



## Guide to Biosimilars for Healthcare Professionals

Deleted: and Patients

**AUT-G0141-3**

**DATE 05 AUGUST 2020**

[This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.](#)



## CONTENTS

EXECUTIVE SUMMARY	3
DEFINITIONS	4
1 PURPOSE OF THIS GUIDANCE	7
2 WHAT IS A BIOLOGICAL MEDICINE?	7
3 WHAT IS A BIOSIMILAR MEDICINE?	8
4 WHEN CAN A BIOSIMILAR BE MARKETED?	8
5 HOW ARE BIOSIMILARS AUTHORISED?	8
5.1 Quality comparability	9
5.2 Pre-clinical comparability	10
5.3 Clinical comparability	10
6 INTERCHANGEABILITY, SWITCHING AND PRESCRIBING	12
7 EXTRAPOLATION OF INDICATIONS	13
8 INTERNATIONAL NON-PROPRIETARY NAME (INN)	14
9 PRODUCT INFORMATION	14
10 PHARMACOVIGILANCE AND ADVERSE REACTION REPORTING	15

## EXECUTIVE SUMMARY

This guidance document provides information on the regulation, prescribing, dispensing, interchangeability and traceability of biosimilar medicines ('biosimilars') in Ireland. The guide is primarily aimed at healthcare professionals, for the purpose of informing and assisting their decision-making processes when prescribing, dispensing or administering biosimilars. It may also be of interest to those working in the area of manufacturing, medicines procurement, distribution and related activities. A separate Q&A for patients and an information video on biosimilars is also available on the HPRA website, [www.hpra.ie](http://www.hpra.ie).

A biosimilar is a biological medicine that is highly similar to another biological medicine (reference medicine) which already has a marketing authorisation and has been approved for use in patients. As such, biosimilars contain a version of the active substance of an approved biological medicine and generally should be used in the same way as the reference medicine and in accordance with its Summary of Product Characteristics (SmPC).

As biological medicines are manufactured from biological sources, they exhibit natural variability and molecular micro-heterogeneity. This complexity and batch-to-batch variability associated with all biological medicines means that biosimilars cannot be considered the same as generic medicines in the traditional sense. The biosimilar pathway is a tailored approach in which extensive physicochemical and functional biological testing is conducted on numerous batches of the biosimilar and reference medicine. This is supported by relevant clinical studies, which together must demonstrate to regulators that the quality, safety and efficacy of both medicines are comparable. This comprehensive testing programme ensures that there are no clinically meaningful differences between the two medicines.

The purpose of this guide is to provide an overview of the regulatory processes through which the quality, safety and efficacy of biosimilars are assessed prior to gaining marketing authorisation. The guide also outlines the current position on interchangeability and switching. In this regard, once approved, biosimilars can be used interchangeably with the reference medicine or with other biosimilars of that reference medicine, under the supervision of a physician. Once a biosimilar has been approved, it can be considered safe to switch to, should a prescribing physician wish to do so.

Deleted: and Patients

Deleted: EXECUTIVE SUMMARY†

†

Deleted: valuable

Deleted: This guidance, while

Deleted: targeted

Deleted: , will

Deleted: relevance

Deleted: others including patients, manufacturers, distributors and

Deleted: involved

Deleted: hospital

Deleted: .

Deleted: medicinal product

Deleted: for its own approved indications.

Deleted: As more patents expire on biological medicines, increased numbers of biosimilars will likely become available in Ireland in the coming years and will be used for treatment of a variety of conditions. †

†

Deleted: a

Deleted: source

Deleted: are significantly more complex than chemical small molecules.

Deleted: , which are similar to already approved biological medicines,

Deleted: For generic medicines, it is relatively more straightforward to demonstrate that one chemical

Deleted: approach is based on a comprehensive

Deleted: head-to-head comparability exercise with th

Deleted: they have similar

Deleted: to the reference medicine such

Deleted: .

Deleted: biosimilar medicines is

Deleted: is primarily aimed at healthcare professional

Deleted: be of interest to those working in the area of

Deleted: †

Deleted: and Patients

## DEFINITIONS

Please note that the definitions outlined below are not considered to be a legal interpretation of these terms. They are provided for guidance purposes only to aid in the interpretation of this document.

**Deleted: Interchangeability**  
Interchangeability between biosimilars and reference products is an ongoing area of debate. While prescribing practices are at the discretion of healthcare professionals, the HPRA does not recommend that patients are switched back and forth between a biosimilar and the reference medicinal product. It is recommended that there is consultation between prescribers, pharmacists and procurement staff in relation to deciding on treatment preferences for using a reference or a biosimilar medicine.  
Page Break  
DEFINITIONS

**Bioequivalence** Two medicines are considered to be bioequivalent when equivalent bioavailability has been demonstrated (the rate and extent of the active substance which is absorbed from the medicine and becomes available in the systemic circulation).

**Biological medicine** A medicine that contains an active substance made by a biological process or derived from a biological source.

**Biosimilar** A biological medicine that is highly similar to another biological medicine which already has a marketing authorisation and has been approved for use in patients (reference medicine). Biosimilars contain a version of the active substance of an already approved medicine.

Deleted: medicinal product

Deleted:

**Biosimilar comparability exercise** A comprehensive series of comparability tests and studies submitted to the regulatory authority, which establishes that a medicine can be approved as a biosimilar. These tests must demonstrate that a biosimilar exhibits comparable quality, safety and efficacy to the reference medicine. For quality comparability testing, a series of physiochemical and biological tests are carried out on the biosimilar and reference medicine to demonstrate similarity on a structural and biological level. Clinical comparability studies normally include clinical trial(s) demonstrating equivalent efficacy between the two medicines.

