out differences in clinical performance between the biosimilar and the reference medicine.

Comparability is a well-established scientific principle of regulatory science: comprehensive comparative quality studies prove that physicochemical properties and biological activity are highly similar.

Comparative clinical and non-clinical studies that support the approval of a biosimilar rule out differences which may affect the medicine's safety and efficacy.

Step 1 Comparative quality studies

In vitro studies compare the protein structure and biological function using sensitive techniques capable of detecting minor differences with clinical relevance between the biosimilar and its reference medicine. These studies are much more sensitive than clinical trials for detecting such differences, as there is often variability among human subjects participating in trials. Differences that may affect clinical safety, efficacy or immunogenicity need to be further studied (e.g. in comparative non-clinical or clinical studies, step 2 and 3).

Step 2 Comparative non-clinical studies

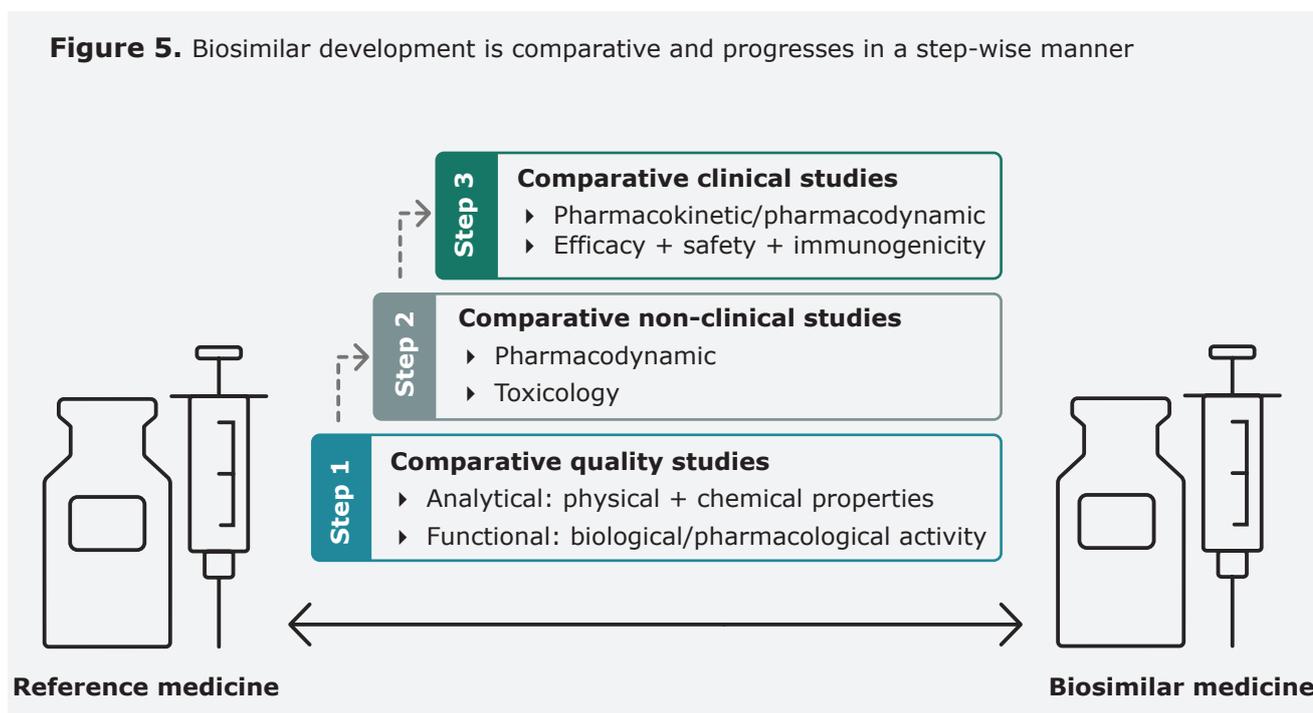
These studies include pharmacodynamic studies in vitro, which look at binding and activation (or

inhibition) of physiological targets and immediate physiological effects in cells. Pharmacodynamic studies in vivo (animal models) are only done if no suitable in vitro model exists. In vivo toxicological studies are only required in certain cases, for example when the biosimilar is produced in a new type of cell or organism, or when the formulation includes new excipients not used previously.

Step 3 Comparative clinical studies

The aim of studies in humans is not to demonstrate safety and efficacy in patients, as these have already been established for the reference medicine. Clinical trials are tailored to confirm biosimilarity and to address any questions that may remain from previous analytical or functional studies.

Figure 5. Biosimilar development is comparative and progresses in a step-wise manner



Approval of biosimilars builds on existing scientific knowledge on safety and efficacy of the reference medicine gained during its clinical use, so fewer clinical data are needed.

