

An Update on Biosimilars in Lymphoma

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Introduction

Biosimilars have been treatment options in a variety of diseases for more than 10 years. In oncology, including in lymphoma treatment, patients may have received biosimilars that increase production of certain blood cells. These **supportive care** drugs do not treat the cancer itself but treat side effects. Relatively new to the market are rituximab biosimilars, that treat the lymphoma directly.

Even though biosimilars have been approved and used in treatment in some parts of the world, they are still not available widely or consistently to patients everywhere. It is anticipated that in the coming years, the use of biosimilars to treat lymphoma will expand considerably.

When biosimilars were first introduced, there were concerns for patients regarding safety, naming, interchangeability and access. Over a decade later, some issues have been addressed but there are still concerns regarding:

- Safety where approval/use guidelines are not available or less regulated;
- Interchangeability with the originating drug or between biosimilar drugs;
- Access.

What is a Biologic?

A **biologic** is a substance that is made from a living organism or its products. Biologics are developed in living systems, including bacterial, yeast and mammalian cells. Most biologic medicines are **proteins**. Proteins are naturally occurring molecules that are essential to biologic activity and a body functioning properly.

Biologics differ from traditional drugs (or **small molecule drugs**) that are made by combining chemicals.

Manufacturing biologic drugs is a complex process. When biologics are developed, this is the process that is followed:

1. Host cells (the bacterial, yeast or mammalian cells, which act as the foundation of the subsequent cell line) are modified to produce recombinant proteins, meaning a protein is manipulated and generated in a lab in various ways to produce large quantities of the protein;
2. Cells are grown under controlled conditions (fermentation), and a cell-line is developed;
3. The drug substance is extracted, purified and **characterised** (explanation of its physical, chemical, biological, and microbiological properties);
4. The drug substance is formulated to the stable finished product and distributed in the form of a vial, syringe or cartridge.

What is a Biosimilar?

Biosimilar or biosimilarity means that the biological product (in this case a drug) is highly similar to the **reference product** (the original biologic drug; also called the innovator product) and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, quality and effectiveness of the product.

A biosimilar drug is a drug that enters the market after the innovator product that has been previously authorised in the country, and with demonstrated similarity to the reference drug. Biosimilars may also be referred to as copy biologics or follow-on biologics.

Biosimilars are not **generics**; rather they are similar but not identical to the original biologic product. Different manufacturing processes may alter a protein product in a way that could affect the safety or effectiveness of the product. Since a biosimilar manufacturer will need to develop a unique cell line with a unique manufacturing process, the biosimilar itself cannot be an exact replica of the reference or **innovator product**. Instead, the biosimilar manufacturer will be required to demonstrate that any differences between the biosimilar and the **reference product** do not result in clinically meaningful differences in safety, purity and potency.

Table 1: Difference between Generics & Biosimilars

	Generic	Biosimilar
Production	Usually by chemical synthesis	Obtained from a biological source
Size	Small molecules with low molecular weight, usually under <900 Da	Large monoclonal antibodies, with high molecular weight of around ~150,000 Da
Structure	Simple	Complex
Biophysical	The structure of the molecule has well defined modifications and is easy to fully characterise	The structure of the molecule has complicated modifications and is difficult to fully characterise
Stability	Relatively stable	Sensitive to storage and handling
Manufacturing	Predictable chemical process and identical copy can be produced	Requires a unique cell line and identical copy is not possible

Biosimilar Approval Requirements

Approval of a biologic follows a government’s regulatory pathway. Biosimilars must demonstrate comparability with the original biologic including efficacy, safety and tolerability.

The earliest guidelines for the development and approval of biosimilars was outlined in Europe in 2005. Since then, more than 30 countries worldwide have developed approval pathways. When a country is developing a biosimilar, the guidelines for the country in which the product will be launched are followed.

Table 2: Biosimilar Guidelines in LC Member Countries

Member Country	Year of initial implementation
Argentina	2011 ¹
Australia	2013 ²
Brazil	2010 ³
Canada	2010 ⁴
China	2015 ⁵
Colombia	2014 ⁶
EEA* and EU**	2005 ⁷
India	2012 ⁸
Israel	2014 ⁹
Japan	2009 ¹⁰
Korea	2009 ¹¹
Mexico	2012 ¹²
Russia	2014 ¹³
Singapore	2009 ¹⁴
South Africa	2010 ¹⁵
Switzerland	2017 ¹⁶
Turkey	2008 ¹⁷
United States	2010 ¹⁸
Venezuela	2012 ¹⁹

*European Economic Area: Norway (Iceland and Liechtenstein are also part of the EEA but are not LC member countries)

** European Union: Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom (Austria, Cyprus, Estonia, Luxembourg, and Malta are also part of the EU but are not LC member countries).

In general, regulatory pathways for biosimilars differ from that of innovator products in that the bulk of the focus of innovator drug development comes from clinical trials on pharmacology (study of the drug's action), safety and efficacy (how well it works).

In comparison, the guiding principle of a biosimilar development program is to establish similarity between the biosimilar and the reference product, ensuring that the previously proven safety and efficacy of the reference medicinal product also applies to the biosimilar. To do so, a comprehensive description of the **physicochemical** and biological features must be conducted.