**Centralised procedure** The European Union-wide procedure for the authorisation of medicines, where there is a single application and a single evaluation resulting in a single authorisation throughout the European Union including the European Economic Area (EEA).

Deleted:

**EMA** The European Medicines Agency, the agency responsible for the scientific evaluation of applications for European Union (EU) marketing authorisations for medicines in the centralised procedure.

Deleted:

**Generic medicine** A medicine (usually a chemically synthesised small molecule) which has the same qualitative and quantitative composition as

	<p><a href="#">a reference medicine. For generic medicines, bioequivalence with the reference medicine must be demonstrated.</a></p>
<b>HPRA</b>	<p><a href="#">The Health Products Regulatory Authority. The HPRA is the competent authority responsible for licensing medicines and other health products in Ireland. The HPRA was formerly known as the Irish Medicines Board (IMB).</a></p>
<b>Indication Extrapolation</b>	<p><a href="#">When a biosimilar has been shown to have comparable performance in a sensitive patient population, it may then be approved in some or all of the indications approved for the reference medicine, without the need for further clinical comparability trials. For extrapolation to be acceptable, the medicine must have the same mechanism of action in each indication, and extrapolation is only approved by regulatory authorities on a case-by-case basis, taking into account the justification provided.</a></p>
<b>Interchangeability</b>	<p><a href="#">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 medicine with a biosimilar (or vice versa), or replacing one biosimilar with another.</a></p>
<b>International Non-Propriety Name (INN)</b>	<p><a href="#">The INN is a unique name given to an active substance which is globally recognised and is public property. The INN is used to facilitate the identification of active substances and the INN system is managed by the World Health Organisation (WHO).</a></p>
<b>Market exclusivity</b>	<p><a href="#">Companies which produce a reference biological medicine are granted a period of market exclusivity (typically 10 years from the first date of authorisation). It is only once this period has expired that other manufacturers may market their authorised biosimilar medicine.</a></p>
<b>Marketing authorisation</b>	<p><a href="#">A licence granted by a regulatory authority (for example, the HPRA or the EMA), which allows a company to market a medicine. This is granted on the basis of a comprehensive dossier submitted by the marketing authorisation holder who must demonstrate that the medicine has acceptable quality, safety and efficacy.</a></p>
<b>Reference medicine</b>	<p><a href="#">A medicine which has already been authorised within the EU and is used as the basis for a generic or biosimilar medicine. The reference medicine must be at the end of its market</a></p>

**Deleted:** and Patients

**Deleted:** When a reference medicine is approved for use in more than one therapeutic indication, a biosimilar may not be required to demonstrate efficacy in all indications.

**Deleted:** product

**Deleted:**

**Deleted:**

**Deleted:**

**Deleted: Generic medicine**

**Deleted:** A medicinal product (usually a chemically synthesised small molecule) which has

**Deleted:** qualitative and quantitative composition as

**Deleted:** . Generic medicines must demonstrate bioequivalence

**Deleted:** the reference product.

**Moved (insertion) [1]**

**Moved (insertion) [3]**

**Moved (insertion) [2]**

**Deleted: HPRA**

**Deleted:** The Health Products Regulatory Authority. The HPRA is the competent authority responsible for licensing medicines and other health products in Ireland. The HPRA was formerly known as the Irish Medicines Board (IMB).

**Deleted: Interchangeability**

**Deleted:** Interchangeability is where one medicine can be safely used instead of another. Interchangeability generally takes place in consultation with the prescriber. In contrast substitution takes place at pharmacy level and does not require the prescriber's intervention.

**Deleted:** )

**Deleted:** which

**Deleted:**

exclusivity period before a generic or biosimilar version can be marketed.

**Substitution**

The practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber. In Ireland, biological medicines are prohibited from automatic substitution at pharmacy level under current legislation.

**Switching**

Switching is when a prescriber decides to exchange one medicine for another medicine with the same therapeutic intent.

Deleted: and Patients

Deleted: ¶

Moved up [1]: International Non-Propriety

Moved up [1]: International Non-Propriety

**Moved up [3]:** The INN is a unique name given to an active substance which is globally recognised and is public property. The INN is used to facilitate the identification of active substances and the INN system is managed by the World Health Organisation (WHO).

Deleted: Market exclusivity

Deleted: Market exclusivity

Deleted: Reference medicine

Deleted: Reference medicine

Formatted Table

Formatted Table

Moved up [2]: Name (INN)

Moved up [2]: Name (INN)

**Moved up [3]:** The INN is a unique name given to an active substance which is globally recognised and is public property. The INN is used to facilitate the identification of active substances and the INN system is managed by the World Health Organisation (WHO).

## 1 PURPOSE OF THIS GUIDANCE

The purpose of this guidance is to explain the regulatory assessment process that is mandated in medicines legislation for the authorisation of [biosimilars](#). The guidance covers a range of topics relevant to this, including explanations of the differences between a 'reference biological medicine' and a '[biosimilar](#)', differences between [biosimilars](#) and 'small [molecule](#) generic medicines'; the requirements for biosimilars to achieve marketing authorisation (regulatory approval) and how this takes account of the specific nature of these medicines. The guidance also discusses issues surrounding the prescribing, dispensing, interchangeability and pharmacovigilance of biosimilars in the context of the Irish [marketplace](#).