From a scientific and regulatory point of view, the reference medicine's entire clinical development programme does not need to be repeated. This means that patients and healthy volunteers will not be subjected to unnecessary clinical trials.

Comparability: a scientific principle routinely used after manufacturing changes to medicines on the market

Comparability is not a new regulatory concept, but a well-established scientific principle that has been used for decades in the manufacture of medicines

made by biotechnology^{3, 4, 5}. Companies producing biological medicines are likely to adapt or improve the manufacturing process several times during the commercial life of a product (e.g. by increasing production scale). Comparing batches before and after a manufacturing change ensures consistency, so that there are no changes in safety or efficacy.

A change to the manufacturing process must always be approved by regulators. The extent of the comparability studies required following a manufacturing change to a biological medicine will depend on the expected impact on quality, safety and efficacy of the medicine. Most often, analytical and functional data are sufficient, and clinical trials to prove safety and efficacy are not needed (table 5, scenario 1 and 2). Clinical trials are needed only if an impact on safety and efficacy is anticipated (scenario 3).

Table 5. Comparability studies needed following changes to the manufacturing process of a medicine produced by biotechnology

Type of manufacturing change	Expected impact	Comparability studies needed
1. Minor change (e.g. adding a more sensitive test method to characterise the active substance)	Does not affect the pharmaceutical quality of the medicine (no impact on product specifications)	Limited physicochemical studies comparing batches before and after the change
2. Significant change (e.g. changes to the cell system used to produce the active substance)	May affect product characteristics or specifications but not expected to affect safety or efficacy	Comprehensive physicochemical and functional in vitro studies
3. Major change (e.g. certain changes in the medicine's formulation)	May possibly affect safety or efficacy	Comprehensive physicochemical and in vitro functional studies complemented as needed by non-clinical and clinical studies

Most of the widely used biological medicines on the market have seen several changes to their manufacturing process and these often result in minor differences from the version initially approved or the version used in the clinical trials filed for approval.

Regulators have built up extensive experience to conclude that such differences do not affect the medicine's quality, safety and efficacy.

Comparative trials are designed to confirm biosimilarity and clinical performance

Comparison of the biosimilar with the reference medicine involves extensive comparability studies to assess any possible impact on safety and efficacy. The approach is equivalent to when major changes are introduced to the manufacturing process for a medicine made by biotechnology (scenario 3 in table 5).

Clinical trials for biosimilars do not need to include all the pivotal studies conducted for the reference medicine to prove safety and efficacy in humans.

Comparative clinical trials are specifically designed to rule out clinically relevant differences in safety or efficacy between the biosimilar and the reference medicine, and to confirm biosimilarity.

There are certain key aspects that need to be considered for the design of comparative clinical trials:

- ▶ The goal is to rule out potential product-related differences that could affect pharmacokinetics (PK), efficacy or safety, including immunogenicity.
- ▶ PK studies should be conducted in a homogeneous and sensitive population (healthy volunteers or patients) to detect any possible differences between the biosimilar and its reference medicine. Healthy volunteers can be selected if they represent the most appropriate population to detect such differences and if the medicines' toxicity is not a cause of concern.
- ▶ To compare the pharmacological effects, a sensitive endpoint that allows detection of product-specific differences should be chosen.
- ▶ Endpoints measuring pharmacodynamic activity ('PD endpoints') can be used when available and when relevant for the medicine's clinical effect. In many settings, these endpoints are more sensitive than clinical outcomes to detect potential differences between a biosimilar and the reference medicine. PD endpoints are usually based on laboratory tests. Examples include:
 - ▶ glucose infusion rate in a glucose clamp study for biosimilar insulins (rather than measures of HbA1c or long-term consequences of diabetes)
 - ▶ absolute neutrophil count for biosimilar granulocyte-colony stimulating factor (rather than number of serious infections)
 - ▶ number of oocytes retrieved during in vitro fertilisation for biosimilar follicle-stimulating hormone (rather than pregnancies or live births)
- ▶ If there are no suitable PD endpoints, a clinical efficacy trial comparing the biosimilar and its reference medicine is generally needed. This trial should be adequately powered, randomised, parallel-group, preferably double-blind, and should use efficacy endpoints. These

endpoints should preferably measure the pharmacological activity of the medicine and be less influenced by patient- or disease-related factors.