The scope of the non-clinical and clinical studies to be performed depends on the level of evidence obtained on the physicochemical, biological and non-clinical **in vitro** data. In addition, the complexity of the product also plays a role. Simpler molecules with well-established action and strong comparative quality data may not require the same degree of clinical data compared to larger molecules like monoclonal antibodies.

Generally, the aim of clinical data is to address slight differences shown in previous steps and to confirm that despite these slight differences, ultimately the result is a comparable clinical performance of the biosimilar and the reference product.

Regulatory agencies look at the ‘totality of evidence’ and will evaluate various types of information to provide an overall assessment that a biological product is biosimilar to an approved reference product. It is also possible that a regulatory body, in its discretion, may determine that a particular element – such as a confirmatory clinical trial - outlined in their approval pathway may not be necessary when looking at the totality of the evidence provided in the application. This requires that similar efficacy and safety can clearly be reasoned from the similarity of physicochemical characteristics, biological activity, potency, **pharmacokinetics** (how an organism affects a drug; also called PK) profile; and **pharmacodynamics** (how a drug affects an organism; also called PD) profile.

In addition, the clinical program needs to support extrapolation to non-studied indications and interchangeability with the original product.

Given the intricacies involved in manufacturing biologics, most biosimilars are being developed by global pharmaceutical companies and biotechs.

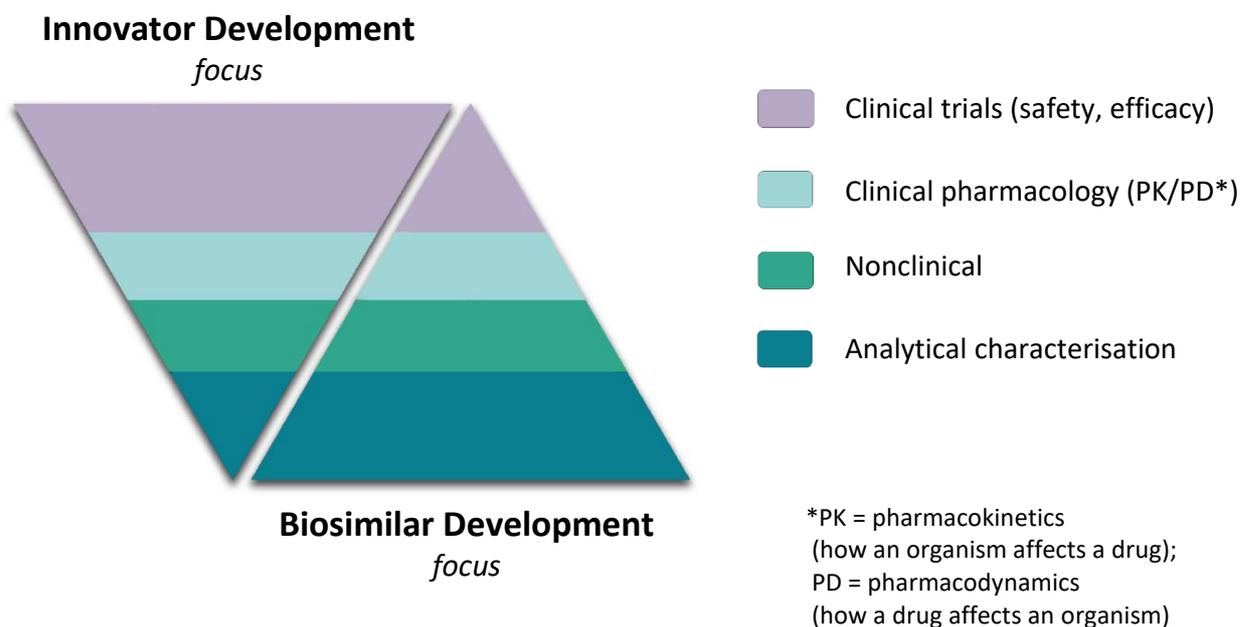


Figure 1: Biologic and Biosimilar Development Process

Table 3: Biosimilar Development Process

Steps	Characteristics
Step 1: Analytical Characterisation	<ul style="list-style-type: none"> • Assessment of structure and function • Amino acid sequence • Differences in glycosylation and post-translation modifications • Ligand binding and other functional tests
Step 2: Nonclinical	<ul style="list-style-type: none"> • Comparative animal toxicology • Animal PK and PD assessment
Step 3: Clinical Pharmacology	<ul style="list-style-type: none"> • PK to assess similarity in a sensitive population (can be healthy volunteers) • Equivalent PK (generally 90% CI* to be within 80%–125% as standard) establishes same dose as reference product • PD with dose-response equivalence can infer clinical efficacy if sensitive and relevant marker is available • Same dosing is appropriate as confirmed by bioequivalence studies
Step 4: Phase III Trial (confirmatory)	<ol style="list-style-type: none"> 1. Equivalence studies 2. Demonstration of similarity in terms of efficacy and safety in ONE indication 3. “Sensitive” primary end points may be different from those used in originator trials 4. May be sufficient for extrapolation across indications, based on high degree of similarity and same mechanism of action 5. Assessment of adverse drug reactions and anti-drug antibodies 6. Assessment of switching/interchangeability (<i>see page 7 for more information</i>)
Step 5: Post Approval Trials	<ul style="list-style-type: none"> • Additional data, such as immunogenicity (<i>see page 9 for more information</i>), to meet regulatory needs

*CI - Confidence Interval is an estimate of how confident the researcher is that the results match what would be found if it was possible to study the entire affected population.