## 2 WHAT IS A BIOLOGICAL MEDICINE?

A biological medicine is a medicine that contains an active substance made by a biological process or derived from a biological source. Most biological medicines are produced from cell cultures of living organisms, such as mammalian cells, bacterial or yeast cells, which have been engineered to produce a specific therapeutic molecule or group of molecules, usually protein(s).

There are many types of biological medicines, which range in complexity, diversity and innovation. Examples of biological medicines include:

- recombinant proteins such as insulin, epoetin (erythropoietin) and follicle stimulating hormone (FSH);
- enzymes, such as imiglucerase and agalsidase, which are used in enzyme replacement therapy;
- monoclonal antibodies, which are highly targeted engineered antibodies used to treat a wide variety of conditions such as cancer and arthritis;
- blood-derived products such as clotting factors;
- [vaccines](#);
- animal-derived products such as heparin.

Biological medicines contain larger and more complex active substances than chemically synthesised molecules and in general tend to be more targeted in their therapeutic activity. As biological active substances are produced by living organisms, there is an inherent natural variability, which is not present with chemical entities. [Indeed, for any biological medicine, no batch is truly identical to previously manufactured batches.](#) Due to this variability [and associated batch-to-batch variation](#), it is not possible to make an exact copy of [any](#) biological active substance. [Therefore](#), the term biosimilar is used to describe [a medicine which is highly similar to a reference biological medicine in terms of its quality, safety and efficacy.](#)

Deleted: and Patients

Deleted: <#>PURPOSE OF THIS GUIDANCE!  
<#>¶

Deleted: biosimilar medicines.

Deleted: biosimilar medicine'

Deleted: biosimilar medicines

Deleted: molecule'

Deleted: market place

Deleted: <#>WHAT IS A BIOLOGICAL MEDICINE?¶

Deleted:

Deleted:

Deleted: recombinant

Deleted:

Deleted: and

Deleted: and vaccines

Deleted: small

Deleted: may

Deleted: be

Deleted: a

Deleted: For this reason, generics of biological medicines are not feasible. A similar version of a biological medicine will have an overall high degree of comparability to the reference biological medicine and

Deleted: this.

### 3 WHAT IS A BIOSIMILAR MEDICINE?

A biosimilar is a biological medicine that is highly similar to another biological medicine (reference medicinal product/reference medicine) that has already been authorised for use in the EU. [As for all medicines, biosimilars must comply with the accepted standards of quality, safety and efficacy as laid down in European legislation and guidance.](#)

[Biosimilars have the same primary structure \(e.g. identical amino acid sequence for proteins\), and they will have a high degree of similarity in molecular and biological terms to the reference medicine. However, the manufacturing process and the raw materials used in the manufacture of the biosimilar will differ from those used by the manufacturer of the reference medicine. Coupled with the natural variability and micro-heterogeneity of biological medicines, this means that unlike chemical generic medicines, manufacturing an exact copy of the reference medicine is not technically possible. Therefore, biosimilars are similar but not identical versions of their reference biological medicine. As such, the regulation and approval procedure for biosimilars are different to that of generic medicines and have been adapted to take account of their unique nature. The key principle on which a biosimilar is approved for use is that any differences between it and the reference medicine have been shown not to affect its safety or efficacy in a clinically significant way.](#)

Biosimilars generally have the same strength, and are used at the same dose, to treat the same medical conditions (if approved to do so) and usually have the same route of administration as the reference medicine. However, in [some cases there may be differences in](#) pharmaceutical form, formulation, excipients or presentation, a biosimilar may [also](#) use different administration devices.

### 4 WHEN CAN A BIOSIMILAR BE MARKETED?

As is the case for chemical medicines, companies which produce the reference biological medicine are granted a period of market exclusivity (typically 10 years from the first date of authorisation). Once this period has expired, other manufacturers can market their biosimilar [medicine](#), provided it has been authorised. [Biosimilars](#) have been approved in the EU since 2006 and to date include biosimilar versions of somatropin, epoetin, filgrastim, [pegfilgrastim](#), follitropin alpha, insulin [glargine](#), [insulin lispro](#), [adalimumab](#), [infliximab](#), [etanercept](#), [enoxaparin](#), [trastuzumab](#), [bevacizumab](#), [rituximab](#) and [teriparatide](#). A list of all [biosimilars](#) authorised centrally in the EU can be found on the [EMA website \(www.ema.europa.eu\)](#).

### 5 HOW ARE BIOSIMILARS AUTHORISED?

Biosimilars are authorised under Article 10(4) of Directive 2001/83/EC, and as for all medicines, biosimilars must obtain a marketing authorisation before they can be marketed in the EU. Biosimilars must be manufactured to the same quality standards as the reference medicine. As

**Deleted:** and Patients

**Deleted:** ¶

¶

¶

¶

**WHAT IS A BIOSIMILAR MEDICINE?¶**

**Deleted:** Unlike chemically synthesised small molecule generic medicines, it is impossible for biosimilars to be exact copies of the reference biological medicine. They are similar but not identical versions of their reference biological medicine. ¶

¶

The active substance of the biosimilar will

**Deleted:** active substance

**Deleted:** . For example,

**Deleted:** an active substance that is a protein, the ...

**Deleted:** likely to be minor differences due to

**Deleted:** complex

**Deleted:** and to variability in the production methods ...

**Deleted:** and

**Deleted:** reference medicine must have a similar ...

**Deleted:** and

**Deleted:** profile.

**Deleted:** biosimilars can differ relative to the referenc ...

**Deleted:** this regard include

**Deleted:** and

**Deleted:**

**Deleted:** The manufacturing process of biological ...

**Deleted:**

**Deleted:** medicinal product

**Deleted:** Biosimilar medicines

**Deleted:** and

**Deleted:** .

**Deleted:** biosimilar medicines

**Deleted:** [EMA website \(www.ema.europa.eu\)](#). Several ...

**Deleted:** <#> **HOW ARE BIOSIMILARS** ...

**Deleted:** of the European Parliament



for all medicines, the manufacturing site must be licensed to ensure that good manufacturing practices are in place and the site is subject to periodic inspections by regulatory authorities.

