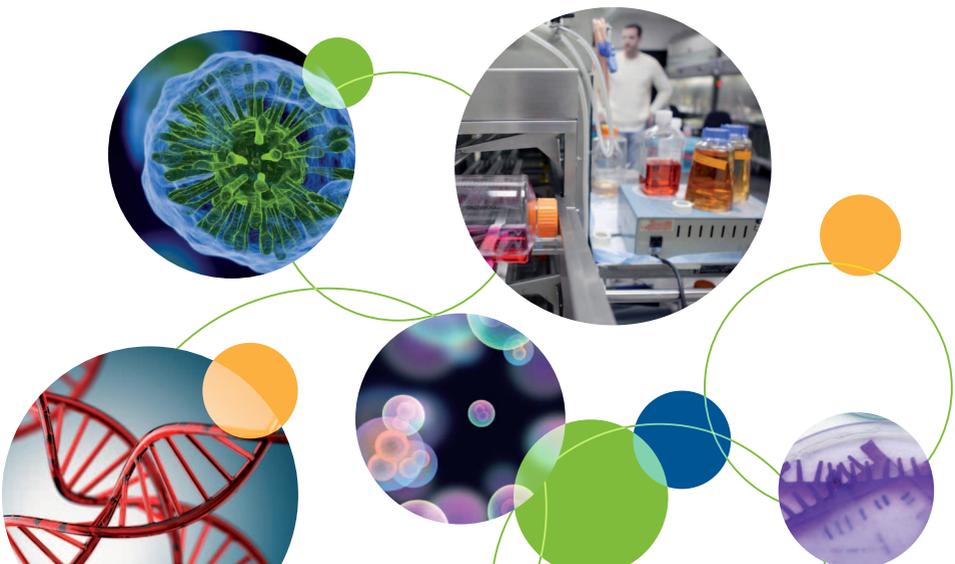


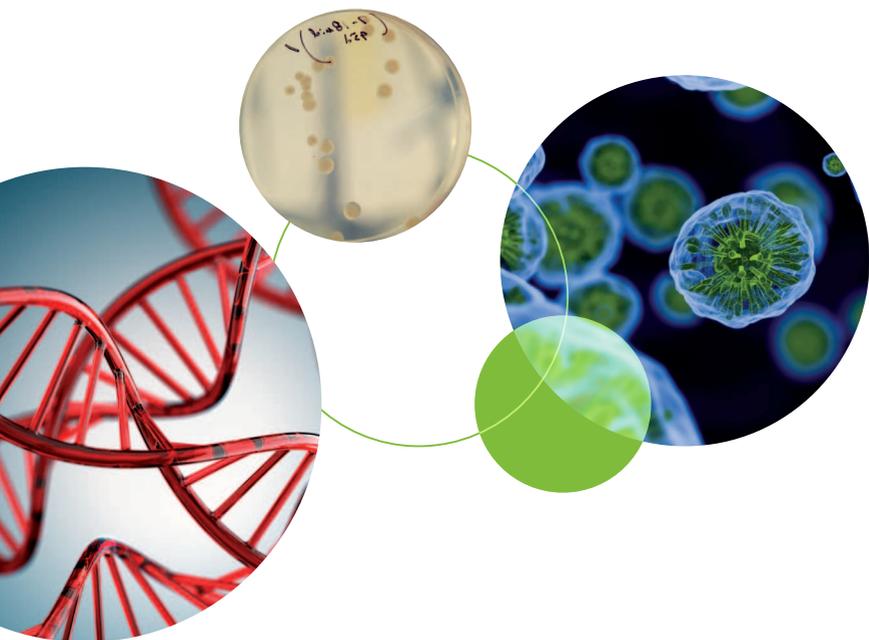


International Alliance of  
Patients' Organizations

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# Quick Guide on Biological and Biosimilar Medicines





### With our thanks

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## Key definitions

**Chemical medicine/drug (also called small molecule medicine):** A medicine which is manufactured without the involvement of living organisms. These contain chemical compounds with defined structures and characteristics.