Equivalence studies

Clinical trials involving a biosimilar always compare the reference product with the biosimilar. These are double-blind randomised studies so neither the patients nor the physicians know who is receiving which study drug, but they know they are not receiving a placebo. These studies are used typically for biosimilar products and are intended to demonstrate that the biosimilar product is not inferior and not superior to the reference product, within a prespecified margin.

In addition, it is important to note that data used in the demonstration of similarity are only valid at the time of market authorisation due to the possibility of drift caused by manufacturing changes. A biologic manufactured 10 years ago will not be the same as the one manufactured today or tomorrow because the biologic is being produced in a living cell using a complex process, and even very minor changes that are unintended can result in slight changes in the attributes or characteristics of the product. This is known as *manufacturing or production drift*. There are also changes in manufacturing processes over time. This happens with all biologic drugs, including the innovator drugs and does not only apply to biosimilars.

Extrapolation of indications

A biosimilar product may be licensed in one or more additional indications for which the reference product is licensed, if appropriate scientific reasoning is provided. The decision to extrapolate is based on the demonstration of similarity through extensive comparability studies as well as considering other critical factors such as the mechanism of action, PK, PD and disease **pathophysiology** (the processes or mechanisms that cause a disease to develop and progress) in each condition.

Ongoing Concerns

Therapies approved in markets without defined guidelines

In less regulated markets, there are 'alternative' or 'similar' biologicals available, even though no specific guidelines exist for their approval. This is more likely to be seen in developing markets, where there is a need for treatments at affordable prices. The regulatory requirements may be less rigorous and without a need for demonstration of biosimilarity. These 'alternative' biologicals cannot be compared to those approved in countries with rigorous comparability exercises.

An example of this is 'similar biologics' approved in India before the Indian 'similar biologics' guideline came into effect in 2012. They were approved using an ad-hoc abbreviated procedure on a case-by-case basis. Examples of similar biologics are provided later in this document (see Availability, starting on page 12).

This can affect people who live in a developing market and those who obtain their biosimilar from a developing market.

Patients should be carefully monitored by their doctor to ensure treatment goals are met and side effects are carefully documented and treated as needed.

Interchangeability

Interchangeability refers to replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another. Replacement can be done by:

Switching: which is when the prescriber decides to exchange one product for another product with the same therapeutic purpose.

Substitution (automatic): which is the practice of dispensing one product instead of another equivalent and interchangeable medicine at pharmacy level with or without prescriber consultation.

In either of these situations, a patient may or may not be informed of the replacement, depending on local regulations.

Globally, regulations pertaining to interchangeability and substitution differ. The following three examples show the diversity of these regulations:

- The USA has particularly stringent conditions. In the USA, the FDA requires that to allow interchangeability, additional requirements must be met including the assessment of risk in terms of safety and reduced efficacy of switching back and forth between an interchangeable product and a reference product in any given patient, as laid out in the [Biologics Price Competition and Innovation Act](#)^{20,21}. Currently, no biosimilar has been approved by the FDA as being interchangeable with its reference product as none have the required switching studies available where patients are treated in clinical trials with the innovator drug and its biosimilars in various orders, needed to obtain interchangeability status.
- In Europe, the decision to allow interchangeability and substitution of the reference biological usually occurs at a national level and is not determined by the EMA²². There is quite a bit of variability in how this is implemented. It may be a regional or local (hospital) decision, and/or a physician decision, and/or a pharmacist decision, and/or allowed only in treatment-naïve patients, and/or a patient-decision.
- In Canada, these decisions rest at the provincial level and Health Canada notes that authorisation of a biosimilar is not a declaration of equivalence to the reference biologic drug²³.

Any decision on switching should involve the prescriber in consultation with the patient and should consider any policies that the country might have regarding the prescribing and use of biological drugs.

The patient should ask each time they go for treatment which drugs they will be receiving and if they are different in any way to the drugs received previously.

It is important for the patient to keep track of any side effects experienced and report them back to their medical team. Most rituximab biosimilars are administered in combination with other drugs so any of the drugs used could be causing side effects.

As all medications have unique tracking numbers, including biosimilars, the treating facility will have a record of which drug a patient received.

Naming

The lack of consistency in naming means that the same biological entity can have different names or identifiers in different parts of the world.

Biosimilars that have been approved to date by the EMA have the same molecular name or International Non-proprietary Name (INN) as the reference product. In other countries that have approved biosimilars, some have used the same INN, while others have used a modified INN.

One of the concerns with using the same INN for the biosimilar as the reference product is that if any issues arise, such as adverse events or long-term issues such as bronchitis, it will not be clear as to which product caused them. Another concern with using the same INN is that while some countries may have a well-established **pharmacovigilance** system that is able to monitor and track the effects of a biosimilar versus a biologic once it has been licensed for use, other countries may not have such well-developed pharmacovigilance systems.

Most treating centres in Europe use the trade name when prescribing a product, rather than the INN to address this concern. The trade name is unique to the drug. As well, each drug has its own tracking number.