The biosimilar approval process is a tailored approach depending on the molecule in question. The scientific principles on which the approval is based include a comprehensive head-to-head biosimilar comparability exercise, in which a biosimilar must demonstrate similarity to the reference medicine in terms of quality characteristics, biological activity, safety and efficacy. The approval process for a biosimilar involves a detailed scientific evaluation by the relevant regulatory authority of the biosimilarity comparability exercise and the final conclusion on biosimilarity is based on the totality of evidence provided.

The majority of biosimilars are authorised through what is known as the centralised procedure, whereby a medicine will obtain a single marketing authorisation allowing it to be marketed and used throughout the EU as laid down in [EU Regulation No. 726 of 2004](#). The centralised authorisation procedure is coordinated by the EMA and a rapporteur and co-rapporteur are appointed from two EU member states to assess the application dossier submitted by the company. All member states participate in the assessment and have the opportunity to comment, raise queries and ultimately indicate their support for approval or rejection of the marketing authorisation application. Once a medicine has gained positive approval from the EMA, the European Commission then issues a [single](#) marketing authorisation, which [allows the medicine to be marketed](#) in all EU member states.

The comparability exercise is a tiered approach, which is based on three steps as described below:

- First step: quality comparability (physiochemical and biological)
- Second step: pre-clinical comparability (in vitro and [if relevant](#), in vivo studies)
- Third step: clinical comparability (pharmacokinetics, pharmacodynamics, safety and efficacy)

### 5.1 Quality comparability

Quality comparability relies upon a large number of physiochemical and biological tests, which examine molecular structure, protein modifications, size, charge, presence of aggregates, impurities, [protein content](#) and biological activity/potency. Quality comparability must demonstrate that the medicine is highly similar to the reference medicine. To do this, multiple batches of the reference medicine are analysed using a battery of analytical tests. For each test, the results are used to establish the "reference range"; this represents the range of variability for batches of the reference medicine that are already on the market. Multiple batches of the biosimilars are also analysed, and the results must be shown to fall within the reference range in order to be accepted as a biosimilar. Any slight differences between the biosimilar and reference medicine must be identified and shown to have no impact on safety or efficacy.

This concept of quality comparability has been in place for many years and is frequently used when an authorised biological medicine undergoes a change in its manufacturing process. In

**Deleted:** and Patients

**Moved (insertion) [4]**

**Deleted:** [EU Regulation No. 726 of 2004](#).

**Deleted:** is valid in all EU member states, that is, a single EU marketing authorisation permits marketing

**Deleted:** Generic copies of chemical small molecule medicines have the same qualitative and quantitative composition in terms of active substances as the reference medicine and are authorised on the basis of appropriate bioavailability studies to demonstrate bioequivalence with the reference medicine. Such chemical small molecules can be shown by analytical control methods and compliance with pharmacopoeial standards to be identical to the reference active substance. Unlike these small molecules, manufacturing an exact copy of a biological medicine is not possible and therefore additional data are required to demonstrate safety and efficacy before approval. ¶  
¶

**Moved up [4]:** The biosimilar approval process is a tailored approach depending on the molecule in question. The scientific principles on which the approval is based include a comprehensive head-to-head biosimilar comparability exercise, in which a biosimilar must demonstrate similarity to the reference medicine in terms of quality characteristics, biological activity, safety and efficacy. The approval process for a biosimilar involves a detailed scientific evaluation by the relevant

**Formatted:** Not Expanded by / Condensed by

**Formatted:** Not Expanded by / Condensed by

**Formatted:** Not Expanded by / Condensed by

**Deleted:** In addition, the physiochemical and biological tests must identify and characterise any differences ...

**Formatted:** Not Expanded by / Condensed by

**Formatted:** Font: English (Ireland)

**Formatted:** Not Expanded by / Condensed by

**Formatted:** Not Expanded by / Condensed by

**Formatted:** Not Expanded by / Condensed by

**Formatted:** Not Expanded by / Condensed by

**Formatted:** Not Expanded by / Condensed by

**Formatted:** Not Expanded by / Condensed by

**Deleted:** and Patients

these situations, manufacturers must carry out a detailed comparability exercise to demonstrate that the manufacturing change does not result in a medicine with altered quality characteristics. The manufacturers of biological reference medicines continually improve their manufacturing processes and as a result some differences will occur over time. The manufacturers develop sufficient knowledge of their processes to determine the likely impact of such changes on the products themselves. When changes are made to the manufacturing process, the manufacturer evaluates the relevant quality attributes of the medicine to demonstrate that modifications did not occur that would adversely impact the safety and efficacy of the medicine. If significant changes in quality characteristics are found, then new pre-clinical and/or clinical trials may be required to provide assurance that there has been no negative impact on the safety or efficacy of the medicine. Evaluations of such changes are conducted by the regulatory authorities. Therefore, changes to a biological medicine over its lifecycle are considered normal, provided that it has been demonstrated that any differences following a change do not affect safety and efficacy. Thus, regulators have utilised the concept of comparability in assessing biological medicines for many years.