**Generic medicine:** A generic medicine contains the same active pharmaceutical ingredient as, and is bioequivalent to, an original branded medicine. Generic medicines are identical in the active pharmaceutical substance, dose, strength, route of administration, safety, efficacy and intended use, and can therefore be substituted for the original branded medicine.

**Biotechnology:** The United Nations Convention on Biological Diversity defines biotechnology as “any technological application that uses biological systems, living organisms or derivatives thereof, to make or modify products or processes for specific use”.

**Biological medicine (also called biopharmaceutical medicine, biotechnology medicine or biotherapeutic medicinal product):** The active substance of a biological medicinal product is a biological substance. A biological substance is a substance that is produced by, or extracted from, a biological source. A combination of physico-chemical-biological testing, its production process and control is needed to characterise it and determine its quality.

**Biosimilar medicine:** A biosimilar medicine is a highly similar version of an already-approved biological medicine.

*World Health Organization definition (also called a similar biotherapeutic product):* A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already-licensed reference biotherapeutic product.

*European Medicines Agency definition:* A biological medicine that is developed to be similar to an existing biological medicine. When approved, its variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness.

*US Food and Drug Administration definition:* A biological product that is highly similar to a US-licensed reference biological product, notwithstanding minor differences between the biological product and the reference product in terms of safety, purity and potency of the product.

**Pharmacovigilance:** The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.

## Introduction

*This Quick Guide provides the reader with an introduction to biological and biosimilar medicines, why they are important, how biosimilars are different from the original biological medicine (known as the reference product) and also different from generic medicines, and what patients need to know to use them safely and effectively. It forms part of a wider Information and Advocacy Toolkit on Biological and Biosimilar Medicines for patients' organizations which contains a Briefing Paper with more detailed information regarding these medicines, fact sheets, information on what patients' organizations can do and links to a number of other resources.*

## What are biological and biosimilar medicines?

A **biological medicine** is made from a living organism. This makes it different from traditional chemical medicines, which are made by combining chemical ingredients. Biological medicines are made using biotechnology techniques (i.e. those which modify living organisms to produce a product or perform a function). Since their introduction in the 1980s, biological medicines have become primary treatments for many diseases such as **cancers, diabetes, multiple sclerosis, heart attacks, stroke** and **autoimmune diseases** such as **rheumatoid arthritis**.

A **biosimilar medicine** is developed to be highly similar to a biological medicine that has already been approved. It is legal to manufacture a biosimilar medicine based on the same active ingredient as the original biological medicine after the patent has expired. A generic medicine is considered to be an identical version of the original branded chemical medicine. A biosimilar medicine is a **highly similar**, but not identical, version of a biological medicine. However any differences between the biosimilar and its reference medicine will have been shown not to affect quality, safety or efficacy.

## Why are biological and biosimilar medicines important?

Biological medicines are used in the treatment of a number of diseases. Some disorders are caused by deficiencies in specific proteins, such as:<sup>1-3</sup>

- growth hormone (leading to short stature and other symptoms)
- insulin (causing diabetes)
- clotting factors (resulting in haemophilia and other bleeding disorders)
- erythropoietin (causing anaemia)

- granulocyte colony stimulating factor (causing infections and other disorders)
- a large variety of lysosomal storage enzymes (resulting in Gaucher's, Fabry's, Pompe's and other lysosomal storage diseases).

Biological medicines are made up of **proteins** that are naturally produced in the body. When a biological medicine is given to a patient, it functions like the natural protein, resolving symptoms and preventing or slowing the progression of the disease. Vaccines are also a type of biological medicine.