In 2016, the World Health Organization (WHO) released a guidance on how biosimilars should be named. The naming system proposed by the WHO was voluntary and was intended to provide a unique identification code – Biological Qualifier – that is distinct from the INN²⁴. This code would consist of four consonants plus an optional two digits as a checksum, with each code being assigned randomly. No consensus has been reached on whether WHO should continue with its biological qualifier proposal in assigning international non-proprietary names for biosimilars. Therefore, WHO is not currently pursuing this initiative.

In January 2017, the FDA finalised a guidance on the naming of biologics and biosimilars²⁵. Under this naming convention, the non-proprietary name designated for each originator biological product, related biological product, and biosimilar product will be a proper name that is a combination of the core name and a distinguishing suffix that is without meaning and composed of four lowercase letters.

A consistent, global naming scheme continues to be discussed, with the hope that distinguishable, non-proprietary names may improve tracking for various stakeholders as well as minimising unintentional substitution and improving access to biosimilars.

Safety

Immunogenicity is a measure of the immune response to a therapeutic drug. With all biologics and biosimilars there is the potential for an immunogenic response because it is a foreign protein that is being infused into the body.

While the efficacy and safety of a biosimilar may be similar to the reference product, immunogenicity may be different and could result in unwanted responses. Factors that can affect immunogenicity include the properties of the biologic, such as **glycosylation**, issues with production and the formulation, the way it's administered, dose, length of treatment and patient characteristics. Consequently, at all stages in the development of a biosimilar, immunogenicity is assessed to ensure it is comparable with the reference product.

It has been suggested that a risk management plan be part of biosimilar guidelines to protect those situations where the risk of unwanted responses is likely to occur, especially if a patient is switched from one therapy to another, i.e., from the reference product to the biosimilar or vice versa, or is receiving ongoing treatment.

In 2012, the EMA issued a guideline for manufacturers regarding the assessment of immunogenicity in monoclonal antibodies intended for use in humans²⁶. It was recommended that a risk management plan be included that showed how risks would be identified as well characterised, and address how risks would be minimised and monitored, including detailed strategies for reducing any risks that would be followed once the biosimilar was approved. In general, the risk plan depends on the type of biologic and its product characteristics as well as the outcome of the risk assessment. For biological medicines with a low immunogenicity profile (e.g. filgrastim), patients are usually tested for antibodies frequently at the beginning and at the end of the clinical study and usually require shorter follow-up period and only routine pharmacovigilance measures post approval. In cases where clinically relevant immunogenic responses have been observed (e.g. epoetins) immunogenicity testing is more frequent, there is a longer patient follow-up and specific post-marketing clinical studies may be required.

The FDA has also issued guidance for industry in which safety and immunogenicity data need to be collected and evaluated²⁷. The guidance also notes that this information may need to be supplemented with additional evaluations either before or after approval. The extent and timing of the clinical immunogenicity assessment will vary depending on a range of factors such as the extent of similarity between the biosimilar and the reference product as well as the incidence and clinical consequences of immune responses for the reference product. For example, when the reference product is known to have the potential for immune-mediated toxicity, tests capable of detecting antibodies (and their neutralizing potential) should be developed to analyse samples obtained from the clinical pharmacology studies. If the clinical consequence is severe, a more extensive stand-alone immunogenicity assessment is usually required to support a demonstration of biosimilarity. If the immune response to the reference product is rare, a premarketing evaluation to assess any differences in immune responses between the two products may be sufficient to support biosimilarity. In some cases, safety may need to be evaluated through post-marketing surveillance or studies.

Immunogenicity by biologics is usually always monitored once the drug is on the market. Post-market surveillance is necessary to generate data on use, efficacy, and safety, which may not have been apparent during premarket trials and informs the optimal use of the drug in diverse populations. Post-market surveillance is dependent on healthcare professionals being able to track data in an established, accessible database.

Current Landscape

Cost savings

Biosimilars play an important role in pharmaceutical innovation and healthcare system sustainability. Access to biosimilars can potentially reduce the cost of cancer therapies and generate savings that can be reinvested in healthcare.

The cost reduction of a new biosimilar depends heavily on the market – greater reductions in price are seen if there are several biosimilar competitors for a single reference product. It should be noted contracting, discounts and rebates offered by the manufacturers makes it difficult to understand true pricing differences.

The global biologics market was worth USD 46 billion in 2002 and is projected to grow to USD 390 billion by 2020²⁸. For payers, however, this growth of the biologics market has presented new challenges and difficult decisions as they try and balance access to cutting edge medicines while facing growing budgetary pressures. For instance, in the UK, the National Institute for Health and Care Excellence (NICE) has restricted or did not recommend at least one indication of several biologics leading to the development of The Cancer Drugs Fund (CDF). This fund was established in October 2010 as a response to address the rejection by NICE to significant numbers of new cancer medicines²⁸.

Biosimilars are priced lower than their reference products. The savings are not as significant as seen with generics. Regardless, savings of 10-30% are usually realised. Cumulative potential savings to health systems in the EU and the US, because of the use of biosimilars, could exceed EUR 50 billion and reach as much as EUR 100 billion in the next few years alone²⁸.