**Formatted**

**Deleted:** Such an evaluation should indicate whether or not confirmatory pre-clinical or clinical trials are required. ...f significant changes in quality are found, then new pre-clinical and/or clinical trials may be required to provide assurance that there has been no negative impact on the safety or efficacy of the medicine. Evaluations of such changes are conducted by the regulatory authorities and knowledge of the biological medicinal product characteristics assists the regulators in the evaluation of key attributes of both the reference and subsequent biosimilar medicinal products

### 5.2 Pre-clinical comparability

Pre-clinical (also known as non-clinical) studies describe the testing in cell culture and in animals that is normally required for new medicines in order to determine their safety profile prior to administration in humans. Unlike the situation for generic medicines which do not require pre-clinical testing, a pre-clinical testing package is required for biosimilars.

**Deleted:**

Pre-clinical testing is aimed at understanding functional aspects of the biosimilar and how the molecule behaves in terms of its impact on cellular function. Pre-clinical testing can include both cell-based and in limited cases *in vivo* animal testing and provides assurance that any minor difference seen in physiochemical comparability will not have any impact on the desired functionality of the molecule. Pre-clinical studies relate to the mechanism of action and are capable of uncovering possible subtle differences in the functionality of the biosimilar. Tests can be varied depending on the nature of the molecule and may address several aspects, including target binding, receptor interaction, cellular effects (signal transduction, viability, etc.), biological activity, as well as pharmacology and toxicology if necessary. For biosimilars, pre-clinical *in vivo* animal testing is generally not necessary and the amount and type of any *in vivo* testing required is evaluated on a case-by-case basis. For example, in the case of pharmacokinetic and pharmacodynamic studies, animal data would be superseded by human data. Likewise, *in-vitro* assays may often be more specific and sensitive in detecting differences between the biosimilar and the reference medicine than studies in animals, these assays can be considered as paramount for the pre-clinical comparability exercise.

**Deleted:** medicine...and how the molecule behaves in terms of its impact on cellular function. Pre-clinical testing can include both cell-based and in limited cases *in vivo* animal tests...esting and provides assurance that any minor difference seen in physiochemical comparability will not have any impact on the desired functionality of the molecule. Pre-clinical studies relate to the mechanism of action and are capable of uncovering possible subtle differences in the functionality of the biosimilar. Tests can be varied depending on the nature of the molecule and may address several aspects, including target binding, receptor interaction, cellular effects (signal transduction, viability, etc.), biological activity, as well as pharmacology and toxicology if necessary. For biosimilar products...iosimilars, pre-clinical *in vivo* animal testing may...s generally not always be

### 5.3 Clinical comparability

Efficacy trials conducted on biosimilars are not aimed at proving the medicine works per se (as that has been shown by the reference medicine); rather they are designed to investigate if any clinically meaningful differences exist between the biosimilar and the

**Deleted: ¶**  
The clinical data required to demonstrate biosimilarity far exceed that which would be required for a chemical generic medicine, where pharmacokinetic bioequivalence studies alone are sufficient. ¶

reference medicine (Weise, M. et al. *Biosimilars: What Clinicians Should Know*. Blood 2012; 120:5111-5117). [Physiochemical, molecular and biological characterisation represent the cornerstone of establishing biosimilarity and such tests are more sensitive than clinical studies in detecting any potential differences.](#) The clinical comparability exercise should [therefore](#) be viewed in conjunction with the demonstration of similarity provided by the physiochemical, biological and pre-clinical studies.

Clinical comparability is a stepwise approach and normally includes data on pharmacokinetics (PK), pharmacodynamics (PD) as well as clinical efficacy and safety trials. Studies on safety and efficacy should demonstrate that there are no clinically meaningful differences between the biosimilar and reference medicine and that there are no significant differences in the benefit/risk profile. The target population for efficacy trials is generally the most sensitive patient population in which any differences in clinical end-points can be most easily detected. [The clinical data required to demonstrate biosimilarity exceed that which would be required for a chemical generic medicine, where pharmacokinetic bioequivalence studies alone are sufficient.](#)

Immune reactions against biological medicines are a well-known phenomenon. Immunogenicity can be caused by several factors, including the presence of non-human amino acid sequences, the attachment of certain sugars which are not expressed in humans, protein aggregation and the presence of residual proteins from the cells in which the medicine was manufactured. Consequently, immunogenicity is required to be measured for all biological medicines. Therefore, safety data for [biosimilars](#) will include immunogenicity testing (up to one year for a chronic medical condition) in order to identify any differences in immune reactions between the biosimilar and reference medicines.

For the majority of [biosimilars](#), clinical efficacy trials will be needed. In certain cases, comparative PK/PD studies between the biosimilar and the reference medicine may be sufficient to demonstrate clinical comparability and thus a clinical efficacy trial may not be required. This is only acceptable when a clinical measurement can be made which accurately predicts patient outcome using what is referred to as a surrogate marker. Surrogate markers are usually based on laboratory tests which reflect some aspect of the disease process and can be used as a substitute for a standard clinical end point. A strong well-validated association must exist between the chosen surrogate marker(s) and patient outcome, i.e. it must be able to predict patient benefit. Many surrogate markers are already well-described and are considered sufficient to assess clinically meaningful differences between two medicines. Examples include the use of absolute neutrophil count to assess the effect of granulocyte-colony stimulating factor (G-CSF) and magnetic resonance imaging of disease lesions to compare two  $\beta$ -interferons. For [biosimilars](#) approved on the basis of comparative PK/PD studies, a full evaluation of immunogenicity data is [generally](#) still required.