There are many barriers to patient access to new medicines, one of which is the cost. When a new medicine is discovered, a period of patent protection is provided to the original manufacturer to stimulate innovation and allow recovery of research and development costs. Although biological medicines have revolutionised the treatment of a number of diseases that were previously untreatable, access for patients globally can be limited or difficult due to their high introductory price. Biological medicines tend to be much more expensive than chemical medicines to develop due to high development, material and manufacturing costs and, therefore, may be more costly and inaccessible during the patent period.<sup>4</sup> One of the drivers to producing **biosimilar medicines** is to make them **accessible to more patients** and provide **more treatment options**. Like generic medicines, biosimilar medicines can be produced upon expiration of the reference product's patent.

### What should patients be aware of when taking biological medicines?

Biological medicines cannot be taken orally as the proteins that they are made of are either digested or not absorbed at all. They are often **injected** or **infused** into a vein or under the skin. Patients may experience some reactions, such as redness, swelling or soreness, at the site of injection. These may vary in severity and frequency.

Biological medicines are larger and more complex than chemical medicines, such as aspirin (a painkiller), and they are more likely to be treated by the body as foreign products and cause an **immune reaction** such as allergy or hypersensitivity.<sup>5</sup> These reactions are often mild and subside over time. However, a rare but serious reaction can occur when the body produces neutralising antibodies. These antibodies destroy not only the protein in the biological medicine, but also any of the body's own protein that the medicine replaces or supplements. This can be a life-threatening situation as it can result in there being no protein left in the body at all.<sup>6</sup>

## How do differences between biological and chemical medicines affect patients?

### Variability in the manufacturing process

Traditional chemical medicines such as paracetamol or aspirin are made through chemical reactions which can be easily reproduced and well controlled.<sup>7</sup> They are often small and stable molecules, so it is possible to completely characterise their structure using a number of relatively simple analytical methods.<sup>3</sup>

The process to manufacture a biological medicine is more complex and sensitive than for chemical medicines. The majority of biological medicines are produced using cells whose genes have been modified to produce a certain protein. Here is how it works:<sup>1,7</sup>

1. First the genetic code (a sequence of DNA) of a chosen protein (e.g. a hormone, antibody, blood product) is identified and a functional DNA sequence created.
2. The genetic code is inserted into various host cell lines (e.g. bacteria or yeast), so that the host cells produce this protein.
3. The host cell line that produces the protein most effectively is chosen.
4. This cell line is then grown in machines called bioreactors; this process is called fermentation.
5. The protein is separated out of the bioreactor (e.g. through filtration).
6. The protein is purified, stabilised and processed into a medicine (e.g. insulin injections).