Improved patient outcomes have also been noted with biosimilars currently on the market, for example, biosimilar filgrastim which is used to prevent febrile neutropenia caused by chemotherapy. In the UK, biosimilar filgrastim was launched in 2008. In the period between January 2009 and January 2014, overall consumption of filgrastim increased by 104%²⁸. The launch of biosimilar filgrastim led to improved patient outcomes, by enabling greater numbers of patients to access these treatments.

Usage

In Europe, in general, there is a faster uptake of biosimilars. The patents associated with biologics often expire earlier in Europe than other countries. However, individual European nations have had distinctly different levels of uptake. These differences are largely due to local variation in pricing and reimbursement, education levels, population characteristics, and stakeholder incentives. Biosimilar use seems to be higher in central and eastern EU countries, which reflects incentivised policies that act as a driver for faster uptake and lower pricing²⁹.

For example, some countries in Europe are employing gainsharing practices to increase biosimilar use. The implementation of gainsharing follows different approaches and can be customised to a healthcare system. Possible models include utilising any savings system-wide to improve access for patients, allowing individual hospitals to keep all or a portion of any savings realised by using a less expensive biosimilar vs. the originator drug, or letting individual physicians re-invest savings from prescribing biosimilars into other needed services for patients³⁰.

In North America, uptake of biosimilars has seen a lot of setbacks. Inconsistent use and a lack of understanding of the terminology, evolving regulatory guidance, and questions about how biosimilars may be prescribed and dispensed, have contributed to an uncertain environment. In addition, cost savings are not transparent and are complex to discern³¹.

Availability

In Europe, to date, over 150 biosimilars referencing 14 originator products have been approved by the EMA³². Generally, biosimilars have been available in Europe for longer due to earlier patent expiries when compared to other countries. A full list of biosimilars approved by the EMA is available on their [website](#).

In the US, to date, 8 biosimilars referencing 6 originator products have been approved by the FDA, the majority of which were approved in 2017, including one product for use as a supportive care agent in the cancer setting (Amgen’s Neupogen)³³. With the expiration of several biologic patents, a wave of biosimilars is expected in the United States, and cancer treatments are likely to consist of a significant proportion of the approved biosimilars.

Currently, the only biosimilar to treat lymphoma is rituximab. Rituximab is a chimeric monoclonal antibody against the protein CD20, which is primarily found on the surface of immune system B-cells. It is indicated for the treatment of patients with certain types of CD20-positive lymphoma. The originator product, Roche’s MabThera/Rituxan (rituximab), was approved by the US Food and Drug Administration (FDA) in November 1997 and by the European Medicines Agency (EMA) in June 1998. The patents on MabThera/Rituxan expired in the US in September 2016 and in Europe in February 2013³⁴.

There are more than 20 rituximab biosimilars currently approved or in development.

Table 4a: Approved & Marketed Rituximab Biosimilars³⁴

Biosimilar Name	Manufacturer	Approval Date				
		EU	USA	Australia	Korea	Argentina
Blitzima	Celltrion Healthcare Hungary Kft.	Jul 2017				
Novex	Laboratorio Elea					Oct 2014
Ritemvia	Celltrion Healthcare Hungary Kft.	Jul 2017				
Rituzena (previously Tuxella)	Celltrion Healthcare Hungary Kft.	Jul 2017				
Rixathon/ Riximyo	Sandoz GmbH	Jun 2017	Rejected Apr 2018	Nov 2017		

Truxima	Celltrion Healthcare Hungary Kft.	Feb 2017	Rejected Apr 2018	Apr2018	Nov 2016	
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Table 4b: 'Similar Biologics'* Rituximab Approved & Marketed³⁴

Product Name*	Manufacturer	Approval Date	
		India	Latin America
AcellBia/Usmal	Biocad	Jun 2017	June 2017***
Maball	Hetero Group	Aug 2015	
MabTas	Intas Pharmaceuticals	Feb 2013	
Reditux**	Dr. Reddy's Laboratories	Apr 2007	Not reported
RituxiRel	Reliance Life Sciences	Feb 2015	
Rituximab	Zenotech Laboratories	Feb 2013	

* 'Similar biologics' launched in India before the Indian 'similar biologics' guideline came into effect on 15 September 2012, were approved using an ad-hoc abbreviated procedure on a case-by-case basis.

**Also available in Bolivia, Chile, Ecuador, Paraguay, Peru.

***Bolivia, Honduras

The rituximab biosimilars mentioned above are administered via intravenous administration. However, the originator company has released their 'next generation' version of rituximab under a new patent, a subcutaneous (under the skin) administration of rituximab that has been approved for use in many countries globally. Administering biologics subcutaneously instead of intravenous infusions can reduce administration time drastically, while maintaining similar efficacy and safety. Due to this, many patients prefer subcutaneous administration. However, a biosimilar of the subcutaneous version of rituximab will not be available until patent expiry.

Biosimilars are also in use for supportive care for patients with lymphoma, as described below. Supportive care drugs do not treat the cancer itself but treat side effects.

Epoetin alfa is a form of a naturally occurring protein (**erythropoietin**) that stimulates the bone marrow to produce red blood cell levels. It is used to treat chemotherapy-induced anaemia in lymphomas and other disorders. The original product, trade name Epopo or Eprex, is manufactured and marketed by Amgen and was approved for use by the FDA in 1993 and the EMA in 2007. Janssen Biotech has a product licence agreement with Amgen to sell the same product under the name Procrit³⁵.