**Deleted:** and Patients

**Deleted:**

**Deleted:**

**Deleted:** relies upon the solid foundations provided by the quality comparability and

**Deleted:** The quality comparability exercise, demonstration of similarity and the safety and efficacy profile of the reference medicine provide the basis for acceptance of a tailored clinical testing programme for a biosimilar medicine.

**Deleted:** biosimilar medicines

**Deleted:**

**Deleted:** biosimilar medicines

**Deleted:** biosimilar medicines

Deleted: and Patients

## 6 INTERCHANGEABILITY, SWITCHING AND PRESCRIBING

In its guidance document 'Biosimilars in the EU – Information Guide for Healthcare Professionals', the EMA defines interchangeability as referring 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 medicine with a biosimilar (or vice versa) or replacing one biosimilar with another'. As part of the approval process, biosimilars must demonstrate that there are no clinically meaningful differences between the biosimilar and the reference medicine. Therefore, biosimilars can be used interchangeably with the reference medicine or with other biosimilars of that reference medicine, under the supervision of a physician.

Switching, as defined in the above EMA guidance document, 'is when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent'. It is not the same as automatic substitution, where a medicine is substituted for another by a pharmacist without the input of the prescriber (see more on this below).

European legislation does not require dedicated clinical 'switching studies' where patients change from the reference medicine to the biosimilar and vice versa. While some theoretical concerns regarding increased immunogenicity following a switch have been suggested, the theoretical basis for such concerns does not appear robust (Kurki P et. al. BioDrugs, 2017, 31(2):83-91). Consequently, once a biosimilar has been approved, it can be considered appropriate to switch, should a prescribing physician wish to do so. Decisions to switch a patient's medicine should be carried out in line with agreed hospital or local policies. In the cases of medicines intended for administration by patients or caregivers, necessary training on devices may be required. Further information on prescribing in the context of switching may be accessible from the HSE.

Appropriate clinical monitoring and surveillance should be maintained after any switching. Traceability systems must be in place so any adverse reactions (ADRs) can be attributed to the correct medicine. To facilitate traceability, any biological medicine prescribed, dispensed or sold should be clearly identifiable by brand name or, as appropriate, INN accompanied by the name of the marketing authorisation holder. This will also help ensure that substitution does not inadvertently occur when the medicine is dispensed by the pharmacist. In order to facilitate accurate reporting in the event of an ADR, the batch number should also be recorded (see Section 10).

Deleted: drug

Under the Health (Pricing and Supply of Medical Goods) Act 2013, the HPRA publishes a list of medicines which may be substituted for each other in the community pharmacy setting. When generic medicines are made available to patients in this way, it is known as 'generic substitution'. It is important to highlight that under this legislation biological medicines are specifically excluded from being added to interchangeable medicine lists. As such, they cannot be subjected to pharmacy substitution.

Moved (insertion) [5]

Moved (insertion) [6]

Deleted: extrapolation of indications†

## 7 EXTRAPOLATION OF INDICATIONS

The reference biological medicine may be authorised in more than one clinical indication and clinical trials will have been conducted with the reference medicine to demonstrate efficacy in each indication for which it is approved. For a biosimilar, confirmatory clinical studies are not required to demonstrate equivalence in every approved indication, as this has already been done for the reference medicine. Therefore, the process of extrapolation is used for biosimilars (Weise, M. et al. Biosimilars: the science of extrapolation Blood 2014; 124:3191-3196). It should be noted that a biosimilar might not be authorised for use in all indications approved for the reference medicine, therefore it is important for healthcare professionals to review the summary of product characteristics (SmPC), and package leaflet in order to be aware of the approved indications.

Clinical efficacy studies in biosimilars are normally carried out in a single indication, which represents the most sensitive patient population with the most sensitive clinical endpoints. Once biosimilarity has been demonstrated in one indication, extrapolation to other indications could be permissible. The demonstration of biosimilarity through the combination of analytical testing and relevant non-clinical and clinical studies forms a scientific bridge between the biosimilar and the reference medicine that allows for the extrapolation of safety and efficacy information from the reference medicine to the biosimilar. However, the decision to allow indication extrapolation is made for each biosimilar on a case-by-case basis. The quality and pre-clinical comparability data provide a foundation upon which indication extrapolation can be approved. Extrapolation is based on the overall evidence of comparability and sound scientific justification. For extrapolation to be approved, the scientific justification must include assurance that the mechanism of action of the medicine in terms of achieving the therapeutic effect is the same across each indication. Where this is not the case, additional clinical studies and/or analytical studies may be required. It is imperative that the method of action is well understood in each indication and that evidence is sought/provided that will demonstrate the biosimilar's clinical and immunogenic effect. Details of extrapolated indications, and the basis on which they have been accepted, are outlined in the European Public Assessment Report (EPARs) for all centrally authorised biosimilars. EPARs are available on the EMA website. Further information on EPARs is provided under the 'Product Information' heading below.