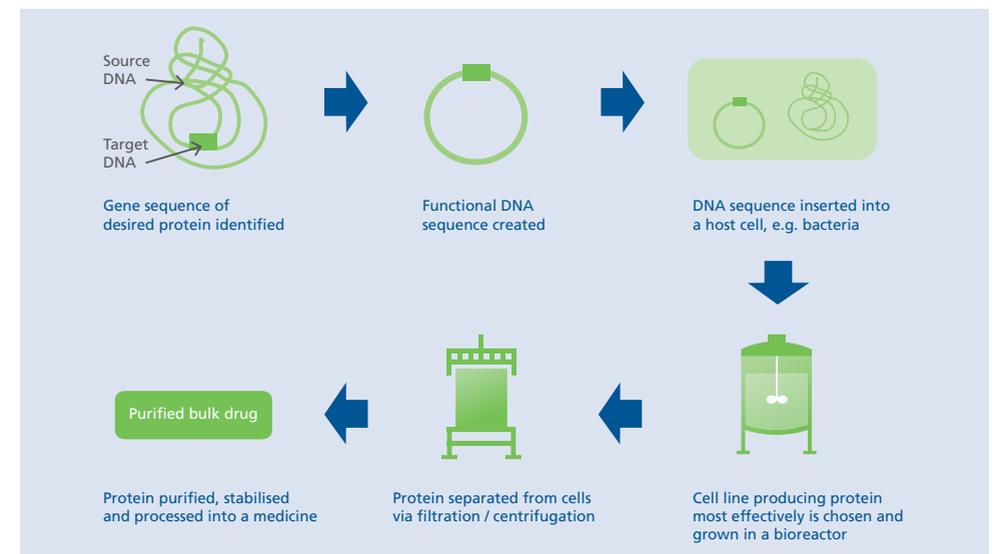


Figure 1. Steps in the production of a biological medicine

Even small variations in the manufacturing process, including the host cell line which is used, the growth conditions, compounds used to stabilise the protein, and manufacturing conditions, can lead to changes in the final medicine. No two batches of a biological medicine (even from the same manufacturer) are ever exactly the same.

### Larger and more complex molecules

Biological medicines tend to be much larger and have a more complex structure than chemical medicines.<sup>8</sup> There are several important consequences for patients. Biological medicines can degrade depending on how they are handled and stored and, therefore, have to be transported and stored carefully to avoid spoiling.<sup>6</sup>

Most chemical medicines can be used in both primary and secondary settings and can be self-administered (i.e. taken in pill form in the home). As biological medicines are used to treat more severe diseases, they are often prescribed by specialists and administered in hospital.

Finally, these large and structurally complex biological medicines are more likely to be recognised by the body as foreign and cause an immune reaction.<sup>3</sup> The ability to cause an immune reaction is called **immunogenicity**.

**Table 1. Major differences between traditional chemical medicines and biological medicines**

Traditional chemical medicines	Biological medicines
Unlikely to cause an immune reaction in the body due to small size	More likely to cause an immune reaction in the body due to large molecular size and composition
Often taken orally in tablet or capsule form	Often administered by injection or infusion
Usually prescribed by general practitioner or primary care physician	Usually used for the treatment of more severe diseases and often prescribed by specialists
Can often be self-administered at home	Often administered in hospital with the help of medical staff or self-administered through sub-cutaneous injections

### How are biosimilar medicines different from the reference biological medicine?

It is relatively easy to manufacture an exact generic copy of a branded chemical medicine through a series of chemical reactions. This is not the case for biosimilar medicines.

As the name implies, a biosimilar medicine is developed to be a **highly similar** version of a biological medicine that has already been approved. The medicine that has already been approved is often called the 'reference product' or 'originator product'. It is almost impossible to make an exact copy of any given biological medicine, including biosimilar medicines, for three reasons:

- Firstly, as biological medicines are made in living organisms there will always be some differences in their characteristics and structure, even if this does not affect how the medicine works.
- Secondly, they are large and have a complex structure making it difficult to work out their structure completely.
- Thirdly, the final medicine is highly dependent on the manufacturing process. When the patent on the reference biological medicine has expired, the manufacturer is not required to release the precise details of the manufacturing process.<sup>9</sup> Thus, each biosimilar medicine manufacturer has to make their own decisions as to choice of cell line to use, what condition to grow the cells under, which stabilising compounds are used, and how the medicine is packaged and stored.

It is important to note that biosimilars are intentionally developed to match any variability that is seen in the reference products.

### How are medicines approved?

#### Generic medicines

A generic medicine is made from the same chemical compounds and has the same chemical structure as the original branded medicine. To be approved, generics do not need to undergo clinical trials (testing in patients to demonstrate efficacy and safety) as trials were conducted for the original branded medicine. The generic medicine only needs to show that the active ingredient is available to the body at the same rate and to the same extent as it is with the original medicine. A generic is generally considered to be bioequivalent (i.e. it works in the body in the same way) as the original branded medicine.

