

# Guide to **Biosimilars for Healthcare Professionals and Patients**

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## EXECUTIVE SUMMARY

This guidance document provides valuable information on the regulation, prescribing, dispensing and traceability of biosimilar medicines in Ireland. This guidance, while primarily targeted at healthcare professionals, will also be of relevance to others including patients, manufacturers, distributors and those involved in hospital procurement.

A biosimilar is a biological medicine that is highly similar to another biological medicine (reference medicinal product) 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 for its own approved indications.

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.

As biological medicines are manufactured from a biological source, they are significantly more complex than chemical small molecules. This complexity associated with all biological medicines means that biosimilars, which are similar to already approved biological medicines, cannot be considered as generic medicines in the traditional sense. For generic medicines, it is relatively more straightforward to demonstrate that one chemical substance is highly similar or identical to another chemical substance. This is not possible for biological medicines. The standard generic approach (demonstration of bioequivalence with a reference medicine by appropriate bioavailability studies) which is applicable to most chemically-derived medicines is not sufficient to demonstrate similarity of biological/biotechnologically-derived products due to their complexity. The biosimilar approach is based on a comprehensive comparability exercise. For biosimilars the indications are generally those already tested and approved for the reference product. However, this will depend on whether indication extrapolation has been accepted during the regulatory approval. Manufacturers of biosimilars must perform an extensive head-to-head comparability exercise with the reference medicine and demonstrate to regulators that they have similar quality, safety and efficacy to the reference medicine such that there are no clinically meaningful differences between the two. The purpose of this guide is to provide an overview of the regulatory processes through which the quality, safety and efficacy of biosimilar medicines is assessed prior to gaining marketing authorisation. The guide is primarily aimed at healthcare professionals for the purpose of informing and assisting their decision making processes when prescribing and dispensing medicines of this nature. It will also be of interest to those working in the area of medicines procurement and related activities.

In addition to this overview, topics considered to be of high importance to healthcare professionals and others are also covered as follows.

### **Indication extrapolation**

For a biosimilar product to be approved, it is not always necessary to conduct clinical efficacy studies in every indication for which the reference medicine was approved. The biosimilar must demonstrate that there are no clinically meaningful differences relative to the reference medicine in a sensitive patient population i.e. a group of patients where any differences between the two medicines are most likely to be revealed. The scientific justification for extrapolation to other indications not studied in the biosimilar clinical programme is evaluated as part of the assessment process on a case-by-case basis, based on the totality of data (quality, non-clinical and clinical data). In line with this the biosimilar may be approved in all indications for which the reference product is approved. This is referred to as indication extrapolation. It is an important concept for healthcare professionals to be familiar with, given that efficacy trials for the medicine may not have been carried out in all proposed treatment groups. However, extrapolation is based on scientific principles requiring specific structural, physicochemical and biological comparability data justifying its acceptance.

### **Traceability**

There are specific issues surrounding the traceability and pharmacovigilance of all biological medicines including biosimilars. All biologicals, including biosimilars, should be prescribed, dispensed and sold in a way where the product supplied to the patient is clearly identifiable. Similarly all appropriate measures should be taken to clearly identify any biological medicinal product which is the subject of a suspected adverse reaction report, with due regard to its brand name and batch number. Requirements and recommendations for recording relevant information when dispensing biosimilars, and ensuring the maintenance of product traceability are outlined in the guide.

### **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.

## 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.

<b>Bioequivalence</b>	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).
<b>Biological medicine</b>	A medicine that contains an active substance made by a biological process or derived from a biological source.
<b>Biosimilar</b>	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 medicinal product). Biosimilars contain a version of the active substance of an already approved medicine.
<b>Biosimilar comparability exercise</b>	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.
<b>Centralised procedure</b>	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).
<b>EMA</b>	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.
<b>Indication Extrapolation</b>	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. 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 product, 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.

**Generic medicine**

A medicinal product (usually a chemically synthesised small molecule) which has the same qualitative and quantitative composition as a reference medicine. Generic medicines must demonstrate bioequivalence with the reference product.