- ▶ Adequate equivalence margins should be chosen for the primary efficacy endpoint. Margins are established on the basis of knowledge of efficacy with the reference medicine, as well as on clinical judgement. Equivalence margins are set specifically for the indication studied and depend on the endpoint chosen. They should represent the largest difference in efficacy that would not matter in clinical practice; treatment differences within this range would

thus be acceptable because they have no clinical relevance. The principles of selecting equivalence margins are not unique to biosimilar testing: they are routinely used in clinical trials when comparing treatment alternatives, or when comparing the same medicine before and after manufacturing changes that may have a clinical effect³.

- ▶ As for all clinical trials, legal requirements (e.g. Good Clinical Practice) have to be met.

The extent of clinical studies needed for approval depends on several factors, including those outlined in table 6.

Table 6. Factors affecting the number and types of clinical studies to be carried out for approval

Determining factor	Reason for varying amount/type of data
Complexity of the molecule and comparability data available	<p>For simpler molecules with well-established action (e.g. filgrastim) and where comparative quality data are solid, it may be sufficient to compare the effect of the biosimilar and reference medicine with PK and PD studies in healthy volunteers.</p> <p>For larger molecules (e.g. monoclonal antibodies), even when robust quality and in vitro comparability data are provided, a comparative study in patients using a conventional clinical efficacy endpoint is usually required.</p>
Availability of a PD endpoint which correlates with efficacy	Conventional clinical efficacy endpoints are generally not needed if the PD endpoint correlates with clinical benefit.
Safety concerns with the reference medicine or pharmacological class	Safety data are collected throughout the clinical development programme, including during PK and PD studies. The amount of data normally depends on the type and severity of the safety concerns identified for the reference medicine. In principle, adverse reactions related to the pharmacological action can be expected at similar frequency for the biosimilar and reference product, if functional, analytical, PK, PD and efficacy comparability data are robust.

Determining factor	Reason for varying amount/type of data
Potential for immunogenicity	Analytical studies are the first step in assessing potential for immunogenicity. To complement this, clinical data on immunogenicity are generally required; animal studies are of limited value in predicting immune response in humans.
Possibility of extrapolating to other indications	<p>Indications of the reference medicine can be approved for the biosimilar in the absence of specific clinical data generated with the biosimilar ('extrapolation of indications'). This can be accepted if all the scientific evidence available from the comparability studies establishes biosimilarity and can address the specific aspects of the extrapolated indication (e.g. mode of action, potentially unique safety or immunogenicity aspects).</p> <p>Extrapolation of data to other indications is always supported by robust physicochemical and in vitro studies to assess all the possible mechanisms of action.</p>

Immunogenicity

Immunogenicity is always studied for biological medicines^{6, 7}. This is because of the intrinsic ability of proteins and other biological medicines to cause an unwanted immune response, which, in rare cases, could cause a serious adverse reaction (e.g. anaphylaxis or delayed hypersensitivity) or reduced efficacy.

Key considerations on potential immunogenicity of biological medicines

Although immunogenicity could be a potential concern for all biological medicines, there are several important considerations:

Immunogenicity is not a safety concern in itself

Severe reactions due to an increased immune response are very rare and most often an immune response against a biological medicine is not associated with clinical consequences (e.g. anti-drug antibodies could be transient).

The nature of immune reactions depends on many factors

Immunogenicity may be influenced by product characteristics (e.g. changes to the structure of the protein may occur during improper storage or transport, or proteins could form aggregates), but also by treatment-related factors (e.g. the risk may vary with subcutaneous versus intravenous

administration or with continuous versus intermittent treatment regimen) and patient- or disease- related factors (e.g. age, genetic and immune status or concomitant treatments).

Harmful immunogenicity is unlikely after manufacturing changes or after switching

Many biological medicines are intended for long-term management of chronic conditions, and therefore, over time the patient may receive biological medicines with slight differences.

Experience shows that a harmful immune response is unlikely after a change to the manufacturing process of a biological medicine, since comparability studies prove that the batch from the new process is of the same quality and free of impurities or aggregates that can trigger immunogenicity⁸.

There is also no reason to believe that harmful immunogenicity should be expected after switching between highly similar biological medicines⁸.

Immunogenicity is always monitored post-marketing

Immunogenicity of biological medicines is always monitored by regulatory authorities once the medicine is on the market. This is particularly important to learn of rare immune reactions that can only be detected after a long follow-up period in larger numbers of patients.

Immunogenicity data needed for approval of a biosimilar

Clinical immunogenicity studies are generally required for biological medicines. In the case of monoclonal antibodies they are always required, as it is more difficult to predict the incidence of unwanted immunogenicity, the characteristics of the immune response or the clinical consequences. Such studies look both at short-term immune responses (e.g. infusion-related reactions), as well

as long-term (e.g. delayed responses due to an evolving immune reaction).