#### Biosimilar medicines

A biosimilar is not a generic copy of the reference biological medicine. To be approved, a biosimilar medicine has to demonstrate that it is comparable to the

reference product in terms of **quality, safety and efficacy** through a **biosimilar comparability exercise**. The first guidelines were developed by the European Medicines Agency (EMA) in 2005,<sup>10</sup> and the World Health Organization (WHO) published their guidelines in 2010,<sup>9</sup> followed by the US Food and Drug Agency's (FDA) draft guidelines in 2012.<sup>11</sup> All three state that, in order for any biological product to be designated as a biosimilar, it must be approved through a stringent regulatory process.<sup>9</sup> The WHO guidelines were developed to aid local regulatory authorities to develop their national standards for assessing quality, safety and efficacy of biosimilar medicines. The EMA has since developed specific guidelines for comparing the proposed biosimilar to the reference product, covering quality, consistency, manufacturing process, safety and efficacy depending on the type of biosimilar medicine.

Biosimilar medicines require **quality studies, non-clinical studies and human clinical studies**, as well as requiring a **post-approval monitoring** and a **risk management plan** at the time of submission for approval. The data required for each biosimilar medicine may differ; in all cases it will be different than the requirements for the reference biological medicine. The purpose of the comparability exercise is not to evaluate the benefits of the biosimilar medicine, but to show that it is highly similar to the reference product, and has comparable quality, safety and efficacy to the reference product.<sup>8</sup>

#### Biosimilars at a glance

- Biological medicines are **complex and large molecules** that are produced in **living organisms**.
- A biosimilar medicine is a **highly similar** version of a reference product with comparable **quality, safety and efficacy**.
- This is shown through a **biosimilar comparability exercise** which includes quality studies, non-clinical studies and human clinical trials.
- **Post-approval monitoring** and a **plan to manage risk** to assure efficacy and safety in use is also required for approval.
- Biosimilars are developed in order to provide **alternative products** usually at **lower cost** and to **increase options** for clinicians, payers and healthcare systems in general.

#### What do patients need to know about the safety of biological medicines?

All medicines have a risk of causing an immune reaction as a result of the body recognising it as a foreign product and creating antibodies against it. As antibodies attack a medicine it can become less effective over time. Though biological and biosimilar medicines must meet regulatory standards for safety before they are approved, there are ongoing risks for patient use following approval.

Biological medicines, including biosimilars, are more likely to cause an **immune reaction** in the body than chemical medicines. Most commonly, the antibodies produced in an immune reaction to a biological medicine can cause the medicine to become less effective, and cause allergic reactions that can range from mild to more serious, such as anaphylaxis.<sup>2</sup> In extreme cases, the antibodies may neutralise the biological medicine, making it completely ineffective.

In some cases, the antibodies may also attack the body's own protein (that the biological medicine is supposed to supplement), a condition known as **autoimmunity** which is highly dangerous.<sup>6</sup> For haemophiliacs, for example, if autoimmunity occurs to the biological medicine the antibodies produced will not only destroy the synthetic clotting factor that is given to the patient, but also any natural clotting factor that the body produces.

#### The case of EPREX

Erythropoietin (EPO) is a naturally occurring hormone that stimulates red blood cell production. A biological medicine version of erythropoietin, often referred to as EPO, can have a small but very dangerous risk of causing an immune reaction known as acquired pure red blood cell aplasia (PRCA). Patients with PRCA develop antibodies that attack not only the biological medicine version EPO, but also the body's natural erythropoietin causing a potentially fatal type of anaemia. Between 2000 and 2002 there was a sharp increase in cases of PRCA among patients using a certain version of EPO (i.e. Eprex, an originator product). Careful investigation led to the discovery that the increase in PRCA cases was due to a small manufacturing change in the formulation of Eprex.<sup>6</sup>

The case above shows how a very small change in the manufacturing process of a biological medicine can increase the risk of an immune reaction. Furthermore, even patients who have been taking a biological medicine for a long time may develop an immune reaction, which may even persist after medication is discontinued.<sup>12</sup>