**HPRA**

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).

**Interchangeability**

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.

**Marketing authorisation**

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 which must demonstrate that the medicine has acceptable quality, safety and efficacy.

**Market exclusivity**

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 medicinal product.

**Reference medicine**

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

**International Non-Propriety 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).

## **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 biosimilar medicines. The guidance covers a range of topics relevant to this, including explanations of the differences between a 'reference biological medicine' and a 'biosimilar medicine', differences between biosimilar medicines 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 market place.

## **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);
- recombinant 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 and animal-derived products such as heparin and vaccines.

Biological medicines contain larger and more complex active substances than chemically synthesised small 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. Due to this variability it may not be possible to make an exact copy of a biological active substance. 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 the term biosimilar is used to describe 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.

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 have a high degree of similarity in molecular and biological terms to the active substance of the reference medicine. For example, for an active substance that is a protein, the amino acid sequence is expected to be the same. However, there are likely to be minor differences due to their complex nature and to variability in the production methods. Notwithstanding these differences, a biosimilar and its reference medicine must have a similar biological activity, safety and efficacy profile. 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, biosimilars can differ relative to the reference medicine and typical parameters for consideration in this regard include pharmaceutical form, formulation, excipients or presentation and a biosimilar may use different administration devices.

The manufacturing process of biological medicines can be complex, and variability can be seen from batch to batch (although this is regulated to remain within defined boundaries). 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. These differences in the manufacturing processes and the naturally occurring heterogeneity of biological molecules directly contribute to the variability between the biosimilar and the reference medicine. For these reasons, biosimilar medicines are not considered to be generics as explained above. As such, the regulation and approval procedure for biosimilars is different to that of small molecule generic medicines and has been adapted to take account of their unique nature. The key principle on which a biosimilar medicine is approved for use is that any variability or differences between it and the reference medicine have been shown not to affect its safety or efficacy in a clinically significant way. It is important to note that biosimilars must comply with the accepted standards of quality, safety and efficacy as laid down in European legislation and guidance. While there are differences in the approval processes for biosimilar medicines, this does not mean inferiority to the reference medicine. Further information on the authorisation processes is described in section 7.

#### **4 WHEN CAN A BIOSIMILAR MEDICINE BE DEVELOPED?**

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 medicinal product, provided it has been authorised. Biosimilar medicines have been approved in the EU since 2006 and to date include biosimilar versions of somatropin, epoetin, filgrastim, follitropin alpha, insulin and infliximab. A list of all biosimilar medicines authorised centrally in the EU can be found on the [EMA website \(www.ema.europa.eu\)](http://www.ema.europa.eu). Several biological medicines will be coming off patent over the next few years and therefore the number of biosimilar medicines is likely to grow.

#### **5 HOW ARE BIOSIMILARS AUTHORISED?**

Biosimilars are authorised under Article 10(4) of Directive 2001/83/EC of the European Parliament 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 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 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 marketing authorisation which is valid in all EU member states, that is, a single EU marketing authorisation permits marketing in all EU member states.

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.

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 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 *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 and biological activity/potency. Quality comparability must demonstrate that the medicine is highly similar to the reference medicine. In addition, the physiochemical and biological tests must identify and characterise any differences between the biosimilar and reference medicine in order to determine their impact. The Quality Target Product Profile (QTPP) is a prospective summary of the quality characteristics of a drug product that ideally will be achieved and provide assurance of the desired quality, taking into account safety and efficacy of the drug product. Typical parameters considered in the profile include dosage form; potency; protein content per dose; product concentration; viscosity; impurities etc. This is not exhaustive and other factors may be expected to be considered. During the initial development of a biosimilar, several batches of the reference medicine are analysed in order to establish the QTPP. This information is then used to set target ranges for each of the parameters in the profile, in so far as possible these will be quantitative in nature. The demonstration of biosimilarity will be dependent on meeting these defined criteria.