Immunogenicity data required for approval include incidence, titre and persistence of antibodies against the biological medicine (ADAs), neutralisation assays (because neutralising antibodies may reduce the effect of the medicine), assessment of the clinical impact and measures to manage the potential risk of immunogenicity (e.g. special monitoring of immune-mediated adverse reactions or use of concomitant medication to mitigate infusion reactions).

In general, the amount and type of data will depend on several factors, including:

- ▶ the type of biological medicine and its intended use
- ▶ product characteristics: the great majority of immunogenicity studies focus on how differences at product level may affect an immune response. These include studying changes to the structure or minor variability in the protein (microheterogeneity), or how protein aggregation could occur due to components derived from the formulation or packaging.
- ▶ previous knowledge of immunogenicity: for biological medicines with a low immunogenicity profile (e.g. filgrastim), patients are usually tested for antibodies frequently at the beginning and at the end of the clinical study with a shorter follow-up period and routine pharmacovigilance measures to manage any potential risk. In cases where clinically relevant immunogenic responses have been observed (e.g. epoetins) immunogenicity testing is more frequent, there is a longer patient follow-up with intensified clinical monitoring, and specific post-marketing studies may be required.

Extrapolation

If a biosimilar is highly similar to a reference medicine and has comparable safety and efficacy in one therapeutic indication, safety and efficacy data may be extrapolated to other indications approved for the reference medicine. This means that fewer clinical trials or no trials at all need to be carried out with the biosimilar in certain indications. Extrapolation of data to other indications is always supported by scientific evidence generated in robust comparability studies (quality, non-clinical and clinical).

Extrapolation is a well-established scientific principle which has been used for many years⁹, for example whenever a biological medicine with several approved indications undergoes major changes to its manufacturing process (e.g. new manufacturing site or development of new formulations). The potential effect of these changes on the biological medicine's clinical performance is carefully evaluated with comparability studies (mainly quality and in vitro studies). If clinical studies are needed, these are conducted in one relevant indication and, based on all these data, extrapolation to the other indications is usually possible.

Extrapolation is not a new concept but a well-established scientific principle used routinely when biological medicines with several approved indications undergo major changes to their manufacturing process.

In most of these cases, regulators approve manufacturing changes based on comparability studies and clinical trials are not repeated for all indications.

Criteria for extrapolation

Important considerations need to be borne in mind before an indication for a biosimilar can be approved based on extrapolated safety and efficacy data. These include:

Mechanism of action

The mechanism of action of the active substance should be mediated by the same receptor(s) in both the initial and the extrapolated indication.

If the mode of action of the active substance is complex and involves multiple receptors or binding sites (as is often the case with monoclonal antibodies), it may be difficult to establish the contribution of each receptor or binding site to each indication. In this case, additional studies (non-clinical or clinical) will be needed to prove that the biosimilar and reference medicine will behave similarly in the extrapolated indication.

Relevant study population

Comprehensive comparability studies must show that the biosimilar is highly similar to the reference medicine (by means of safety, efficacy and immunogenicity data) in a key indication in a population in which potential differences in clinical performance can be detected.

Extrapolation across different clinical settings

Data from a given indication (e.g. rheumatoid arthritis) may not be directly applicable in terms of safety or efficacy to an indication falling within another therapeutic area where the mode of action, posology or pharmacokinetics may be different (e.g. oncology). In this case, additional studies may be needed.

Extrapolation of safety data

Safety data can only be extrapolated after a comparable safety profile has been established for the biosimilar in one therapeutic indication. If comparability is shown at structural, functional, pharmacokinetic and pharmacodynamic level, and efficacy is comparable, then adverse reactions due to the biosimilar's pharmacological action can be expected to be the same and to occur at similar frequencies.

Extrapolation of immunogenicity data

Extrapolation of immunogenicity data is not automatic, as it always requires justification. This is because immunogenicity is determined by more than product-related characteristics. Factors relating to patients (age, immune status), disease (comorbidities, concomitant treatments) or treatment-related factors (route of administration, length of exposure) also have to be considered.

The scientific criteria for extrapolation of efficacy and safety data are supported by over 10 years experience of safe and effective use of biosimilars in the EU.

Extrapolation is also supported by regulators' extensive experience in the routine evaluation of manufacturing changes for biologicals, most often without the need to repeat clinical studies in all indications.

Prescribers can have confidence in using biological medicines (including biosimilars) for all their approved indications, as all approved indications of a medicine are granted based on scientific evidence.

Safety of biosimilars

General considerations on safety for biosimilars

Since the introduction of the first biosimilar in clinical use in 2006, an increasing number of biosimilars have been approved and safely used in the EU.