However, immune reactions can be difficult to predict. While it may be possible to identify the risk of immunological reactions to a biological medicine before clinical trials, these occurrences are often rare. Therefore, they are unlikely to be captured in a clinical study, which typically includes only a limited number of patients over a limited period of time.<sup>6,13,14</sup> To collect information about a drug's adverse effects, including immune reactions, in real-world settings, a plan for ongoing monitoring, also known as **pharmacovigilance**, is needed.<sup>15</sup>

**Pharmacovigilance** is defined by the World Health Organization (WHO) as “**the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems**”.<sup>15</sup>

All pharmaceutical companies are required to have pharmacovigilance plans for monitoring and responding to potential adverse events for every medicine that they manufacture. Most regulatory authorities require all biological manufacturers, including biosimilar manufacturers, to provide a pharmacovigilance plan that is specific to each biosimilar medicine.

#### **What information should patients report in case of an adverse event?**

All biological medicines are different from each other, may undergo manufacturing changes during their life cycle, and have the potential to cause adverse effects.

It is therefore important that all biological medicines, including biosimilar medicines, can be identified and tracked separately. This may be challenging as the reference product and the biosimilar medicine may be given the same **International Non-Proprietary Name (INN)**. An INN is the name assigned by the WHO to the active ingredient in the medicine.<sup>16</sup> It is different to the brand name in order to prevent confusion and ensure patient safety. For example, in Europe there are three biosimilar erythropoietins (used to increase red blood cells) whose brand names are Binocrit, Epoetin alfa Hexal and Abseamed. The INN for all three of these biosimilar erythropoietins is ‘epoetin alfa’. The INN for Eprex, the reference erythropoietin, is also ‘epoetin alfa’.

If the healthcare professional prescribes a medicine using the INN only and not the brand name, neither the healthcare professional nor the patient may know exactly which product has been given. Therefore, if an adverse effect occurs it is difficult to tell which medicine caused it.

The Medicines and Healthcare Products Regulatory Agency of the United Kingdom recommends that healthcare professionals use the brand name when prescribing all biological medicines including biosimilars, stating that although the reference and biosimilar medicines may have the same INN, this does not mean they are identical.<sup>17</sup>

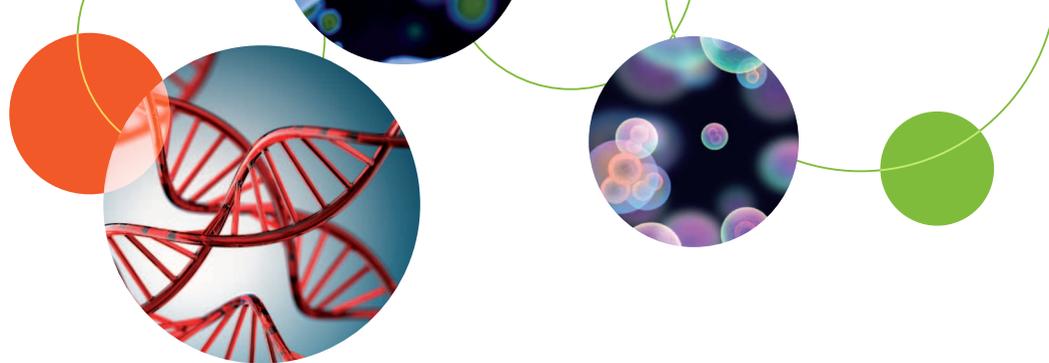
Similarly, the EMA recommends **the brand name, manufacturer's name and the batch number** be used when reporting any adverse effects related to any biological medicine.<sup>18</sup> As there can be batch-to-batch variation in biological medicines, it is important that the batch number is used when reporting adverse events.

How are medicines prescribed in your country? Patients should ensure that when they are prescribed a biological or biosimilar medicine they know the brand name and where to find the batch number of their medicine.