Quality testing is therefore the cornerstone of biosimilarity. The level of data needed to confirm biosimilarity is higher than that needed for demonstration of similarity for chemical generic medicines because of their complexity. For example generic medicines have a defined chemical structure which can more readily be shown to be identical to the chemical structure of an already approved medicine. Due to the complexity and variability of biological medicines such a direct unequivocal demonstration of identical structure is not possible, even with today's sophisticated analytical technology.

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

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. Such an evaluation should indicate whether or not confirmatory pre-clinical or clinical trials are required. 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 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.

Pre-clinical testing is aimed at understanding functional aspects of the biosimilar medicine and how the molecule behaves in terms of its impact on cellular function. Pre-clinical testing can include both cell-based and *in vivo* animal tests 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, pre-clinical *in vivo* animal testing may not always be necessary and the amount and type of *in vivo* testing 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.

## 5.3 Clinical comparability

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.

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 reference medicine (Weise, M. et al. *Biosimilars: What Clinicians Should Know*. Blood 2012; 120:5111-5117). The clinical comparability exercise relies upon the solid foundations provided by the quality comparability and should be viewed in conjunction with the demonstration of similarity provided by the physicochemical, biological and pre-clinical studies. 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.

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.

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 biosimilar medicines 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 biosimilar medicines, 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 biosimilar medicines approved on the basis of comparative PK/PD studies, a full evaluation of immunogenicity data is still required.

## 6 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 medicine, confirmative 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 biosimilar medicines (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), product information leaflet (PIL) and European public assessment report carefully, and to be aware of its approved indications and the basis for these.

Clinical efficacy studies in biosimilar medicines are normally carried out in a single indication which represents the most sensitive patient population with the most sensitive clinical endpoints. While it may not be possible in every case, once biosimilarity has been demonstrated in one indication, extrapolation to other indications could be permissible. However, the decision to allow indication extrapolation is made for each biosimilar medicine 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 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.

It is important to stress that the concept of extrapolation is not unique to authorisation of biosimilars, a similar form of 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.

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

## 7 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 these products and allow resources to be directed toward new innovative medicines. Once similarity has been demonstrated via a comprehensive comparability exercise, the efficacy and safety data that has previously been generated for the reference medicine can be considered to be applicable for the biosimilar. This means that biosimilar medicines can be cheaper than reference medicines as the cost of bringing a biosimilar medicine to the market is less than with a novel biologic medicine due to reduced research and development costs.

Biosimilars have been approved in the EU since 2006. Since that time, there has been a varied uptake in individual member states, with some areas seeing high market penetration and others experiencing a more modest uptake. The uptake of biosimilars is currently growing across the EU and is described in the European Commission document [‘What you need to know about biosimilar medicinal products’](#).

## 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. Regulations on the naming of all biologics/ biosimilars are continuing to evolve at a global level. As stated previously, biological medicines can exhibit variability and therefore biological medicines which have 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 medicine 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 medicine.

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 medicine.

### **9.1 Information for healthcare professionals**

The summary of product characteristics (SmPC) and product information leaflet for every centrally authorised medicine is published on the EMA website in the '[Find Medicine](#)' section. SmPC information 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 can be found on the EMA website under the assessment history of the medicine. The EPAR is particularly useful for biosimilar medicines, as it contains details of the data submitted to prove biosimilarity.

The EMA website is also a useful resource for access to the most recent EU and ICH guidelines which are 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 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 literature of a biosimilar may be based on that of the reference product.

### **9.2 Information for patients**

The European Medicines Agency website contains general information about individual biosimilar medicines which is very useful for patients. The EPAR-product information can be found under the 'Product Information' tab. This includes the medicine's summary of characteristics and the patient information leaflet. A copy of this leaflet will always 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 information leaflet for the medicine. In such circumstances patients should request the leaflet from their healthcare provider. This relates to all medicines and is not unique to biosimilars.

## 10 PHARMACOVIGILANCE AND ADVERSE DRUG REACTION REPORTING

Pharmacovigilance and monitoring of adverse events are usual components of the authorisation process and use of any new medicine, including biosimilars.