Apart from reactions of an immunological nature, most adverse drug reactions (ADRs) can be predicted from the pharmacological action, and occur with both the reference medicine and the biosimilar (e.g. high haemoglobin levels with epoetins). Of more than [25 biosimilars](#) approved in the EU to date none has been withdrawn or suspended for reasons of safety or efficacy.

Over the last 10 years, the EU monitoring system for safety concerns has not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilar medicines and their reference medicines.

Safety monitoring for all biological medicines, including biosimilars

A robust regulatory framework to protect patients' safety

The EU has a well-established system for monitoring, reporting, assessing and preventing adverse drug reactions for all medicines, including all biological medicines. Authorities continuously evaluate the benefit-risk balance of all medicines and take necessary regulatory action (e.g. introducing new warnings in the product information or restricting use) to safeguard public health.

Same safety monitoring for all biological medicines

Safety monitoring of biosimilars follows the same requirements that apply to all biological medicines¹⁰. There is no specific requirement just for biosimilars.

A plan to manage risks always in place

Companies applying for marketing authorisation in the EU must submit a risk management plan (RMP) for each new medicine, including biological medicines. The RMP, which is tailored for each product, includes a pharmacovigilance plan and risk minimisation measures to identify, characterise and minimise a medicine's important risks. The RMP of a biosimilar is based on knowledge and experience gained with the reference medicine.

For all medicines approved in the EU, in addition to the conditions of use in the product information, additional measures (e.g. educational brochures, patient alert cards or inclusion of patients in registries) may be needed to manage a specific risk. When any extra measure is applied to the reference medicine (e.g. educational material), it should also be considered for the biosimilar.

Safety studies after marketing

Post-marketing studies allow monitoring of known risks and also permit detection of rare adverse drug reactions that emerge only when large numbers of patients have been treated for a long period. This is why at the time of approval, regulators may impose on the company an obligation to carry out a post-authorisation safety study (PASS). This also binds the company to register the study in the publicly available EU PAS Register: http://www.encepp.eu/encepp_studies/indexRegister.shtml.

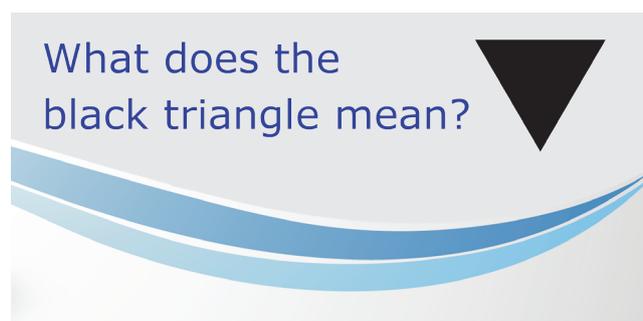
The criteria for deciding whether a post-marketing safety study is needed are the same for all medicines, including biosimilars and their reference medicines. If a PASS has been requested for a reference medicine, it will normally be requested also for the biosimilar.

Collecting spontaneous adverse drug reactions and submitting PSURs

As for all medicines, companies marketing biosimilars must collect all reports of suspected adverse drug reactions and submit periodic safety update reports (PSURs) to regulators. Regulatory authorities review reports for any signal suggestive of a possible unwanted effect. If a signal is suspected, it is evaluated by EMA's scientific committees, which will determine if any action is needed.

Additional monitoring and black triangle

All new medicines are closely monitored after being introduced to the market. Biological medicines approved after 1 January 2011 are subject to so-called 'additional monitoring' and are included in a list of medicines under 'additional monitoring'. This list includes medicines authorised in the EU that are being monitored particularly closely by regulatory authorities, for example because the active substance is new to the market or there are limited data on its long-term use. In this case, they are monitored particularly closely during the first years after approval.



The black triangle symbol identifies medicines under additional monitoring. It is displayed in the SmPC and package leaflet together with the sentence:

"This medicinal product is subject to additional monitoring"

Additional monitoring encourages healthcare professionals and patients to report any suspected adverse drug reactions of new medicines. This enables prompt identification and analysis of information about the medicines to add to the knowledge gained during clinical trials. If a biological medicine (or biosimilar) is labelled with a black triangle, it does not necessarily mean that there are additional safety concerns with it.

Monitoring long-term or long-latency adverse events

Safety monitoring of long-term or long-latency events for biological medicines follows the same principles as for small-molecule medicines. However, detecting and characterising the long-term adverse drug reactions of biological medicines may be difficult using only spontaneous reporting. This is why additional pharmacovigilance activities (such as including patients in registries) could be required in certain cases.

Traceability: importance of identifying biological medicines by tradename and batch number

An important requirement for the safety monitoring of all biological medicines is the need for product and batch traceability during clinical use and at all levels in the supply chain¹⁰. This covers the time from release by the manufacturer and progress through the entire distribution chain until the medicine is administered to the patient.