#### **What issues should patients be aware of regarding which biological medicine they have been prescribed and received?**

Patients need to know which biological medicine (whether reference or biosimilar medicine) they have been prescribed and received. In contrast, as most generic medicines have the same effect in the body as their original branded medicine (also known as bioequivalence), patients can be switched from one to the other with no change in efficacy or safety.<sup>13</sup> In other words, because the generic medicines can be shown to be bioequivalent, they can also be used interchangeably.<sup>1</sup>

While biosimilar medicines are **highly similar** to their reference product in terms of **quality, safety and efficacy**, in most countries they are not considered to be interchangeable, i.e. substitutable. For biological medicines, the concern is being able to trace any adverse effects to the exact medicine whether a reference product or a biosimilar. This may be difficult if different versions have been dispensed without the prescriber's or the patient's awareness. This can occur when the pharmacist decides to substitute one medicine for another, usually because it is cheaper, or when the pharmacist is required by law to substitute one drug for another. This is called **automatic substitution**.<sup>18</sup> Where automatic substitution is allowed, pharmacists are accustomed to changing a branded chemical medicine to a generic medicine, and this practice could be extended to substituting a biosimilar medicine for the reference product.



To assure accurate information collection and patient safety, doctors and patients should be fully aware of the exact medicine being used. Immune reactions to a biological medicine can occur after the patient has been using it for a long time. If automatic substitution or repeated switching between medicines has occurred during treatment, it may be very difficult to tell which product is responsible for the adverse effect.<sup>1,18,19</sup>

### **Can patients be sure that regulatory guidelines around the world will guarantee the quality, safety and efficacy of biological medicines?**

It is widely accepted that the WHO, EMA and FDA guidelines should provide a strong and complete basis for approving biosimilar medicines. Globally, regulatory authorities are developing or evolving biosimilar medicine approval guidelines and pathways to meet emerging opportunities and challenges. As biotechnology advances and more patents of biological medicines expire, a greater number of manufacturers in more countries turn to copies of biological medicines as a way to increase availability of biological medicines to patients. Many countries are in the process of developing guidelines for biological and biosimilar medicines.

While some regulatory authorities use the EMA or the WHO guidelines as a reference, not all of these guidelines meet all of the WHO requirements, potentially compromising patient safety. For example, guidelines in some countries do not require a complete comparability exercise for approval.<sup>20</sup> Similarly, there is concern that in some developing countries, the approval process and the post-approval quality control are not stringent enough.

Moreover, some countries such as Brazil who reference the WHO guidelines allow for two pathways for approval with different levels of data required.<sup>21</sup> Although this may encourage local production of biological medicines and reduce the cost of these medicines, it is difficult to be certain that the medicines being approved are of high quality, safety and efficacy.<sup>22</sup>

It is generally agreed that a full biosimilar comparability exercise as described in the WHO guidelines is required in order for a product to be called a biosimilar. Copies of biological medicines authorised without a full biosimilar comparability exercise are generally referred to as **non-comparable follow-on biologics**.<sup>23</sup> An example is Reditux, a non-comparable follow-on to the monoclonal antibody rituximab used for the treatment of rheumatoid arthritis and some cancers. It was approved in India in 2007 based on less comparable data than is needed to apply for approval in Europe or the United States, and it is not known if they have undergone clinical studies.<sup>24–26</sup>

A current challenge is what to do about non-comparable follow-on biologics approved prior to the introduction of regulatory pathways for the approval of biosimilar medicines. This is the situation in India, which released its guidelines for similar biologics in 2012, as well as in some Latin American countries such as Peru, Chile and Colombia.<sup>20,27</sup>

Although there has been progress in terms of regulation, much work needs to be done in order to harmonise global biosimilar medicine regulatory standards with those of stringent regulators such as WHO, EMA or FDA. This is to ensure that all patients receive products that are high quality, safe and efficacious.