A similar product, darbepoetin alfa is a synthetic form of erythropoietin and is used to treat anaemia, commonly associated with cancer chemotherapy. The originator product, Amgen's Aranesp (darbepoetin alfa), was approved by the US Food and Drug Administration (FDA) in September 2001 and by the European Medicines Agency (EMA) in August 2001³⁶.

Table 5a: Approved & Marketed Epoetin Alfa and Darbepoetin Alfa Biosimilars^{35,36}

Biosimilar Name	Manufacturer	Approval Date			
		EMA	USA	Australia	Japan
Abseamed	Medice Arzneimittel Pütter GmbH & Co. KG	Aug 2007			
Aczicrit	Sandoz			Jan 2010	
Binocrit	Sandoz GmbH	Aug 2007			
Epoetin alfa BS	JCR Pharmaceuticals				Jan 2010
Epoetin Alfa Hexal	Hexal AG	Aug 2007			
Grandicrit	Sandoz			Jan 2010	
Nesp	Kyowa Hakko Kirin				Sep 2013
Novicrit	Novartis			Jan 2010	
Retacrit/ Epoetin Hospira	Pfizer/Hospira UK Limited	Dec 2007	May 2017		
Silapo	Stada Arzneimittel AG	Dec 2007			

Table 5b: 'Similar Biologics'* Epoetin Alfa and Darbepoetin Alfa Approved & Marketed in India^{35,36}

Product name*	Manufacturer	Approval/ launch date in India
Actorise	Cipla/Hetero	Jan 2014
Ceriton	Ranbaxy	Not reported
Cresp	Dr. Reddy's Laboratories	Mar 2010
Darbatitor	Torrent Pharmaceuticals	2014
Epofer	Emcure	Not reported
Epofit/Erykine	Intas Pharmaceuticals	Aug 2005
Eporec	Bioviz Technologies	Aug 2011
Epotin	Claris Lifesciences	Not reported
Erypro	Biocon	Not reported
Relipoietin	Reliance Life Sciences	2008
Repoitin	Serum Institute of India	Nov 2011
Shanpoietin	Shantha Biotechnics/Merieux Alliance	Jan 2005
Wepox	Wockhardt	Mar 2001

*'Similar biologics' launched in India before the Indian 'similar biologics' guideline came into effect on 15 September 2012, were approved using an ad-hoc abbreviated procedure on a case-by-case basis.

Filgrastim is used to stimulate the production of neutrophils (a type of white blood cell) in patients undergoing therapy that causes low white blood cell counts (neutropenia). This medication is used to prevent infection and neutropenic (low white blood cells) fevers caused by

chemotherapy. It may also be used to increase the number of hematopoietic stem cells in the blood before collection by leukapheresis for use in hematopoietic stem cell transplantation. Filgrastim may also be referred to as a granulocyte - colony stimulating factor (G-CSF). The original product Neupogen, manufactured by Amgen, was approved for use by the FDA in 1991³⁷.

Table 6a: Approved & Marketed Filgrastim Biosimilars³⁷

Biosimilar Name	Manufacturer	Approval Date					
		EU	USA	Australia	Japan	Canada	Brazil
Accofil	Accord Healthcare Ltd	Sep 2014					
Filgrastim BS	Fuji Pharma/ Mochida Pharmaceutical				Nov 2012		
Filgrastim Hexal	Hexal AG	Feb 2009					
Fiprima	Eurofarma Laboratorios						Oct 2015
Grastofil	Apotex					Dec 2015	
Grastofil	Apotex Europe BV	Oct 2013					
Nivestim	Hospira UK Ltd	Jun 2010		Sep 2010			
Ratiograstim	Ratiopharm GmbH	Sep 2009					
Tevagrastim/ Filgrastim BS	Teva GmbH	Sep 2008		Aug 2011	Feb 2013		
Zarzio/ Zarxio/ Filgrastim BS	Sandoz GmbH	Jun 2009	Mar 2015	May 2013	Mar 2014		

Table 6b: 'Similar biologics'* Filgrastim approved and marketed in India³⁷

Product name*	Manufacturer	Approval/ launch date in India
Emgrast	Gennova Biopharmaceuticals (Emcure)	Mar 2010
Fegrast	Claris Lifesciences	Not reported
Filgrastim**	Cadila Pharmaceutical	Oct 2013
Filgrastim**	Lupin	Mar 2013
Filgrastim**	USV	Jun 2013
Grafeel	Dr. Reddy's Laboratories	Not reported
Molgramostim	Zenotech Laboratories	May 2013
Neukine	Intas Pharmaceuticals	2004
Neupeg	Intas Pharmaceuticals	2007
Nufil	Biocon	Not reported
Pegex	Gennova Biopharmaceuticals (Emcure)	Jan 2010
Peg-filgrastim	Lupin	Sep 2013

Peg-grafeel	Dr. Reddy's Laboratories	May 2011
Religrast	Reliance Life Sciences	2008

* 'Similar biologics' launched in India before the Indian 'similar biologics' guideline came into effect on 15 September 2012, were approved using an ad-hoc abbreviated procedure on a case-by-case basis.