As required by EU law, every medicine will have an invented name (tradename or brand name) together with the active substance name (i.e. the

International Nonproprietary Name, or INN, which is assigned by WHO).

For identifying and tracing biological medicines in the EU, medicines have to be distinguished by the tradename and batch number and this is particularly important in cases where more than one medicine with the same INN exists on the market. This ensures that, in line with EU requirements for ADR reporting, the medicine can be correctly identified if any product-specific safety (or immunogenicity) concern arises.

Healthcare professionals play an essential role in contributing to the understanding of a medicine's safety profile during clinical use. Biological medicines are approved on the basis of an acceptable safety profile and they should be used according to the recommendations in the summary

of product characteristics (SmPC) and package leaflet. If a suspected ADR is identified for a biological medicine, healthcare professionals should report it, taking care to include the tradename and batch number of the medicine. It is important that healthcare professionals report any suspected ADR of a biosimilar even if the reaction is already listed in the reference medicine's SmPC.

For a biological medicine, its tradename, INN and batch number can be found in the product packaging. A statement has been introduced in the SmPC to remind healthcare professionals of the need to clearly record the tradename and batch number in the patient's healthcare records.

How healthcare professionals can help improve pharmacovigilance for biological medicines:

- ▶ *It is important that the medicine's tradename and batch number are recorded by healthcare professionals at all levels, including dispensing and patient administration.*
- ▶ *Prescribers should include the tradename of the medicine in the prescription.*
- ▶ *Healthcare professionals should ensure that tradename and batch number are reported in case of suspected adverse drug reactions, according to local practice and national regulations.*
- ▶ *In cases where the product is dispensed at a community pharmacy, the tradename and batch number of the biological medicine should be provided to the patient.*
- ▶ *If a patient is switched from one biological medicine to another with the same active substance, it is important to record the tradename and batch number for each of the medicines.*
- ▶ *Healthcare professionals should contact their national medicines regulatory authorities for advice on how to report adverse drug reactions.*

Data included in the prescribing information and EMA assessment reports for biosimilars

Data for prescribing: summary of product characteristics (SmPC)

The EU SmPC includes information and recommendations to enable healthcare professionals to prescribe the medicine and to give advice to patients on its use.

Section 5.1 (pharmacodynamic properties) of the SmPC will identify a medicine as a biosimilar with the following wording:

[Brand name] is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

In the EU, the SmPC of a biosimilar is aligned with that of the reference medicine. The biosimilar's SmPC mentions the name of the active substance (i.e. INN) and not the tradename of the reference medicine. Details of the studies with the biosimilar as well as the tradename of the reference medicine can be found in EMA's assessment report, available on EMA's website.

A biosimilar can be approved for some or all of the authorised indications of the reference medicine, as a company may choose not to apply for all the reference medicine's indications. Healthcare professionals should check that the biosimilar is authorised for the intended indication.

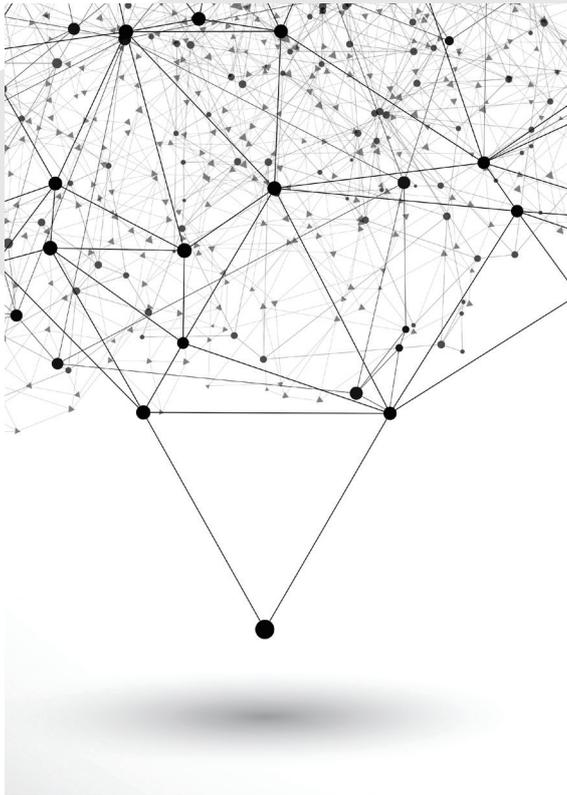
When a company does not apply for all the indications of the reference medicine, efficacy data on the additional indications are not included in the biosimilar's SmPC, however safety data are reflected.