**See the 'What patients' organizations can do' booklet in the Information and Advocacy Toolkit on Biological and Biosimilar Medicines for more information on how patients' organizations can advocate for strong regulation.**

### **Who can access biological medicines?**

Most biological medicines are more expensive than traditional chemical medicines and therefore not available to all patients. Like generic copies of branded chemical medicines, biosimilar versions of reference biological medicines are developed to provide alternative medicines, usually at a lower cost, increasing options for clinicians, payers and healthcare systems. Biosimilar medicines are expected to bring around **15 to 30% price reduction** of the reference product.<sup>28</sup> However, biosimilar medicine manufacturers need to invest in clinical trials, manufacturing and post-approval safety monitoring programmes, as do the manufacturers of new biological medicines. For these reasons, it costs about \$75–250 million to bring a biosimilar medicine to approval, compared to \$2–3 million for a generic medicine.<sup>29</sup> Therefore, although price reductions of 80 to 90% are generally realised for generics, this will not be the case for biosimilars.<sup>28</sup>

The actual reduction in cost of a biosimilar medicine can depend on how the price and reimbursement of a medicine is decided in a particular country.<sup>25</sup> In Europe, each country independently decides on the therapeutic value of a medicine, its price and how it will be reimbursed.<sup>30</sup> However, even though they are cheaper than their reference medicine, biosimilar medicines are still unaffordable for many developing countries. Some manufacturers of both original biological and biosimilar medicines offer differential pricing to low-income and high-income countries to improve availability.

Finally, patients' access to biosimilar medicines is not automatic even if they are available and affordable. Proactive steps need to be taken by all relevant stakeholders.<sup>31</sup> Cultural and geographic factors also affect the availability of biosimilar medicines. For example, in some developing countries or regions generic prescribing and dispensing practices are not widely accepted. This means that more expensive brands are often prescribed and dispensed rather than cheaper versions that could enable more patients to access them.<sup>30</sup>

Barriers to access to biological and biosimilar medicines that meet standards of EMA, WHO or FDA include:

- high price of medicines
- low knowledge and understanding of what biological medicines are and their therapeutic value by governments, clinicians and patients
- poor or lack of regulation of biological and biosimilar medicines
- low or lack of political will to ensure access
- more complex administration methods
- poor diagnosis, screening and testing.

### What information and support do patients need?

Being able to make a fully informed decision to take or prescribe a biosimilar medicine is important for patients, doctors, nurses and pharmacists. Patients must be involved, with their healthcare team, in deciding which treatment to pursue. To that end, patients must have complete information, in understandable language, about the benefits and risks of all the medication options, the requirements for safe and effective use, potential adverse effects, how to recognise them and how to report them, and how to know whether the medication is working as intended.

The information should be available from a reliable intermediary, such as physician, nurse, pharmacist or patients' organization. The challenge for all stakeholders, including healthcare providers, patients and patients' organizations is lack of good information as well as misinformation and misperceptions of biosimilar medicines. Many doctors are hesitant to consider biosimilar medicines as a treatment option for their patients due to concerns regarding their safety, quality, efficacy and interchangeability.<sup>8</sup> Doctors and nurses need unbiased and current information about the science and regulatory processes of biosimilar medicines. This is so they understand that in strictly regulated environments, biosimilar medicines provide high-quality, safe and efficacious alternative medicines which can increase the treatment options for patients and improve access to treatment. It has been highlighted that a lack of awareness and education among nurses could lead to serious medication errors and delays in therapeutic gain for the patient.<sup>32</sup>

All stakeholders have a role in providing information and there is great potential for joint efforts. Healthcare companies and associations, regulators, medical professionals and scientific researchers can bring together technical, scientific and medical data. Patients' organizations and patients can bring expertise on how to best present information, communicate risks and involve patients in decisions which affect their health.

If you would like to find out more about biotechnology or biological and biosimilar medicines, further detailed information can be found in the [Briefing Paper on Biological and Biosimilar Medicines](#) and in other sections of the [Information and Advocacy Toolkit](#).

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