** Where brand-name is not known active substance name is given.

Source: CDSCO (Central Drugs Standard Control Organization)

Conclusion

Over the next decade, several new biosimilars in lymphoma are expected to hit the market globally. Biosimilars will continue to play an important role in the care of patients, especially since they can potentially reduce the cost of cancer therapies and in theory generate savings that can be reinvested in healthcare.

How much can be saved is difficult to determine as the cost reduction of a new biosimilar varies by market and cost may also be reduced by manufacturer contracts, discounts and rebates. The extent of use in treating patients and the healthcare cost savings will also largely depend on prescriber and patient understanding of the safety and efficacy of these medications.

Given that the development and usage of biosimilars globally is relatively novel, there is a significant need for education on biosimilar products and their appropriate use. A broad range of educational materials on core concepts of biosimilars, efficacy and safety concerns as well as clinical practice guidelines are needed for both prescribers as well as patients.

The European Medicines Agency (EMA) and the European Commission recently published an information guide for healthcare professionals on biosimilar medicines³⁸, as well as a resource for patients³⁹. Patient organisations are also credible sources of information and support for patients.

In addition, global harmonisation for regulatory requirements, naming and integration is critical. While there is more alignment in guidelines now, there is still room for improvement in clinical similarity data, safety and pharmacovigilance.

Global standards, especially on the fundamental aspects of biosimilar development, have the potential to benefit patients worldwide by encouraging development and approval of biosimilar products that can then be effectively marketed on a global scale and be more widely accepted as a viable alternative.

Good advice for patients receiving treatment, regardless of whether they are receiving a biosimilar, is to ask each time they go for treatment which drugs they will be receiving and if they are different in any way to the drugs received previously. It is also important for the patient to keep track of any side effects experienced and report them back to their medical team. This will help ensure the health of the patient, as well as contribute to increased knowledge of all available treatments.

References

- 1- Argentina Ministerio de Salud http://www.anmat.gov.ar/webanmat/retiros/noviembre/Disposicion_7729-2011.pdf. Accessed June 9, 2018.
- 2- Australian Dept of Health: Biosimilar Medicines Regulation. <https://www.tga.gov.au/sites/default/files/biosimilar-medicines-regulation.pdf>. Accessed June 9, 2018.
- 3- Brazil: Registro de produtos biológicos. <http://portal.anvisa.gov.br/registros-e-autorizacoes/medicamentos/produtos/biologicos/produtos-biologicos/registro>. Accessed June 9, 2018.
- 4- Health Canada: Information and Submission Requirements for Biosimilar Biologic Drugs. https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/brgtherap/applic-demanded/guides/seb-pbu/seb-pbu-2016-eng.pdf. Accessed June 9, 2018.
- 5- China: Biosimilars. <https://www.fdanews.com/ext/resources/files/03-15/03-15-China-Biosimilars.pdf?1425486653>. Accessed June 9, 2018.
- 6- Columbia: Regulations for biotherapeutics approval in Colombia. <http://gabi-journal.net/regulations-for-biotherapeutics-approval-in-colombia.html>. Accessed June 9, 2018.
- 7- European Medicines Agency: Guideline on similar biological medicinal products. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf. Accessed June 9, 2018.
- 8- India: Guidelines on Similar Biologics. <http://cdsco.nic.in/writereaddata/CDSCO-DBT2016.pdf>. Accessed June 9, 2018.
- 9- Israel: Ministry of Health. https://www.health.gov.il/hozer/dr_127.pdf. Accessed June 9, 2018.
- 10- Japan: Guideline for the Quality, Safety, and Efficacy Assurance of Follow-on Biologics. <https://www.pmda.go.jp/files/000153851.pdf>. Accessed June 9, 2018.
- 11- Korea. http://www.nifds.go.kr/nifds/03_info/sub_02.jsp. Accessed June 9, 2018.
- 12- Mexico. http://dof.gob.mx/nota_detalle.php?codigo=5214882&fecha=19/10/2011
- 13- Russia. <https://www.rosminzdrav.ru/documents>. Accessed June 9, 2018.
- 14- Singapore: Guidance on Registration of Biosimilar Products. http://www.hsa.gov.sg/content/dam/HSA/HPRG/Western_Medicine/Overview_Framework_Policies/Guidelines_on_Drug_Registration/DR_Guide_2016/DR%20guide%202016%20final/Appendix%2015_Guidance%20on%20Registration%20of%20Biosimilar%20Products.pdf. Accessed June 9, 2018.
- 15- South Africa: Biosimilar Medicines. http://www.mccza.com/documents/d259816c2.30_Biosimilars_Aug14_v3.pdf. Accessed June 9, 2018.
- 16- Switzerland: Guidance document Authorisation Biosimilar. file:///C:/Users/SVM/Downloads/ZL101_00_003e_WL%20Guidance%20document%20Authorisation%20Biosimilar.pdf. Accessed June 9, 2018.
- 17- Turkey: Biosimilar Product. <https://www.titck.gov.tr/%C4%B0la%C3%A7/BiyolojikBiyoteknolojik>. Accessed June 9, 2018.
- 18- FDA: Biosimilars. <https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/default.htm>. Accessed June 9, 2018.
- 19- Venezuela. http://www.inhrr.gob.ve/pdf/rc_pdf/proyecto_de_norma_PBS.pdf. Accessed June 9, 2018.
- 20- Improving Access to Innovative Medical Therapies, Subtitle A—Biologics Price Competition and Innovation. <https://www.fda.gov/downloads/drugs/ucm216146.pdf>. Accessed on June 19, 2018.
- 21- FDA: Considerations in Demonstrating Interchangeability With a Reference Product. Guidance for Industry <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf>. Accessed June 19, 2018.
- 22- European Medicines Agency: Biosimilars in the EU. http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf. Accessed June 19, 2018.