### 10.1 Information for healthcare practitioners

An adverse event 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 events. The current pharmacovigilance legislation described in [Directive 2010/84/EU](#) sets out comprehensive requirements for recording of adverse events and, if necessary, prompt regulatory action to safeguard public health.

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 continued benefit-risk assessment. Any specific safety monitoring imposed on the reference medicines or medicine class will also apply to the biosimilar medicine.

As for all newly licensed biological medicines, biosimilars will be subject to additional monitoring following approval, this is indicated by the black inverted triangle symbol displayed in the SmPC and package leaflet. This does not imply that there are any additional safety concerns for biosimilars, as all newly authorised biological medicines are subject to this additional monitoring. A 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 professional are asked to report any suspected adverse reactions.

Reporting of adverse reactions to medicines authorities is mandated for marketing authorisation holders. Adverse reactions are reported through a database maintained by the EMA known as Eudragilance. Healthcare professionals should also report any adverse reactions they are aware of to the HPRA. Details for reporting can be found on the HPRA website ([www.hpra.ie](http://www.hpra.ie)).

Clear identification of medicines is of particular importance for adverse drug reaction reporting and in particular for biological medicines, given their particular characteristics. Such medicines should be clearly identifiable throughout the prescribing, dispensing and pharmacovigilance processes, distinct naming is key to this. Article 102(e) of 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.

## **10.2 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.

## **11 PRESCRIBING AND INTERCHANGEABILITY**

As biosimilar medicines cannot be treated in the same way as generic medicines, prescribing practices and interchangeability between medicines needs to be carefully considered.

### **11.1 Information for healthcare professionals**

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 ensure that substitution of biosimilar medicines does not inadvertently occur when the medicine is dispensed by the pharmacist.

It is not recommended that patients switch back and forth between a biosimilar and reference medicine, as at the current time the availability of data on the impact of this are limited. In the context of all biological medicines, it is important that careful consideration is given by healthcare professionals to decisions of this nature. If it is planned to change the medicine a patient receives from a reference to a biosimilar medicine or vice versa, the treating physician should be involved; this should involve discussion between the prescriber/ patient, and prescriber /dispensing pharmacist.

In a hospital setting it is important that for biological medicines, including biosimilars, there is ongoing engagement between prescribers, dispensers and those with responsibility for procurement. In this way funding agencies, hospital budget holders and healthcare professionals can engage to consider appropriately governed introductions of biological medicines with a view to ensuring optimal use of resources. This will ensure that, as a greater number of biosimilar medicines continues to be brought onto the marketplace, prescribing and procurement practices remain aligned in terms of ensuring the best patient outcomes.

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 in order to help reduce costs for patients and/or the health service. 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 as exists for small chemical molecules.

Further information on a biological medicine (including biosimilars) can be found in the EPAR which is available on the EMA website ([www.ema.europa.eu](http://www.ema.europa.eu)).

### **11.2 Information for patients**

All biological medicines are prescription-only medicines. If you are receiving your medicine for the first time, your physician may prescribe the originator reference medicine or a biosimilar version. The biosimilar medicine will have a different brand name but will contain a similar active substance. The quality, safety and efficacy of the biosimilar medicine will have been shown to be comparable to the reference medicine.

In some circumstances, the medicine you are given may change from the reference medicine to the biosimilar medicine or vice versa. This will have been done following a decision by your prescribing physician and pharmacist. You should discuss this change with your prescribing physician and pharmacist who will be able to address your queries.

Further information on your biological medicine (including biosimilars) can be found in the EPAR which is available on the EMA website ([www.ema.europa.eu](http://www.ema.europa.eu)).

## **12 DIRECTIVE ON THE APPLICATION OF PATIENTS' RIGHTS IN CROSS-BORDER HEALTHCARE ('CROSS BORDER DIRECTIVE')**

The 'Cross Border' Directive 201/24/EU 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 these to record the specific brand name of the medicine to be dispensed, thereby ensuring ease of identification in other countries.