Data on biosimilarity: published in the assessment report

For each medicine approved through EMA, including biosimilars, EMA publishes a group of documents known as the European public assessment report ('EPAR'). In addition to the EU product information (SmPC, package labelling and package leaflet), the EPAR documents contain assessment reports on the scientific evaluation of the medicine at the time of approval and when major changes are introduced (e.g. when a new indication is added).

Details of how each biosimilar was developed and on the comparability studies to demonstrate biosimilarity are given in their assessment reports. These include information on analytical and functional comparability, pharmacokinetics, clinical comparability and immunogenicity. Where applicable, the assessment report also includes the scientific rationale for extrapolation of data.

[Over 25 biosimilars have been approved](#) through EMA for use in the EU as at April 2017. Their assessment reports can be accessed on EMA's website, on the landing page of each medicine, under the tab 'assessment history'.



Implications of the availability of biosimilars

Once the period of market protection of the reference medicine expires (usually 10 years), companies can market approved biosimilars. In general it is expected that biosimilars will be introduced to the market at a lower price than their reference medicine. Thus, they are expected to be less costly for healthcare systems in the EU. This is partly due to a tailored development programme that builds on scientific knowledge gained with the reference medicine and so avoids unnecessary repetition of non-clinical and clinical studies. It can also be due to increased market competition.

The experience over the past 10 years¹¹ indicates that biosimilar competition can offer advantages to EU healthcare systems, as having more treatment alternatives available is expected to improve patients' access to biological medicines with proven pharmaceutical quality.

Interchangeability, switching and substitution: EMA and Member States' responsibilities

Definitions

In the context of biosimilars and reference medicines, it is important for healthcare professionals to be aware of the terminology to refer to interchangeability and substitution practices in the EU.

Interchangeability refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another. Replacement can be done by:

- ▶ **Switching**, which is when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent.
- ▶ **Substitution** (automatic), which is the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber.

In the EU, prescribing practices and advice to prescribers fall under the responsibility of Member States, which have the necessary legal framework in place and issue regulations, guidelines and advice in their areas of competence. As for any medicine, healthcare professionals should choose carefully when prescribing, taking into account the patient's medical history.

For questions on prescribing or interchangeability practices, information may be available at the national competent authority in the relevant Member State (the list can be found [on EMA's website](#)).

Any decision on switching should involve the prescriber in consultation with the patient, and take into account any policies that the country might have regarding the prescribing and use of biological medicines.

EMA and Member States' responsibilities

When EMA carries out the scientific review of a biosimilar, the evaluations do not include recommendations on whether the biosimilar is interchangeable with the reference medicine, and thus whether the reference medicine can be switched or substituted with the biosimilar.

The decision on whether to allow interchangeable use and substitution of the reference biological medicine and the biosimilar is taken at national level. Information on the scientific evaluation performed by EMA's scientific committees is available on EMA's website and could be used to support decisions.



Communicating with patients on biosimilars

If patients have questions on whether a particular biological medicine is a biosimilar, their healthcare professionals can find this information in section 5.1 of the SmPC. The package leaflet, which contains key recommendations for patients on how to use the medicine properly, does not include mention of biosimilarity, as this term only refers to the medicine's development route and is not related to the use of the medicine.

If patients receiving biosimilars in a clinical setting (e.g. in hospital) want information on their biosimilar, they can ask their healthcare professionals for the package leaflet. Alternatively, they can download it from [EMA's website](#).

For questions from patients on what is a biosimilar, and how its safety and efficacy are ensured, patients can consult a questions-and-answers document¹² in patient-friendly language available on the [European Commission's website](#).

When a new medicine is approved by EMA, the Agency also publishes a summary for the general public explaining why the medicine is approved in the EU. These summaries (called 'EPAR summaries'), are available on each medicine's landing page on EMA's website in the form of questions-and-answers documents in all official EU languages. EPAR summaries for biosimilars can be accessed by searching for the medicine's name on EMA's homepage. Alternatively, a live list of EPAR summaries for all biosimilars can be found [on EMA's website](#).

Several national regulatory authorities also provide information on biosimilars in their local language.



EU contribution to the regulation of biosimilars worldwide

The EU's regulation of biosimilars has shaped biosimilar development globally, by establishing the core principles that underpin biosimilar development in other highly regulated areas of the world.

The requirements for biosimilar approval in the US by the FDA are based on the same scientific rationale as in the EU, although specific data requirements may differ between these two regions due to different legal frameworks. Other international regulators such as Australia's TGA directly apply the principles set out in the EU legislation for the development and approval of biosimilars.