- 23- Health Canada: Fact Sheet - Biosimilars. https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/brgtherap/applic-demande/guides/biosimilars-biosimilaires-qa-qr-eng.pdf. Accessed on June 19, 2018.
- 24- WHO: Biological Qualifier, An INN Proposal Programme on International Nonproprietary Names (INN). http://www.who.int/medicines/services/inn/WHO_INN_BQ_proposal_2015.pdf?ua=1. Accessed June 19, 2018.
- 25- FDA: Nonproprietary Naming of Biological Products, Guidance for Industry. <https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf>. Accessed June 19, 2018.
- 26- European Medicines Agency: Guideline on Immunogenicity Assessment of Monoclonal Antibodies Intended for In Vivo Clinical Use. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128688.pdf. Accessed June 19, 2018.
- 27- FDA: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, Guidance for Industry. <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm397017.pdf>. Accessed June 19, 2018.
- 28- IMS Institute for Healthcare Informatics. Delivering on the Potential of Biosimilar Medicines. <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/delivering-on-the-potential-of-biosimilar-medicines.pdf>. Accessed June 19, 2018.
- 29- The Centre for Biosimilars. Policy Differences Among European Nations Affect Biosimilar Uptake. <http://www.centerforbiosimilars.com/news/policy-differences-among-european-nations-affect-biosimilar-uptake>. Accessed June 19, 2018.
- 30- Moorkens E, Vulto AG, Huys I, Dylst P, Godman B, Keuerleber S, et al. (2017) Policies for biosimilar uptake in Europe: An overview. PLoS ONE 12(12): e0190147. <https://doi.org/10.1371/journal.pone.0190147>
- 31- Generics and Biosimilars Initiative. Biosimilars pricing slowing uptake in the US. <http://gabionline.net/Reports/Biosimilars-pricing-slowing-uptake-in-the-US>. Accessed June 19, 2018.
- 32- EMA: European Public Assessment Reports – Biosimilars. http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keyword=Enter+keywords&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=biosimilars. Accessed June 19, 2018.
- 33- FDA: Biosimilar Product Information. <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580432.htm>. Accessed June 19, 2018.
- 34- Generics and Biosimilars Initiative. Biosimilars of Rituximab. <http://www.gabionline.net/Biosimilars/General/Biosimilars-of-rituximab>. Accessed June 19, 2018.
- 35- Generics and Biosimilars Initiative. Biosimilars of Epoetin Alfa. <http://gabionline.net/Biosimilars/General/Biosimilars-of-epoetin-alfa>. Accessed June 9, 2018.
- 36- Generics and Biosimilars Initiative. Biosimilars of Darbepoetin Alfa. <http://gabionline.net/Biosimilars/General/Biosimilars-of-darbepoetin-alfa>. Accessed June 9, 2018.
- 37- Generics and Biosimilars Initiative. Biosimilars of Filgrastim. <http://www.gabionline.net/Biosimilars/General/Biosimilars-of-filgrastim>. Accessed June 9, 2018.
- 38- EMA: Biosimilars in the EU – Information Guide for Healthcare Professionals. http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf. Accessed June 9, 2018.
- 39- EMA: What I need to know about Biosimilar Medicines - Information for patients <http://ec.europa.eu/docsroom/documents/26643>. Accessed June 9, 2018.

Glossary of Terms

Biologic: a substance that is made from a living organism or its products

Biosimilar or biosimilarity: the biological product is highly similar to the reference product and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, quality and effectiveness of the product. Biosimilars may also be referred to as copy biologics or follow-on biologics.

Characterise: explanation of a drug's physical, chemical, biological, and microbiological properties

Erythropoietin: naturally occurring protein that stimulates the bone marrow to produce red blood cells

Generics: a drug that is an equal substitute for a brand-name drug as they are identical in dosage, safety, strength, way they are administered, and what conditions they treat

Glycosylation: process where a carbohydrate attaches to another molecule, usually a protein or a lipid

Immunogenicity: a measure of the immune response to a therapeutic drug

In vitro: studies outside of a living organism, for example in test tubes in a laboratory

Pathophysiology: the processes or mechanisms that cause a disease to develop and progress

Pharmacodynamics profile (PD): how a drug affects an organism

Pharmacokinetics profile (PK): how an organism affects a drug; also called PK

Pharmacovigilance: a system that can monitor and track the effects of a drug, or one drug compared to another, once they have been licensed for use

Physiochemistry: includes both physiology (science that looks at the way living organisms function) and chemistry (science that looks at the composition and properties of substances and the changes they undergo)

Proteins: naturally occurring molecules that are essential to biologic activity and a body functioning properly

Reference product: the original biologic drug; also called the **innovator product**

Small molecule drugs: drugs that are made by combining chemicals

Supportive care: provided to prevent or treat the symptoms of a disease, side effects caused by disease treatment and any related psycho-social concerns

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