It is important to stress that the concept of extrapolation is not unique to authorisation of biosimilars; a similar approach may be used to deal with post-authorisation changes for reference biological medicines. For example, if a major change to the manufacturing process, results in significant differences in physiochemical and/or biological characteristics, and it cannot be ruled out that there might be an effect on safety or efficacy, a confirmatory clinical efficacy study may be required. Such a clinical study is carried out in one of the approved indications of the medicine and the efficacy data are then extrapolated to all the authorised indications.

**Deleted:** and Patients

**Deleted:** medicine, confirmative

**Deleted:** biosimilar medicines

**Deleted:** product information

**Deleted:** (PIL) and European public assessment report carefully, and

**Deleted:** its

**Deleted:** and the basis for these

**Deleted:** biosimilar medicines

**Deleted:** While it may not be possible in every case, once

**Deleted:** medicine

**Deleted:**

**Deleted:**

**Deleted:**

**Deleted:** ,

**Deleted:** form of

**Deleted:**

**Deleted:**

**Deleted:**

**Deleted:** Note: Section 9.1 provides further guidance on accessing information on the quality, preclinical and clinical development of a biosimilar medicine.¶

¶

Page Break

¶

¶

### WHY ARE BIOSIMILAR MEDICINES USED?¶

¶

As a class, biological medicines are generally more expensive than chemical small molecules and can pose a significant impact on healthcare budgets. This is due to the greater complexity in the development and manufacturing processes for biological medicines. Biosimilar medicines may offer a less-costly alternative to the reference medicine due to reduced development costs associated with these products, As such they have the potential to generate savings and efficiencies for healthcare systems, which can help free up resources for other important aspects of healthcare. The availability of biosimilar medicines may increase patient access to ...

## 8 INTERNATIONAL NON-PROPRIETARY NAME (INN)

The INN is a unique name given to an active substance, which is globally recognised and is public property. The INN is used to facilitate the identification of active substances and the INN system is managed by the World Health Organisation (WHO). Currently in the EU, biosimilars have the same INN as the reference medicine. As for all medicines, biological medicines with the same INN should not be considered to be identical; for example, two biological medicines which have the same INN may have different indications or dosing requirements among other factors.

## 9 PRODUCT INFORMATION

The summary of product characteristics (SmPC) for a biosimilar will contain the same clinical information as the SmPC of the reference medicine and section 5.1 of the SmPC will state that the medicine is a biosimilar. However, there may be differences in authorised indications, which will be described in section 4.1 of the SmPC. If the reference medicine is benefiting from patent protection for some indications, these cannot appear in the medicine information of the biosimilar.

There may also be differences related to excipients, shelf life, storage conditions, etc. If precautions are necessary because of an excipient, they will be described both on the label and in the package leaflet of the biosimilar.

The SmPC and package leaflet for every centrally authorised medicine is published on the EMA website and can be located using the 'Search for medicines' in the 'Find Medicine' section (<https://www.ema.europa.eu/en/medicines>). SmPCs and further information about biosimilars is also available at [www.hpra.ie](http://www.hpra.ie).

The European public assessment report (EPAR) published on the EMA website ([www.ema.europa.eu](http://www.ema.europa.eu)) will contain detailed information on the manufacturing process, the medicine characterisation, biosimilarity exercise, pre-clinical studies, clinical pharmacology studies (PK and PD), immunogenicity data and clinical efficacy studies. It will also discuss how these studies were assessed by regulators. The EPAR of centrally authorised medicines contains details of the data submitted to prove biosimilarity and can be found on the EMA website under the assessment history of the medicine. The EPAR product information can be found under the 'Product Information' tab. This includes the medicine's summary of product characteristics and the package leaflet. A copy of this leaflet is required to accompany a medicine and patients are encouraged to read this. Where treatment is being provided within a healthcare setting through infusion or other means, provision should be made to ensure the patient has access to the package leaflet for the medicine.

The EMA website is also a useful resource for access to the most recent EU and ICH guidelines used in the authorisation of biosimilars. These include an overarching biosimilar guideline, as well as individual quality and pre-clinical/clinical guidelines. There are also separate guidelines

Deleted: and Patients

Deleted: ¶  
¶

Deleted: Regulations on the naming of

Deleted: biologics/ biosimilars are continuing to evolve at a global level. As stated previously

Deleted: can exhibit variability and therefore biological medicines which have

Deleted: . For

Deleted: ,

Deleted: <#>PRODUCT INFORMATION¶  
<#>¶

Deleted: medicine

Deleted: medicine.

Deleted: medicine.

Deleted: <#>Information for healthcare professionals¶  
<#>¶

Deleted: <#>summary of product characteristics (

Deleted: <#>)

Deleted: <#>product information

Deleted: <#>'Find Medicine' section. SmPC information

Formatted: Font: Segoe UI, 10 pt, Font color: Accent 3

Deleted: <#>[www.hpra.ie](http://www.hpra.ie).

Deleted: ([www.ema.europa.eu](http://www.ema.europa.eu))

Deleted:

Deleted: particularly useful

Deleted: biosimilar medicines, as it contains details of the data submitted to prove biosimilarity

Deleted: which are

dealing with individual medicine classes. The EMA scientific guidelines on biosimilar products can be found at the hyperlink [here](#).

Healthcare professionals should note that the clinical information contained in the product [information](#) of a biosimilar may be based on that of the reference [medicine](#).