The World Health Organization (WHO) has developed its own guidelines for biosimilars (called 'similar biotherapeutic products' or SBPs) and biosimilar monoclonal antibodies, with the aim of providing guidance to regulatory agencies worldwide. These WHO guidelines incorporate many of the scientific principles used by EMA and its scientific committees in EU guidelines, as EU experts have been closely involved in the preparation of the WHO guidelines.

EMA continues to share the extensive experience gained in the EU on biosimilars with other regulators around the world and participates in a number of international forums such as the International Pharmaceutical Regulators Forum.

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Abbreviations

ADA	Anti-drug antibody
ADR	Adverse drug reaction
BMWP	Biosimilar Working Party (EMA's working party of EU experts on biosimilars)
CHMP	Committee for Human Medicinal Products (EMA's scientific committee formed by EU experts who review and recommend marketing approval)
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
EPAR	European public assessment report
EU PAS Register	EU post-authorisation study register
FDA	Food and Drug Administration (the US medicines regulatory authority)
GMP	Good manufacturing practice
INN	International nonproprietary name
PASS	Post-authorisation safety study
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PRAC	Pharmacovigilance and Risk Assessment Committee (EMA's scientific committee formed by EU experts on safety of medicines)
PSUR	Periodic safety update report
RMP	Risk management plan
SBP	Similar biotherapeutic products (WHO term for biosimilars)
SmPC	Summary of product characteristics (the EU prescribing information)
TGA	Therapeutic Goods Administration (Australia's medicines regulatory authority)
WHO	World Health Organisation

Anti-drug antibody	Antibodies produced by the body's immune system against an active substance (particularly a large molecule, such as a protein). ADAs against a medicine can result in loss of efficacy or in immunological reactions.
Adverse drug reaction	An unwanted medical event following the use of a medicine. Suspected ADRs are those that have been reported to authorities but which are not necessarily caused by the medicine.
Bioequivalence	When two medicines release the same active substance into the body at the same rate and to the same extent under similar conditions.
Biosimilarity	Demonstration of high similarity to a reference biological medicine in terms of chemical structure, biological activity and efficacy, safety and immunogenicity profile, mainly based on comprehensive comparability studies.
Biotechnology	Technology that relies on biological systems, living organisms or components from living organisms (such as genes or enzymes) to make a specific product. A medicine obtained by biotechnology often has been produced by inserting a gene into cells so that they can produce the desired protein.
Centralised procedure	Approval process of medicines which involves a single application, a single evaluation and, for successful applications, a single authorisation valid throughout the European Union. It is mandatory for certain types of medicines, including all medicines produced by biotechnology and medicines for specific conditions such as cancer, neurodegeneration and autoimmune diseases.
Comparability	Head-to-head comparison of a biosimilar with its reference medicine to rule out any significant differences between them in terms of structure and function. This scientific principle is routinely used when a change is introduced to the manufacturing process of medicines made by biotechnology, to ensure that the change does not alter safety and efficacy.
Extrapolation	Extension of the efficacy and safety data from a therapeutic indication for which the biosimilar has been clinically tested to another therapeutic indication approved for the reference medicine.
Glycosylation	Modification of a protein after its production, which involves the addition of carbohydrate (sugar) groups. Depending on the amount and type of sugar groups added, the biological activity can change.

* The definitions included in this document and in the glossary are descriptions, not regulatory definitions.

INN	International Nonproprietary Name, a unique name that identifies active substances. The list of INNs, which is globally recognised and public property, is maintained by WHO.
Interchangeability	Refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect.
Microheterogeneity	Minor molecular variability among biological substances due to natural biological variability and slight alterations to production methods.
Pharmacodynamic studies	Studies of the biochemical and physiological effects of a medicine in the body, including mechanism of action.
Pharmacokinetic studies	Studies of how a medicine is processed by the body, including its absorption, distribution, biotransformation and excretion.
Pharmacovigilance	Activities to detect and assess adverse reactions and other effects of medicines in use.
Periodic safety update report	Report that a company marketing medicines in the EU must submit to regulatory authorities periodically (e.g. every six months) that includes new reports of suspected adverse drug reactions.
Post-translational change	Modification of a protein after its production, which involves the attachment of molecules or groups such as phosphates or carbohydrates (sugars).
Recombinant DNA technology	Technology that involves combining sequences of DNA that do not occur naturally, for example inserting a gene for producing a therapeutic protein.
Reference medicine	A biological medicine approved in the EU, which is chosen by a company developing a biosimilar as a reference for the head-to-head comparison of quality, safety and efficacy.
Specifications	Acceptance limits for important quality standards which an active substance or a finished medicine must meet.
Substitution	Substitution is the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber.
Switching	Switching is when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent.



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