## 10 PHARMACOVIGILANCE AND ADVERSE REACTION REPORTING

Pharmacovigilance and monitoring of [suspected](#) adverse [reactions](#) are usual components of the authorisation process and use of any [medicine](#), including biosimilars. An adverse [reaction](#) is defined as a response to a medicine which is noxious and unintended (including lack of efficacy). Within the EU there is a well-developed pharmacovigilance framework for the monitoring, evaluation and prevention of drug-related adverse [reactions](#). The current [pharmacovigilance](#) legislation described in [Directive 2001/83/EC, as amended](#), sets out [comprehensive requirements for recording and reporting of suspected adverse reactions](#).

As is the case for all biological medicines, the clinical safety of biosimilars must be monitored closely on an ongoing basis during the post-approval phase, including continuous benefit-risk assessment. Any specific safety monitoring imposed on the reference [medicine](#) or medicine class will also apply to the biosimilar.

[All new](#) medicines, [including](#) biosimilars, [are](#) subject to [additional](#) monitoring following approval [which includes the display of](#) the black inverted triangle symbol in the SmPC and package leaflet. This does not imply that there are any additional safety concerns for biosimilars. [A new](#) medicine remains under additional monitoring for five years or until the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) decides to remove it from the list. As for all medicines, healthcare [professionals](#) are asked to report any suspected adverse reactions [associated with medicines that are subject to additional monitoring requirements](#).

Reporting of [suspected](#) adverse reactions, [is mandatory](#) for marketing authorisation holders (MAH) [in accordance with legal obligations and guidance in place across the EU](#). Healthcare professionals should also report any [suspected](#) adverse reactions they [become](#) aware of to the HPRA [via the available reporting options \(www.hpra.ie\)](#).

Clear identification [and traceability](#) of medicines is [important when reporting suspected](#) adverse [reactions](#), and in particular for biological medicines, given their particular characteristics. [As described in the EMA guide on biosimilar medicines for healthcare professionals: 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. Biological medicines should be clearly identifiable throughout the prescribing, dispensing and pharmacovigilance processes.](#)

Deleted: and Patients

Deleted: here

Formatted

Field Code Changed

Formatted

Deleted: literature...nformation of a biosimilar may be

Deleted: <#>Information for patients!

Deleted: events

Deleted: new

Deleted: ¶

Deleted:

Formatted

Deleted: Directive 2010/84/EU

Formatted: Font: 10 pt

Formatted

Deleted: 2010/84/EU and Directive 2012/26/EC

Formatted

Deleted: events

Formatted

Deleted: and, if necessary, prompt regulatory action

Formatted

Deleted: .

Deleted: ed

Deleted: medicines...edicine or medicine class will also

Deleted: As for all newly licensed biological...ll new

Deleted: closer

Deleted:

Deleted: , this is indicated by...which includes the

Deleted: to medicines authorities...is mandatory

Deleted: www.hpra.ie).

Deleted: of particular importance

Deleted:

Deleted: for ...dverse drug ...eactions reporting

Deleted: Such...s described in the EMA guide on

[recording of the name and batch number of the medicine](#) is key to this. Article 102(e) of Directive [2001/83/EC \(inserted by Directive 2010/84/EU\)](#) requires that adverse reaction reports record the brand name or, as appropriate, INN accompanied by the name of the marketing authorisation holder and batch number of the biological medicine prescribed, dispensed, or administered which is the subject of a suspected adverse reaction report. Note: if the INN is used, it must be used in conjunction with the name of the marketing authorisation holder to ensure that the specific product can be identified. [This requirement is also specified in national legislation \(Regulation 33 \(7\) of S.I. 272/2012 - Medicinal Products \(Control of Placing on the Market\) \(Amendment\) Regulations 2012.](#)

[The need to record the brand name of biological medicines is also covered in the 'Cross Border' Directive 2011/24/EU, which](#) provides a system of enabling patients entitled to healthcare in Ireland to avail of that healthcare in other EU member states and Switzerland. The Directive has been brought into effect under Irish national legislation and includes provision to enable prescriptions written in Ireland to be dispensed in other countries and vice versa, subject to the fulfilment of certain minimum criteria. In relation to such prescriptions for biological medicines, this includes a requirement for [prescribers](#) to record the specific brand name of the medicine to be dispensed, thereby ensuring ease of identification in other countries.

**Deleted:** and Patients

**Deleted:**

**Deleted:** ¶

**Deleted:** Information for patients ¶

¶  
All newly authorised biological medicines continue to be monitored for safety after they are approved. This is the same for biosimilars and therefore the product information leaflet will include the inverted black triangle symbol and the statement 'This medicine is subject to additional monitoring'. This will allow quick identification of new safety information. This does not imply that there are any additional safety concerns for biosimilar medicines, as this monitoring applies equally to all newly authorised biological medicines, it is used to encourage the reporting of any suspected adverse reactions. Patients can help by reporting any side effects themselves directly to the HPRA, and/or to their healthcare professional.¶

¶

Prescribing and interchangeability¶

**Moved up [5]:** ¶

Under the Health (Pricing and Supply of Medical Goods) Act 2013, the HPRA publishes a list of medicines which

**Deleted:** in order to help reduce costs for patients and/or the health service.

**Moved up [6]:** When generic medicines are made available to patients in this way, it is known as 'generic substitution'. It is important to highlight that under this

**Deleted:** As such they cannot be subjected

**Deleted:** pharmacy substitution as exists for small chemical molecules. ¶

¶

**Deleted:** are prescription-only medicines. If you are receiving your medicine for the first time, your physician may prescribe the originator reference medicine or a ¶

**Deleted:** 201

**Deleted:** these

**Deleted:** ¶

¶

¶